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N-Oxidation of 4-Chloropyrimidine Derivatives

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The reaction of 2,6-disubstituted-4-chloropyrimidines (I) with hydrogen peroxide in acetic acid does not afford their N-oxides but results in the rearrangement of chlorine to give 2,6-disubstituted-5-chloro-4-pyrimidones (II). The preparation of chloropyrimidine N-oxides (IV) is successful when mono-permaleic acid is used as an oxidizing reagent.

A lot of papers[2] were published on the N-oxidation reaction of pyrimidine derivatives, however, the N-oxidation of the chloropyrimidine has not been established in the literature. Present paper reports that the preparation of the 4-chloropyrimidine N-oxides is successful when mono-permaleic acid is used as an oxidizing reagent, and on treatment with hydrogen peroxide in acetic acid, none of the N-oxide is obtained but the rearrangement of chlorine is observed. Chloropyrimidines used in this reaction are as follows: 4-chloro-2,6-dimethylpyrimidine (Ia), 2-ethyl-4-chloro-6-methylpyrimidine (Ib), 2-isopropyl-4-chloro-6-methylpyrimidine (Ic), 2-phenyl-4-chloro-6-methylpyrimidine (Id), 4-chloro-6-phenylpyrimidine (Ie), 2,4-dichloro-6-methylpyrimidine (If), and 4-chloro-6-methylpyrimidine (Ig).

Employing the general method of the N-oxidation reaction,[3] 2-ethyl-4-chloro-6-methylpyrimidine (Ib) was treated with hydrogen peroxide in acetic acid, colorless needles of mp 167—168° (IIb) were obtained accompanied with the formation of 2-ethyl-6-methyl-4-pyrimidone (IIIb) (mp 158—159°). The elemental analysis of the former product provided its empirical formula as $C_7H_9ON_2Cl$ which agreed with 2-ethyl-4-chloro-6-methylpyrimidine N-oxide (IVb).

However, the infrared (IR) absorption spectrum of this compound indicates the presence of the amide carbonyl at 1667 cm^{-1} and the absence of the N-oxide absorption near 1250 cm^{-1}.

Furthermore, in the nuclear magnetic resonance (NMR) spectrum the signal owing to an NH proton is appeared at 12.85 ppm but none of the ring proton can be observed. These spectral data do not support the structure of the N-oxide (IVb), but suggest that the structure of this compound should be 2-ethyl-5-chloro-6-methyl-4-pyrimidone (IIb).

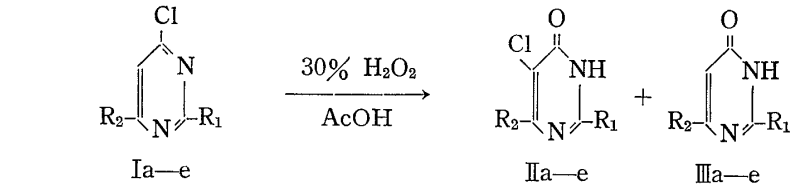
Similarly, from Ia—Ie the chloropyrimidone derivatives (IIa—IIe) were obtained in pretty good yield.

In the case of 4-chloro-6-phenylpyrimidine (Ie), in which none of the substituent presents in the 2-position, reaction proceeds similarly to give monochloro-phenylpyrimidone ($\nu_{C=O}$, 1695 cm^{-1}). Although there are some isomers, such as 2-chloro-6-phenyl-4-pyrimidone (IIe') or 4-chloro-6-phenyl-2-pyrimidone (IIe''), we propose 5-chloro-6-phenyl-4-pyrimidone (IIe) as the proper structure.

In fact, when IIe was treated with phosphorous oxychloride, dichlorophenylpyrimidine (V) was obtained in good yield, which was apparently different from 2,4-dichloro-6-phenylpyrimidine (VII) prepared from 6-phenyluracil (VI) and phosphorous oxychloride.[4]

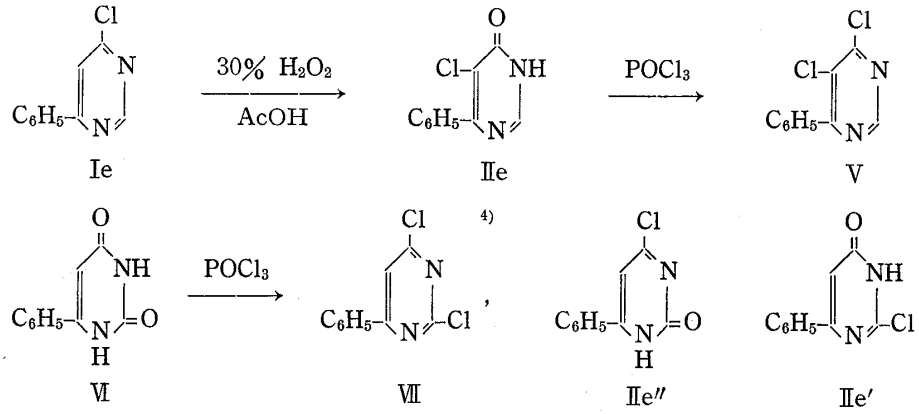
1) Location: *Kita-4, Sendai.*
2) For example, D. Brown and S. Mason, "The Pyrimidines," Interscience Publisher, John Wiley and Sons, N. Y., 1962, pp. 382.
3) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1954).
4) T. Matsukawa and B. Ohta, *Yakugaku Zasshi*, **70**, 134 (1950).

Furthermore, in the NMR spectrum of V the signal of the ring proton appeared at 8.90 ppm, which is assignable as the absorption of a proton at the 2-position. As shown in Table II, in the NMR spectra of 4-chloro-6-phenylpyrimidine (Ie) and 2,4-dichloro-6-phenylpyrimidine (VII) the absorption of the 5-proton appears at near 7.7 ppm and that of the 2-proton at 9.0 ppm. In view of the above facts, it seemed reasonable to assume that the structure of the product from Ie is 5-chloro-6-phenyl-4-pyrimidone (IIe). Table I summarizes the result of the above reaction.



Ia—e IIa—e IIIa—e

	Ia	Ib	Ic	Id	Ie
R_1	CH_3	C_2H_5	iso-C_3H_7	C_6H_5	H
R_2	CH_3	CH_3	CH_3	CH_3	C_6H_5



Ie IIe V

VI VII[4] IIe″ IIe′

Chart 1

Table I. Reaction of I with H_2O_2 in AcOH

Product / Starting material	II mp (°C)	II Yield (%)	II IR ($\nu_{C=O}$)	III mp (°C)	III Yield (%)
Ia	199	37	1667	197	32
Ib	168	50	1669	159	17
Ic	160	69	1696		
Id	235	73	1650		
Ie	237	65	1695		

Table II. NMR of Ie, V and VII

	2-proton	5-proton	6-phenyl
Ie	9.05	7.75	7.40—8.20 (m)
V	8.90	—	7.40—7.90 (m)
VII	—	7.65	7.45—8.20 (m)

ppm, solvent $CDCl_3$ m=multiplet

The mechanism of the formation of the 5-chloro-4-pyrimidones from the 4-chloro compounds will be proposed as shown in Chart 2. Namely, first stage of this reaction might be

hydrolysis of I by the S_N reaction to give III, and the resulting chloro-anion was oxidized by hydrogen peroxide giving chlorine, which reacted with III as an electrophilic reagent to give II.

Actually, when 2-ethyl-6-methyl-4-pyrimidone (IIIb) was warmed with a mixture of conc. hydrochloric acid and acetic acid in the presence of hydrogen peroxide, 2-ethyl-5-chloro-6-methyl-4-pyrimidone (IIb) was obtained in 50% yield. This observation supports the mechanism proposed above. Thus, hydrogen peroxide as an N-oxidation reagent towards the 4-chloropyrimidines seems to be unadequate because hydrolysis occurs simultaneously giving the chloride ion, which on oxidation transforms to chlorine.

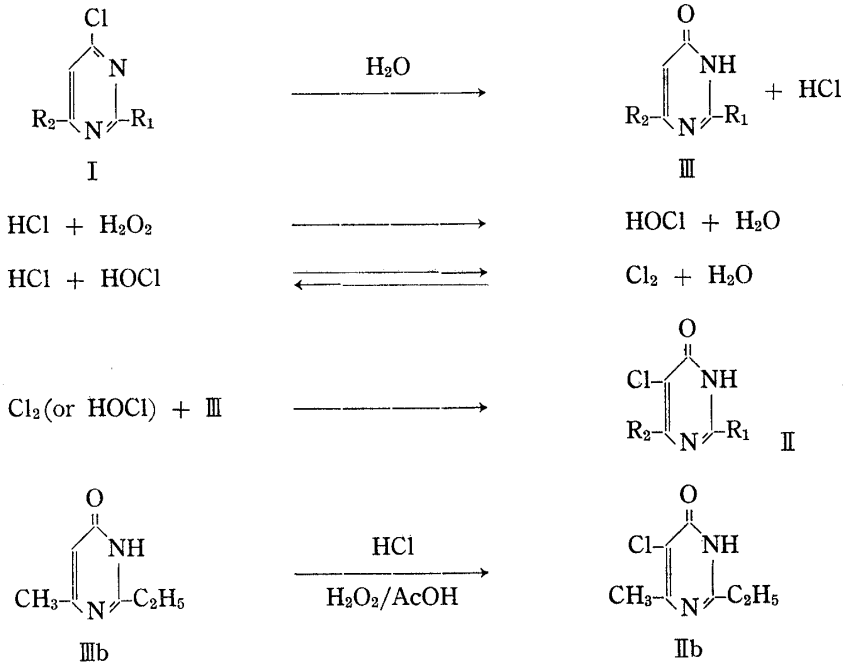


Chart 2

Thereby, attempts were made to react with anhydrous peroxide for the sake of avoiding hydrolysis, and mono-permaleic acid was used as an N-oxidizing reagent.

Recently, Hamana, *et al.*[5] reported the N-oxidation of 2-chloroquinoline with mono-permaleic acid to give the N-oxide in good yield. According to the procedure described by Hamana,[5] 4-chloro-2,6-dimethylpyrimidine (Ia), was treated with mono-permaleic acid, colorless needles of mp 100—102° were obtained, whose empirical formula was corresponding to the N-oxide of Ia.

The IR absorption spectrum of this cmpound is different from that of IIa and indicates the presence of the N-oxides function at 1225 cm^{-1}.

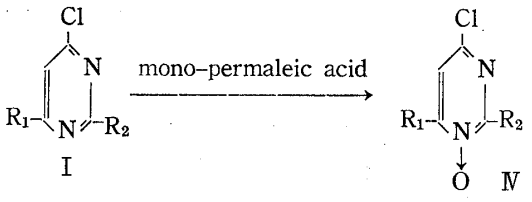
On treatment with sodium methoxide this was converted to 2,6-dimethyl-4-methoxy-pyrimidine 1-oxide (VIIIa), whose structure was characterized on admixture with an authentic sample prepared by the method reported in the previous paper.[6]

Although both of 2,4-dichloro-6-methylpyrimidine (If), and 4-chloro-6-phenylpyrimidine (Ie) did not transform to the N-oxides by this procedure, the alkylchloropyrimidines (Ia—c) were converted to the 1-oxides in pretty good yield.

Table III shows the results of this reaction.

5) M. Yamazaki, N. Honjo, K. Noda, Y. Chono, and M. Hamana, *Yakugaku Zasshi*, **86**, 749 (1966).
6) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 1096 (1967).

Table III.



I IV

Product IV	R_1	R_2	mp (°C)	Yield (%)	IR (ν_{N-O}) cm^{-1}	Recov. of I (%)
IVa	CH_3	CH_3	102	34	1225	0
IVb	CH_3	C_2H_5	76	57	1244	5
IVc	CH_3	iso-C_3H_7	95	74	1244	3
IVe	C_6H_5	H	—	—	—	67
IVf	CH_3	Cl	—	—	—	62

Experimental

2,6-Dimethyl-5-chloro-4-pyrimidone (IIa)——To a solution of 2,6-dimethyl-4-chloropyrimidine (Ia) (1.42 g) in AcOH (14 ml) was added 30% H_2O_2 (2.6 ml). The mixture was heated at 70—80° in a water-bath for 6 hr, and condensed under reduced pressure. The resulting residue was extracted with acetone. The acetone soluble fraction was condensed giving a white crystalline solid, which was purified by recrysallization from acetone to give colorless prisms of mp 197—199°. Yield, 0.6 g (37%). *Anal.* Calcd. for $C_6H_7ON_2Cl$ (IIa): C, 45.42; H, 4.41; N, 17.66. Found: C, 45.73; H, 4.57; N, 17.64. NMR ($CDCl_3$, TMS, ppm): 2.46 (3H, singlet, 6-CH_3), 2.51 (3H, singlet, 2-CH_3), 13.35 (1H, singlet, NH).

The acetone insoluble fraction was neutralized with K_2CO_3 to give a crystalline substance. Recrystallization from acetone gave colorless needles of mp 195—197°. Beilstein test for chlorine was negative. This was identified as 2,6-dimethyl-4-pyrimidone (IIIa) by the comparison of IR spectrum and mixed mp test with an authentic sample prepared according to the method reported by Pinner.[7] Yield, 0.52 g (32%).

2-Ethyl-5-chloro-6-methyl-4-pyrimidone (IIb)——a) Employing the similar procedure described above, the reaction of 2-ethyl-4-chloro-6-methylpyrimidine (Ib) (1.85 g) with 30% H_2O_2 (2.6 ml) in AcOH (18 ml) afforded 1.05 g (50%) of 2-ethyl-5-chloro-6-methyl-4-pyrimidone (IIb), colorless needless of mp 167—168°, as an acetone soluble fraction and 0.3 g (16%) of mp 159°, from the acetone insoluble residue, undepressed on admixture with an authentic specimen of 2-ethyl-6-methyl-4-pyrimidone (IIIb). *Anal.* Calcd. for $C_7H_9ON_2Cl$ (IIb): C, 48.69; H, 5.21; N, 16.23. Found: C, 49.26; H, 5.26; N, 16.44. NMR ($CDCl_3$, TMS, ppm): 1.36 (3H, triplet, $C\underline{H}_3$-CH_2-, J=7.95 cps), 2.75 (2H, quartet, CH_3-$C\underline{H}_2$-, J=7.95 cps), 2.48 (3H, singlet, 6-CH_3) 12.85 (1H, singlet, NH).

b) To a solution of 2-ethyl-6-methyl-4-pyrimidone (IIIb) (1.38 g) in AcOH (10 ml) was added conc. HCl (1.6 ml) and 30% H_2O_2 (2 ml). The mixture was heated at 70—80° for 6 hr. Similar treatment described above gave 0.86 g (50%) of 5-chloro-2-ethyl-6-methyl-4-pyrimidone (IIb), mp 166—168°. Recovery of starting IIb was identified as its HCl-salt, mp 235° (decomp.). Yield, 0.82 g (48%).

2-Isopropyl-5-chloro-6-methyl-4-pyrimidone (IIc)——a) Following the procedure given for IIa, the reaction of 2-isopropyl-4-chloro-6-methylpyrimidine (Ic) (2.6 g) with 30% H_2O_2 (3.3 ml) in AcOH (18 ml) afforded 1.95 g (69%) of 2-isopropyl-5-chloro-6-methyl-4-pyrimidone (IIc),mp 159—160°, colorless needles (acetone). *Anal.* Calcd. for $C_8H_{11}ON_2Cl$ (IIc): C, 51.49; H, 5.90; N, 15.00. Found: C, 51.56; H, 6.05; N, 15.17 NMR ($CDCl_3$, TMS, ppm): 1.60 (6H, doublet, $(C\underline{H}_3)_2CH$-, J=7.8 cps), 2.92 (3H, singlet, 6-CH_3), 3.54 (1H, septet, $(CH_3)_2C\underline{H}$-, J=7.8 cps), 14—16 (1H, singlet, broad, NH).

b) According to the same procedure described in the above run (IIb, method b), the reaction of 2-isopropyl-6-methyl-4-pyrimidone (IIIc) (0.76 g) with conc. HCl (1 ml) and 30% H_2O_2 (1.5 ml) in AcOH (5 ml) gave 0.65 g. (69%) of IIc, mp 161—163°.

2-Phenyl-5-chloro-6-methyl-4-pyrimidone (IId)——Following the procedure given for the first run, the reaction of 2-phenyl-4-chloro-6-methylpyrimidine (Id) (4.08 g) with 30% H_2O_2 (7.5 ml) in AcOH (30 ml) gave 3.22 g (73%)of 2-phenyl-chloro-6-methyl-4-pyrimidone (IId), mp 233—235°, colorless prisms (MeCOEt). *Anal.* Calcd. for $C_{11}H_9ON_2Cl$ (IId): C, 59.40; H, 4.16; N, 12.69. Found: C, 59.70; H, 4.08; N, 12.70.

5-Chloro-6-phenyl-4-pyrimidone (IIe)——Following the similar fashion as above, the reaction of 4-chloro-6-phenylpyrimidine (Ie) (0.95 g) with H_2O_2 (1.2 ml) in AcOH (8 ml) afforded 0.67 g. (65 %) of

7) A. Pinner, *Ber.*, **22**, 1616 (1889).

5–chloro–6–phenyl–4–pyrimidone (IIe), mp 235—237°, colorless prisms (MeCOEt). *Anal.* Calcd. for $C_{10}H_7ON_2Cl$ (IIe): C, 58.37; H, 3.40; N, 13.56. Found: C, 58.77; H, 3.62; N, 13.73.

4,5-Dichloro-6-phenylpyrimidine (V)——A mixture of 5–chloro–6–phenyl–4–pyrimidone (IIe) and $POCl_3$ (10 ml) was refluxed for 20 min. After evaporation *in vacuo*, the residue was poured into ice–water. The solution was neutralized with K_2CO_3, and extracted with ether. The ether soluble fraction was condensed to give a crystalline residue, which was dissolved in benzene and purified by alumina chromatography. Recrystallization from petroleum ether (bp 40°) afforded colorless prisms of mp 72—74°. *Anal.* Calcd. for $C_{10}H_6N_2Cl_2$ (V): C, 53.35; H, 2.66; N, 12.42. Found: C, 53.47; H, 3.05; N, 12.31.

2,6-Dimethyl-4-chloropyrimidine 1-Oxide (IVa)——To a solution of maleic anhydride (24 g) in $CHCl_3$ (80 ml) was added 30% H_2O_2 (3.4 g) with ice–cooling. After stirring for 2 hr, 2,6–dimethyl–4–chloropyrimidine (Ia) (1.43 g) was added. The reaction mixture was allowed to stand in a refregirator for five days free maleic acid precipitated was filtered off, and the filtrate was washed with 10% K_2CO_3 and dried over K_2CO_3, filtered, and condensed *in vacuo*. The residue was dissolved in petroleum ether (bp 40°) and purified by alumina chromatography. Recrystallization from petroleum ether gave colorless needles of mp 100—102°. Yield, 0.55 g (34%). *Anal.* Calcd. for $C_6H_7ON_2Cl$ (IVa): N, 17.26. Found: N, 17.67.

2-Ethyl-4-chloro-6-methylpyrimidine-1-Oxide (IVb)——Following the procedure given for IVa, the reaction of 2–ethyl–4–chloro–6–methylpyrimidine (Ib) with mono–permaleic acid prepared from maleic anhydride (24 g) and 30% H_2O_2 (3.4 g) afforded the N–Oxide (IVb), colorless needles of mp 76—78° (petroleum ether). Yield, 0.98 g (57%). *Anal.* Calcd. for $C_7H_9ON_2Cl$ (IVb): N, 16.22. Found: 16.16.

2-Isopropyl-4-chloro-6-methylpyrimidine 1-Oxide (IVc)——Employing the method given for the above run, the reaction of 2–isopropyl–4–chloro–6–methylpyrimidine (1.7 g) with mono–permaleic acid prepared from maleic anhydride (24 g) and 30% H_2O_2 (3.4 g) afforded 1.38 g (74 %) of IVc, colorless needles of mp 93.5—95° (petroleum ether). *Anal.* Calcd. for $C_8H_{11}ON_2Cl$ (IVc): C, 51.47; H, 5.89; N, 15.01: Found: C, 51.96; H, 6.36; N, 15.31:

2,6-Dimethyl-4-methoxypyrimidine 1-Oxide (VIIIa)——To a solution of 2,6–dimethyl–4–chloropyrimidine 1–Oxide (IVa), was added a MeONa–MeOH solution prepared from Na (0.07 g) and MeOH (3 ml). After refluxing for 10 min, the mixture was filtered. The filtrate was condensed. The resulting residue was purified by alumina chromatography using $CHCl_3$ as a solvent to give a crystalline solid. Recrystallization from benzene–petroleum ether gave colorless leaflets of mp 84—85°, whose IR spectrum was identical in every respect with that of an authentic specimin[5] of VIIIa.

2-Ethyl-4-methoxy-6-methylpyrimidine 1-Oxide (VIIIb)——2–Ethyl–4–chloro–6–methylpyrimidine 1–Oxide (0.23 g) was treated with NaOMe–MeOH (Na 0.036 g, MeOH 5 ml). Similar treatment as above gave colorless leaflets (benzene–petroleum ether), mp 61—63°, which was characterized as 2–ethyl–4–methoxy–6–methylpyrimidine 1–oxide (VIIIb) by the comparison of IR spectrum with an authentic sample.[5] Yield, 0.21 g (74%).