UDC 547.854.1

124. **Hiroshi Yamanaka**: Studies on 4-Alkoxy-6-methylpyrimidine N-Oxides.

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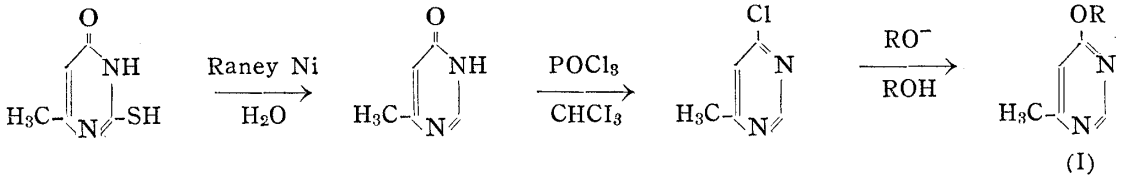
There is practically no example reported in literature for preparation of N-oxides from pyrimidine by direct oxidation of pyrimidine derivatives with hydrogen peroxide or organic peracid except the one of Ochiai, Ishikawa, and Sai[1] who, in 1945, obtained N-monoxide by reaction of 4-methylpyrimidine with monoperphthalic acid in ether. Therefore attempts were made to prepare N-oxide from pyrimidine derivatives and to elucidate the chemical properties of the N-oxides. A part of this work was briefly reported.[2] The present paper describes a few results on experiments with 4-alkoxy-6-methylpyrimidines (I).

It is known that, in general, oxidation of aromatic heterocyclic compounds of weak basicity, such as pyrazines and quinoxalines, is markedly affected by steric hindrance of a substituent attached to the carbon adjacent to nitrogen atom.[3] This is true in the case of pyrimidine and a substituent in 2-position greatly affects the reaction. (This point will be taken up in a separate paper.) This is reason for the choice of (I) as the sample in the present work.

(I) was prepared in the usual manner from 6-methyl-4-pyrimidinol[4] by the following route. Among the products, 4-butoxy- (Ic) and 4-benzyloxy-6-methylpyrimidine (Id) are new compounds.



(I)

Corresponding N-oxides were obtained by standing these pyrimidine derivatives with monoperphthalic acid in ether for 4~7 days at room temperature or reacting with 30% hydrogen peroxide in glacial acetic acid at 60~65° for 6~8 hours. In general, the yield was good and practically the same result was obtained from the use of peracid or hydrogen peroxide except in the case of 4-phenoxy-6-methylpyrimidine N-oxide (IIc), which was obtained in a slightly better yield by the use of peracid. This is probably due to the facile hydrolysis of the phenoxyl group in 4-position.

Reduction of the N-oxides (II) here obtained with phosphorus trichloride in chloroform or catalytically over Raney nickel in methanol,[5] which will be described in the following paper, results in facile regeneration of the original base (I) and this proves that the compounds (II) obtained were true N-oxides. Analytical values indicated them to be all N-monoxides. Several recrystallizations or chromatographic purification through alumina failed to produce two kinds of isomers and all melting points were distinct that it is obvious that they are a unity. However, no synthetic proof has been made as to which of the nitrogen atoms carries the oxygen although it is assumed that the nitrogen atom further from the alkoxyl group has been oxidized, as illustrated in Chart 1 because it has been

* Oshika, Shizuoka (山中 宏).

1) E. Ochiai, M. Ishikawa, Z. Sai: Yakugaku Zasshi, **65**, 14 (1945).
2) E. Ochiai, H. Yamanaka: This Bulletin, **3**, 175 (1955).
3) R. A. Baxter, *et al.*: J. Chem. Soc., **1947**, 1859.
4) Org. Syntheses, **35**, 80 (1955).
5) E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, **6**, 323 (1958).

proved that the N-oxide in analogous 4-alkoxyquinazoline N-oxide is present in 1-position,[6] and steric hindrance was found to exist in 4-substituted pyrimidine on N-oxidation.[3]

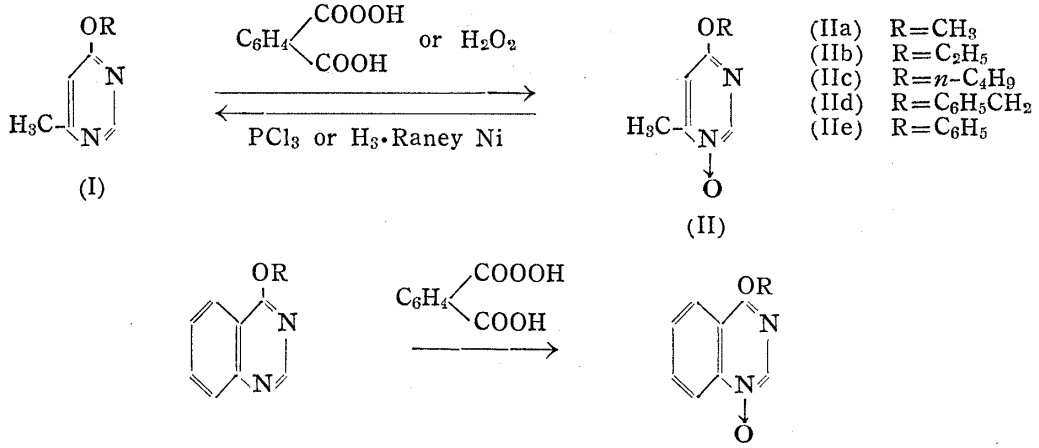


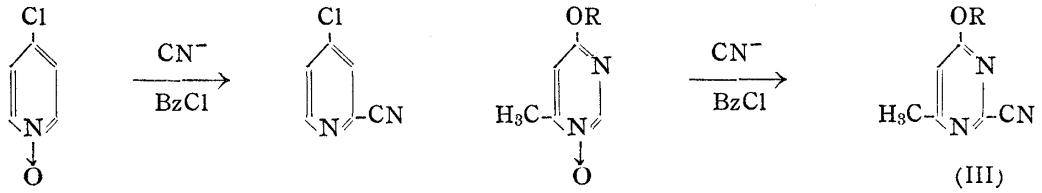
TABLE I.

	Original base (I)		N-Oxide (II)		
RO-	b.p.(°C/mm. Hg)	Picrate, m.p. (°C)	m.p. (°C)	Yield(%)	Appearance
CH_3O	166~168	117	135.5~136.5	72	White plates
C_2H_5O	182~183	101~104	120~121.2	76	White plates
C_4H_9O	90~95/7	96~97	82~83.5	77	White plates
$C_6H_5CH_2O$	140~141/4	142~144	98~99.5	70	White prisms
C_6H_5O	125~127/7	172~174	120~122	58	White prisms

Further examination of the reaction mother liquor or treatment of the N-oxide obtained with peracid failed to yield the anticipated N,N-dioxide and only ammonia, probably formed by decomposition of the ring, was detected.

The representative of anionoid substitution reaction in N-oxides of aromatic heterocyclic compounds is the Reissert reaction. Owing to the nature of this reagent, it is not possible to raise the reaction temperature and the reaction proceeds smoothly with bicyclic compounds like quinoline and isoquinoline N-oxides but in monocyclic compounds like N-oxides of pyridine derivative, the starting material is usually recovered due to insufficient activity in 2-position, the only successful example being the reaction of 4-chloropyridine 1-oxide.[7]

On the other hand, the 2-position in the monocyclic compound (II) is expected to be more active to anionoid substitution reaction by the addition of resonance effect of nitrogen atom in the ring and that of the N-oxide group. Actually, the Reissert reaction of (II) proceeded very smoothly and the corresponding 4-alkoxy-6-methylpyrimidine-2-carbonitrile (III) was obtained in a good yield. Melting points and yield of these nitriles are listed in Table II.



(IIIa) R=CH_3 (IIIb) R=C_2H_5
(IIIc) R=C_4H_9 (IIId) R=$C_6H_5CH_2$
(IIIe) R=C_6H_5

6) H. Yamanaka: This Bulletin, **7** (1959). To be published.
7) E. Ochiai, I. Nakayama: Yakugaku Zasshi, **65A**(9~10), 7 (1945).

TABLE II.

(III) RO-	Appearance	m.p. (°C)	Yield (%)
CH_3O	White needles	97～99	90
C_2H_5O	White long needles	59～61	85
C_4H_9O	Liquid	($b.p_5$ 127～128)	70
$C_6H_5CH_2O$	White prisms	66～68	77
C_6H_5O	White prisms	104～106	48

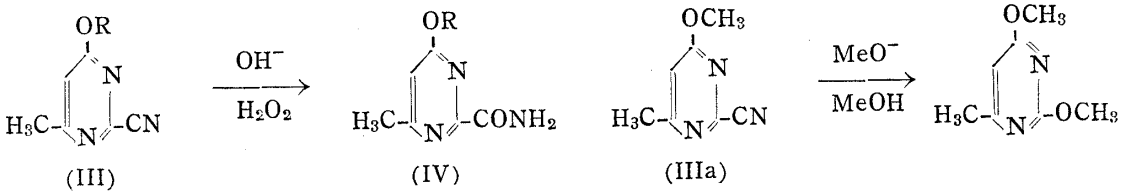
The nitrile so formed undergoes very facile hydrolysis to the corresponding acid amide (IV) on being treated with hydrogen peroxide and alkali carbonate in acetone. Because the reaction conditions are mild, the alkoxyl group in 4-position remains intact, even in the case of phenoxyl and benzyloxyl groups. Properties of these acid amides are summarized in Table III.

TABLE III.

(IV) RO-	Appearance	m.p. (°C)	Yield (%)
CH_3O	White needles	170～171	90
C_2H_5O	White prisms	122～123.5	85
C_4H_9O	White prisms	83～84	80
$C_6H_5CH_2O$	White prisms	83～85	72
C_6H_5O	White needles	150～152	69

A characteristic reaction of the nitrile in 2-position of these pyrimidines is its substitution with alkoxyl ion. For example, reaction of (IIIa) with sodium methoxide in methanol results in the introduction of methoxyl group in 2-position from which cyano group is liberated and 2,4-dimethoxy-6-methylpyrimidine is obtained in a good yield. This fact not only gives direct proof that a nitrile group had been introduced into the 2-position by Reissert reaction but suggests that this kind of nitrile behaves like a halogen atom in various anionoid substitution reactions.

The writer expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, Dr. T. Ukai, President of this College, and to Prof. E. Hayashi of this College, for unfailing guidance and encouragement during the course of this work. He is also indebted to Misses Y. Saito and N. Kamoto of this College for elemental analyses.



(III) (IV) (IIIa)

(IVa) R=CH_3 (IVb) R=C_2H_5
(IVc) R=C_4H_9 (IVd) R=$C_6H_5CH_2$
(IVe) R=C_6H_5

Experimental

Preparation of 4-Alkoxy-6-methylpyrimidines (I)—i) 4-Butoxy-6-methylpyrimidine (Ic): To a solution of 2.7 g. of metallic Na dissolved in 100 cc. of BuOH, 10 g. of 4-methyl-6-chloropyrimidine was added in small portions while cooling the outside of the vessel with running water because the reaction occurs suddenly with evolution of heat. After completion of addition, the mixture was warmed for 15 mins. on a boiling water bath and BuOH was removed as much as possible under a reduced pressure. Water was added to the residue and the mixture was extracted with benzene. After drying over anhyd. Na_2SO_4, benzene was evaporated and the residual oil was distilled under a reduced pressure, affording 12.1 g. (95%) of colorless, clear oil, $b.p_7$ 90～95°.

Picrate: m.p. 96～97° (from dil. MeOH). *Anal.* Calcd. for $C_9H_{14}ON_2 \cdot C_6H_3O_7N_3$ (4-Butoxy-6-methylpyrimidine picrate): N, 17.72. Found: N, 17.80.

(ii) 4-Benzyloxy-6-methylpyrimidine (IId): To a solution of 1.2 g. of metallic Na dissolved in 80 cc. of benzyl alcohol, 5.2 g. of 4-chloro-6-methylpyrimidine was added in small portions and the solution was refluxed for 30 mins. Benzyl alcohol was then evaporated as much as possible under a reduced

pressure, water was added to the residue, and this was extracted with benzene. The benzene residue was distilled under a reduced pressure to collect a fraction of $b.p_4$ 140~141°. Yield, 5.8 g. (72%).

Picrate: m.p. 142~144° (from benzene). *Anal.* Calcd. for $C_{12}H_{12}ON_2 \cdot C_6H_3O_7N_3$ (4-Benzyloxy-6-methylpyrimidine picrate): C, 50.35; H, 3.49; N, 16.32. Found: C, 50.31; H, 3.66; N, 15.97.

(iii) 4-Phenoxy-6-methylpyrimidine (IIe): To a solution of sodium ethoxide, prepared from 2.0 g. of metallic Na and 20 cc. of EtOH, 15 g. of phenol was added, the mixture was refluxed, and 9.0 g. of 4-chloro-6-methylpyrimidine was added. The mixture was refluxed for 30 mins., EtOH was evaporated under a reduced pressure, and water was added to the residue. The oil that separated out was taken up in benzene, the benzene layer was washed thoroughly with 10% NaOH, and dried over anhyd. Na_2SO_4. Treatment as in the procedure (i) afforded a fraction of $b.p_7$ 125~127°. Yield, 10 g. (77%).

Picrate: m.p. 172~174° (from benzene).

N-Oxidation of 4-Alkoxy-6-methylpyrimidine with Hydrogen Peroxide in Glacial Acetic Acid-General Procedure: The base was dissolved in 5~10 volumes of glacial AcOH, 1.5 times the calculated amount (as N-monoxide) of 30% H_2O_2 added, and the mixture was warmed on a water bath at 60~65° for 3 hrs. Further 0.5 time the calculated amount of 30% H_2O_2 was added and the mixture was warmed at the same temperature for 3 hrs. AcOH was distilled off under a reduced pressure, a small amount of water was added to the residue, and the solution was again distilled. The residue was thoroughly basified with excess of K_2CO_3, the mixture was washed once with a small volume of ether, and extracted several times with $CHCl_3$. The chloroform layer was dried over anhyd. Na_2SO_4, evaporated, and the residual oil crystallized on being cooled. The crystals were dissolved in $CHCl_3$, the solution passed through alumina layer to effect discoloration, and recrystallized from petr. ether-benzene mixture.

4-Methoxy-6-methylpryimidine N-oxide[2] (IIa), m.p. 135.5~136.5°; yield, 72%.

4-Ethoxy-6-methylprimidine N-oxide (IIb), m.p. 120~121°; yield, 76%. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.59; H, 6.54; N, 18.17, Found: C, 54.51; H, 6.54; N, 18.17.

4-Butoxy-6-methylpyrimidine N-oxide (IIc), m.p. 82~83.5°; yield, 77%. *Anal.* Calcd. for $C_9H_{14}O_2N_2$: C, 59.32; H, 7.74. Found: C, 59.22; H, 7.63.

4-Benzyloxy-6-methylpyrimidine N-oxide (IId), m.p. 98~99.5°; yield, 70%. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.73; H, 5.53; N, 12.95.

4-Phenoxy-6-methylpyrimidine N-oxide (IIe), m.p. 120~122°; yield, 46%. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.32; H, 4.98; N, 13.84.

N-Oxidation of 4-Alkoxy-6-methylpyrimidines (I) with Monoperphthalic Acid—(i) Preparation of ether solution of monoperphthalic acid: In accordance with the formula of Bohme,[8] this was prepared from 15 g. of phthalic anhydride and active oxygen was determined by iodometry before use. An average of 0.013 g. of active oxygen was found in each cc.

(ii) General procedure: The base was mixed with an equal amount of ether, the ether solution of the above monoperphthalic acid containing 1.5 times the calculated amount of active oxygen was added, and the mixture was allowed to stand in a cool, dark place. After 1~3 days, oily substance began to separate out and the oil crystallized after around one week. The ether layer was decanted, the crystals were decomposed with 10% K_2CO_3 solution, and salted out with excess of anhyd. K_2CO_3. The alkaline mixture was extracted several times with $CHCl_3$, the extract was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated. The residual oil underwent crystallization on being cooled and the crystals were recrystallized from petr. ether-benzene mixture. With the exception of (IIe), the yield was practically no different from that by H_2O_2-AcOH method.

(iii) 4-Phenoxy-6-methylpyrimidine N-oxide (IIe): Ether solution of monoperphthalic acid containing 1.5 times the calculated amount of active oxygen was added to a solution of 12 g. of (Ie) dissolved in 12 cc. of ether and the mixture was allowed to stand for one week in a cool, dark place. This was treated according to the general procedure and 7.5 g. (58%) of (IIe), m.p. 120~122°, was obtained, which showed no depression of m.p. on admixture with the corresponding sample obtained from H_2O_2-AcOH method. Admixture with the 4-ethoxy compound (IIb), m.p. 120~121°, melted at around 80°.

Reaction of 4-Benzyloxy-6-methylpyrimidine N-Oxide (IId) and Phosphorus Trichloride—A solution of 0.3 g. of (IId) dissolved in 1.5 cc of $CHCl_3$ was cooled in an ice bath and a solution of 0.3 cc. of PCl_3 dissolved in 1.5 cc. of $CHCl_3$ was added dropwise. After allowing the mixture to stand for 30 mins. at room temperature, it was refluxed for 30 mins., cracked ice was added to decompose the chlorides of P, and aqueous layer was separated. The aqueous solution was neutralized and salted out with excess of anhyd. K_2CO_3 and extracted with ether. The ether layer was dried over anhyd. K_2CO_3, the solvent was evaporated, and 0.1 g. of residual orange oil was purified as a picrate of m.p. 141~143°, undepressed on admixture with the picrate, m.p. 141~143°, of (Id).

Catalytic Reduction of 4-Ethoxy-6-methylpyrimidine N-Oxide (IIb) with Raney Nickel—A

8) Org. Syntheses, **20**, 70 (1940).

solution of 0.3 g. of (IIb) dissolved in 20 cc. of MeOH, with Raney Ni catalyst (prepared from 1.0 g. of Al-Ni alloy (1:1), was hydrogenated at atmospheric pressure and ordinary temperature. The reaction stopped after absorption of 43 cc. of H_2 (equiv. to 1 mole). The catalyst was filtered off and MeOH was evaporated from the filtrate, leaving 0.2 g. of an oily substance. It was purified as a picrate of m.p. 101~104°, undepressed on admixture with the picrate, m.p. 101~104°, of (Ib).

4-Alkoxy-6-methylpyrimidine-2-carbonitriles (III) : Reissert Reaction of N-Oxides (II)—(i) 4-Benzyloxy-6-methylpyrimidine-2-carbonitrile (IIId): To a solution of 2.0 g. of (IId) dissolved in 15 cc. of water, 1.1 g. of KCN was added and dissolved to make a uniform solution, and 20 g. of BzCl was added to it in small portions, with shaking. Exothermic reaction took place and orange oily substance separated out at first, which gradually solidified as the reaction progressed. After allowing the mixture to stand over night, the crystals were collected by filtration, dissolved in ether, and the ether solution was washed thoroughly with 10% NaOH. After drying over anhyd. K_2CO_3, ether was evaporated and the orange yellow oily residue crystallized on being stimulated. Recrystallization from petr. ether afforded 1.6 g. (77%) of white prisms, m.p. 66~68°. *Anal.* Calcd. for $C_{13}H_{11}ON_3$ (4-Benzyloxy-6-methylpyrimidine-2-carbonitrile): C, 69.32; H, 4.92; N, 18.66. Found: C, 69.25; H, 4.91; N, 18.56.

(ii) 4-Phenoxy-6-methylpyrimidine-2-carbonitrile (IIIe): To a solution of 2.0 g. of (IIe) and 0.8 g. of KCN dissolved in 25 cc. of water, 1.5 g. of BzCl was added and the reaction mixture was treated as in (i). The crude crystals obtained therefrom were purified by passage through alumina layer as benzene solution and recrystallized from petr. ether-benzene mixture to white prisms, m.p. 104~106°. Yield, 1.0 g. (48%). *Anal.* Calcd. for $C_{12}H_9ON_3$ (4-Phenoxy-6-methylpyrimidine-2-carbonitrile): C, 68.23; H, 4.30; N, 19.90. Found: C, 68.38; H, 4.29; N, 20.18.

(iii) 4-Butoxy-6-methylpyrimidine-2-carbonitrile (IIIc): Treatment of 1.8 g. of (IIc), 1.0 g. of KCN, 1.6 g. of BzCl, and 15 cc. of water, in a manner similar to those described under (i) afforded a crude oil, which was purified by low-pressure distillation. Liquid, $b.p_5$ 127~128°; yield, 1.5 g. (70%). This compound (IIIc) is the only one among this series to be in liquid state at room temperature.

(iv) 4-Ethoxy-6-methylpyrimidine-2-carbonitrile (IIIb): Treatment of 1.3 g. of (IIb), 0.7 g. of KCN, 1.3 g. of BzCl, and 20 cc. of water in exactly the same manner as for (i) and recrystallization of the substance formed afforded 1.3 g. (85%) of long silky needles, m.p. 59~61°. *Anal.* Calcd. for $C_8H_9ON_3$ (4-Ethoxy-6-methylpyrimidine-2-carbonitrile): C, 58.88; H, 5.56; N, 25.75. Found: C, 58.86; H, 5.58; N, 25.83.

4-Alkoxy-6-methylpyrimidine-2-carbonamides (IV) : Hydrolysis of (III)—(i) 4-Ethoxy-6-methylpyrimidine-2-carbonamide (IVb): To a mixture of 0.32 g. of (IIIb) in 0.6 cc. of 10% Na_2CO_3 solution, acetone was dropped in until (IIIb) went into uniform solution and 5 cc. of 10% H_2O_2 was added dropwise, by which the reaction occurred with effervescence and evolution of heat. The mixture was allowed to stand for 3 hrs., acetone and water were distilled off under a reduced pressure, and the residue was extracted with $CHCl_3$. The crystalline residue obtained on evaporation of $CHCl_3$ was recrystallized from benzene to white prisms, m.p. 122~123.5°. Yield, 0.3 g. (85%). *Anal.* Calcd. for $C_8H_{11}O_2N_3$ (4-Ethoxy-6-methylpyrimidine-2-carbonamide): C, 53.03; H, 6.12; N, 23.19. Found: C, 52.99; H, 6.20; N, 23.24.

(ii) 4-Butoxy-6-methylpyrimidine-2-carbonamide (IVc): Treatment of 0.57 g. of (IIIc), 0.7 cc. of 10% Na_2CO_3, 6 cc. of 10% H_2O_2, and acetone by the same method as above and recrystallization from petr. ether-benzene mixture afforded 0.5 g. (80%) of white prisms, m.p. 83~84°. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$ (4-Butoxy-6-methylpyrimidine-2-carbonamide): C, 57.40; H, 7.33; N, 20.08. Found: C, 57.74; H, 7.18; N, 20.06.

(iii) 4-Benzyloxy-6-methylpyrimidine-2-carbonamide (IVd): The same treatment of 0.45 g. of (IIId) as above and evaporation of acetone left crystals. Recrystallization from dil. MeOH afforded 0.35 g. (72%) of white prisms, m.p. 83~85°. *Anal.* Calcd. for $C_{13}H_{13}O_2N_3 \cdot {}^1/_2H_2O$ (4-Benzyloxy-6-methylpyrimidine-2-carbonamide): C, 61.90; H, 5.16; N, 16.67. Found: C, 61.96; H, 5.63; N, 17.03.

(iv) 4-Phenoxy-6-methylpyrimidine-2-carbonamide (IVe): Reaction of 0.4 g. of (IIIe) same as above and recrystallization from dil. MeOH afforded 0.3 g. (69%) of long white needles, m.p. 150~152°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$ (4-Phenoxy-6-methylpyrimidine-2-carbonamide): C, 62.87; H, 4.84; N, 18.33. Found: C, 62.77; H. 4.89; N, 18.59.

Reaction of 4-Methoxy-6-methylpyrimidine-2-carbonitrile (IIIa) and Methoxide Ion—To a solution of 0.05 g. of metallic Na dissolved in 10 cc. of MeOH, 0.3 g. of (IIIa) was added and the mixture was refluxed on a water bath for 1 hr. MeOH was then distilled off, water was added to the residue, and the oily substance that precipitated out was taken up in ether. After drying, ether was evaporated and 0.25 g. of low-melting white needle crystals were recrystallized from petr. ether to crystals of m.p. 67~68°, undepressed on admixture with 2,4-dimethoxy-6-methylpyrimidine.

The aqueous solution was acidified with HNO_3 and addition of 5% $AgNO_3$ produced voluminous white precipitate of cyanide ion.

Summary

Several 4-alkoxy-6-methylpyrimidines were prepared and they were derived to N-oxides by the application of hydrogen peroxide in glacial acetic acid solution or monoperphthalic acid in ether. These were all N-monoxides and were derived to corresponding 4-alkoxy-6-methylpyrimidine-2-carbonitrile by the Reissert reaction. The nitriles so obtained were converted to the corresponding acid amides by treatment with alkaline hydrogen peroxide. Treatment of 4-methoxy-6-methylpyrimidine-2-carbonitrile with sodium methoxide afforded 2,4-dimethoxy-6-methylpyrimidine, confirming the position of cyano group.

(Received May 15, 1958)

UDC 547.853.4

125. Hiroshi Yamanaka: On the Reactivity of 2,6-Dimethylpyrimidine-4-carbonitrile.

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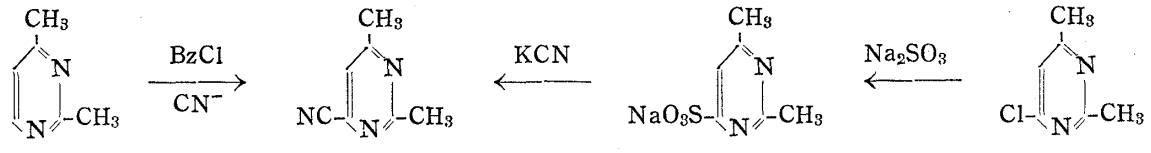
Examples of pyrimidine derivatives possessing cyano group bonded directly to the 2- or 4-position in the ring are almost nonexistent in past literature and their chemical properties are consequently unknown. Some time ago, Ochiai and Yamanaka[1] reported a synthetic process for that kind of pyrimidine derivatives by the application of Reissert reaction to pyrimidine N-oxide, or the derivation of corresponding chloro derivative to sulfonic acid by reaction with sodium sulfite and dry distillation of this acid with potassium cyanide. For example, treatment of 2,4-dimethylpyrimidine N-oxide with potassium cyanide and benzoyl chloride affords 2,6-dimethylpyrimidine-4-carbonitrile (I), though in a low yield. (I) is also obtained by dry distillation (at around 300°), under a reduced pressure, of potassium cyanide and sodium 2,6-dimethylpyrimidine-4-sulfonate, formed on refluxing 2,6-dimethyl-4-chloropyrimidine with sodium sulfite in water.

In the present series of experiments, various chemical reactions of (I) were carried out in order to elucidate the chemical nature of the cyano group at 4-position in the pyrimidine ring.

Reaction of (I) with methylmagnesium iodide in dehyd. ether, by the usual process, affords 4-acetyl-2,6-dimethylpyrimidine, m.p. 31~33° (phenylhydrazone, m.p. 106°), in 40% yield, and the effect of ring nitrogen is not so marked.



Passage of dry hydrogen gas through dehyd. ethanol solution of (I) results in immediate precipitation of a crystalline mass of a substance assumed to be imido-ester hydrochloride. Its hydrolysis with potassium carbonate solution and ether extraction, followed by low-pressure distillation of the product, gives ethyl 2,6-dimethylpyrimidine-4-carboxylate (II), m.p 35~36°, in 74% yield. Application of 80% hydrazine hydrate to (II) in ethanol affords 2,6-

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1) E. Ochiai, H. Yamanaka: This Bulletin, **3**, 175 (1955).