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.

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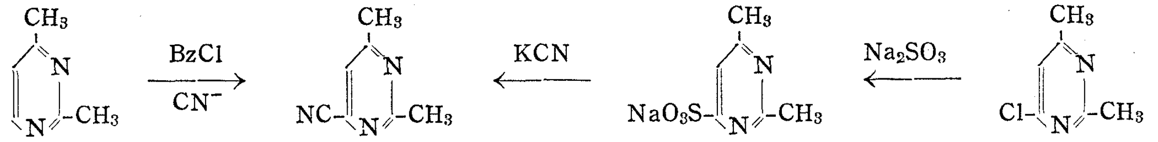
125. **Hiroshi Yamanaka**: On the Reactivity of 2,6-Dimethylpyrimidine-4-carbonitrile.

(*Shizuoka College of Pharmacy**)

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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* Oshika, Shizuoka (山中 宏).

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

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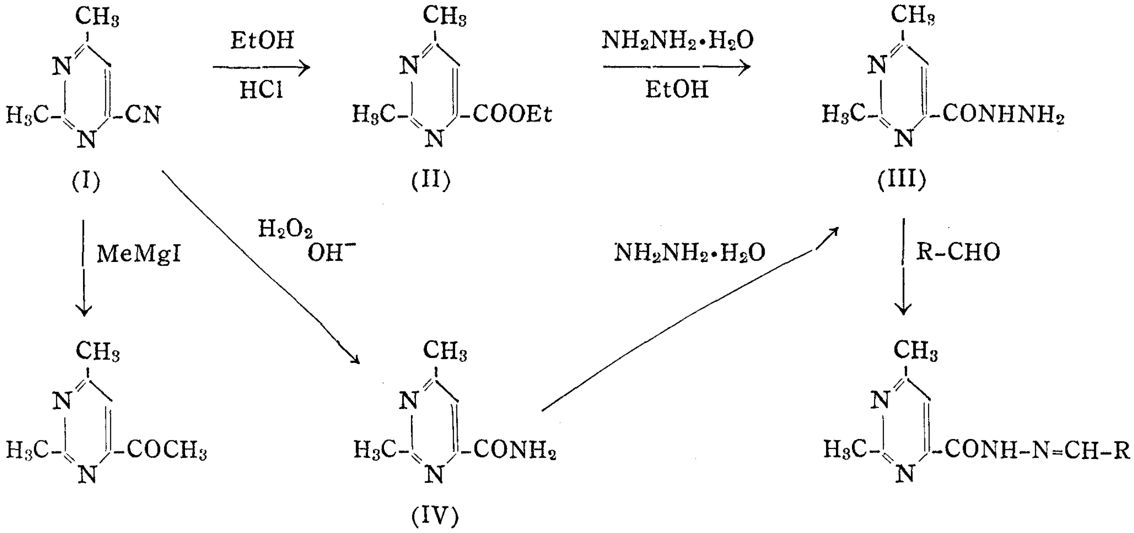
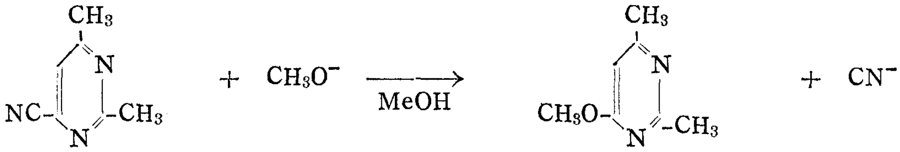
dimethylpyrimidine-4-carboxylic acid hydrazide (III), m.p. 143~144°, in 87% yield. Condensation of (III) with some aldehydes affords the corresponding hydrazones; that of m.p. 167~167.5° in 82% yield from benzaldehyde, that of m.p. 204~205° in 72% yield from 2,4-methylenedioxybenzaldehyde, and that of m.p. 152~154° in 59% yield from glucuronolactone.

Hydrolysis of (I) according to the method of Radziszewski[2] by the addition of dil. hydrogen peroxide solution and sodium hydrogen carbonate solution in acetone effects facile hydrolysis to the acid amide and 2,6-dimethylpyrimidine-4-carbonamide (IV), m.p. 184~185°, is obtained in almost quantitative yield. (IV) is converted to (III) in a good yield on treatment of (IV) with 40% hydrazine hydrate at 80°, with liberation of ammonia. It is considered that this procedure is better in both yield and procedural technique for the preparation of (III) rather than going through the ester.



As shown above, the cyano group in 4-position of the pyrimidine ring behaves generally like the nitrile, such as the one in 2-position of quinoline, but it also shows rather unexpected characteristic of undergoing facile anionoid substitution, which is without example in aromatic heterocyclic compounds. For instance, refluxing of (I) in methanol with sodium methoxide results in substitution of the cyano group with methoxyl to form 2,6-dimethyl-4-methoxypyrimidine (picrate, m.p. 121~122°).



This is considered to be due largely to the overlapping of resonance effect of the two nitrogen atoms in the pyrimidine ring and the phenomenon is characteristic of cyano group in 2- and 4-positions of pyrimidine.

The writer expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, to Dr. Ukai, the Dean of this College, and to Prof. E. Hayashi of this College for their kind guidance and encouragement throughout the course of this work. He is deeply indebted to Miss Y. Saito for elemental analyses.

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2) B. Radziszewski: Ber., **17**, 1289 (1884).

Experimental

Preparation of 4-Acetyl-2,6-dimethylpyrimidine—To a solution of 0.53 g. of 2,6-dimethylpyrimidine-4-carbonitrile (I) dissolved in 20 cc. of ether, a Gringnard reagent, prepared from 0.2 g. of metallic Mg, 1.0 g. of MeI, and 20 cc. of dehyd. ether, was added dropwise under stirring and yellow powder began to separate out immediately. The mixture was refluxd for 2 hrs., allowed to cool to room temperature, and excess of the Grignard reagent was decomposed with cracked ice. The mixture was acidified with 10% HCl, the aqueous layer was separated, and warmed on a water bath at 70~80° for 30 mins. This was thoroughly basified with K_2CO_3 and extracted with ether. After drying over anhyd. K_2CO_3, ether was evaporated and 0.4 g. of orange yellow, oily residue was either submitted to low-pressure distillation to collect the fraction of b.p$_{20}$ 100~110° or dissolved in benzene and passed through alumina layer. Needles, m.p. 31~33°. Yield, 0.25 g. (41%). *Anal.* Calcd. for $C_8H_{10}ON_2$ (4-Acetyl-2,6-dimethylpyrimidine): C, 63.98; H, 6.71; N, 18.65. Found: C, 63.94; H, 6.68, N, 17.66. Phenylhydrazone: m.p. 106° (from dil. EtOH).

Preparation of Ethyl 2,6-Dimethylpyrimidine-4-carboxylate (II)—Dry HCl gas was bubbled through a solution of 1.0 g. of (I) dissolved in 8 cc. of dehyd. EtOH under ice cooling, until saturation. Crystals began to separate out as soon as HCl gas was introduced. The mixture was allowed to stand at room temperature over night, basified with 10% K_2CO_3 solution, and again allowed to stand for 2 hrs. at room temperature. This mixture was further salted out by addition of solid K_2CO_3 and extracted with ether. After drying over anhyd. K_2CO_3, ether was evaporated and 1.4 g. of oily residue was distilled under a low pressure to collect the fraction of b.p$_5$ 140~150° (bath temp.). The fraction solidified to give 1.0 g. (74%) of crystals melting at 35~36°.

2,6-Dimethylpyrimidine-4-carbohydrazide (III)—A mixture of 1.0 g. of (II) dissolved in 10 cc. of EtOH and added with 0.45 g. of 80% hydrazine hydrate was allowed to stand at a room temperature by which needle crystals began to separate out after 1~2 hrs. and the whole gradually solidified. Crystals were collected by filtration, washed with EtOH, and recrystallized from EtOH to 0.8 g. (87%) of colorless columnar crystals, m.p. 143~144°. *Anal.* Calcd. for $C_7H_{10}ON_4$ (III): C, 50.59; H, 6.07; N, 33.72. Found: C, 50.88; H, 5.75; N, 33.88.

Condensation of (III) and Various Aldehydes—(i) Condensation with Benzaldehyde: A mixture of 0.4 g. of (III) and 0.4 g. of benzaldehyde in 10 cc. of EtOH was refluxed for 1 hr., allowed to cool to room temperature, and microneedle crystals began to separate out on scratching the wall of the vessel. The whole mixture solidified and recrystallization from a large amount of EtOH afforded 0.5 g. (82%) of needles, m.p. 167~167.5°.

(ii) Condensation with 3,4-Methylenedioxybenzaldehyde: A mixture of 0.5 g. of (III) and 0.5 g. of 3,4-methylenedioxybenzaldehyde in 10 cc. of EtOH was treated as in (i) and recrystallization of the product from EtOH afforded 0.65 g. (72%) of pale yellow needles, m.p. 204~205°. *Anal.* Calcd. for $C_{15}H_{14}O_3N_4$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.19; H, 5.02; N, 18.50.

(iii) Condensation with Glucuronolactone: A mixture of 0.25 g. of (III) and 0.3 g. of glucuronolactone in 7 cc. of EtOH was refluxed on a water bath for 2 hrs., EtOH was evaporated, and the translucent, syrupy residue underwent crystallization. Recrystallization from benzene-EtOH mixture afforded 0.3 g. (59%) of white needles, m.p. 152~154°. *Anal.* Calcd. for $C_{13}H_{16}O_6N_4 \cdot H_2O$: C, 45.61; H, 5.30; N, 17.17. Found: C, 45.53; H, 5.77; N, 16.37.

2,6-Dimethylpyrimidine-4-carbonamide (IV)—To a suspension of 0.27 g. of (I) in 2 cc. of 10% H_2O_2, 4 cc. of acetone was added to bring it into uniform solution and a few drops of saturated $NaHCO_3$ solution was added to it, by which exothermic reaction occurred with effervescence and crystals began to separate out after about 2 hrs. Acetone and water were evaporated under a reduced pressure, the residue was extracted with $CHCl_3$, and $CHCl_3$ was distilled off from the extract, leaving 0.25 g. (82%) of white prisms, m.p. 183~185°. This almost pure product was recrystallized from acetone and melted at 184.5~185°. *Anal.* Calcd. for $C_7H_9ON_3$ (IV): C, 55.61; H, 6.00; N, 27.80. Found: C, 55.54; H, 6.03; N, 27.84.

Reaction of (IV) with Hydrazine—A mixture of 0.20 g. of (IV) and 0.4 g. of 40% hydrazine hydrate was warmed on a boiling water bath for 2 hrs., by which crystals of (IV) began to dissolve gradually with evolution of NH_3. The reaction mixture was allowed to cool to room temperature and stimulation of the vessel wall resulted in crystallization. The crystals were dried on a porcelain plate and recrystallized from EtOH to white columnar crystals, m.p. 143~144°, undepressed on admixture with (III) obtained through the ester. Yield, 0.18 g. (82%).

Reaction of (I) and Sodium Methoxide—To a solution of 0.14 g. of metallic Na dissolved in 3 cc. of MeOH, 0.4 g. of (I) was added and the mixture was refluxed on a water bath for 2 hrs. MeOH was evaporated from the mixture, 2 cc. of water was added to the residue, and this was extracted with ether. After drying over anhyd. K_2CO_3, ether was evaporated and 0.15 g. of oily residue was obtained. This was derived to its picrate in ether and the picrate was recrystallized from MeOH to orange prisms, m.p. 121~122°, undepressed on admixture with 2,6-dimethyl-4-methoxypyrimidine picrate, m.p. 121~122°.

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The aqueous solution left after extraction of ether was acidified with HNO_3 and a few drops of 5% $AgNO_3$ solution was added by which white precipitate of silver cyanide formed.

Summary

Reactivity of cyano group in 4-position of 2, 6-dimethylpyrimidine-4-carbonitrile was examined. This compound behaves like ordinary nitriles in forming 4-acetyl compound with methylmagnesium bromide, 4-carboxylic acid ester with dehydrated alcohol and hydrogen chloride, and 4-acid amide with alkaline hydrogen peroxide. However, it showed specificity in undergoing substitution with methoxyl ion to form 4-methoxy compound. The ester or acid amide obtained by such reaction was reacted with hydrazine hydrate to afford 2,6-dimethylpyrimidine-4-carbohydrazide. Condensation with few other aldehydes was also carried out.

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126. **Tsukasa Kuraishi**: 4,5-Substituted Pyridazines. VII.[1]
Synthesis and Acylation of 3,4-Dichloro-5-aminopyridazine.

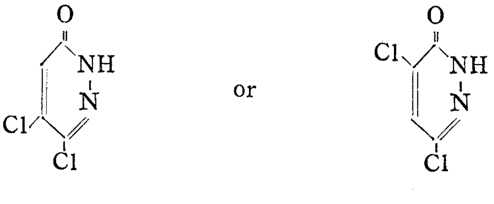
(*Pharmaceutical Faculty, University of Nagasaki**)

Previously, the author reported the preparation of two isomers of monoaminodichloropyridazines having m.p. 151° and 178°.[2]

Although they were led to 4-aminopyridazine by catalytic reduction, the structure of 4- or 5-amino-dichloropyridazine (VII and VIII) had not been established.

This paper is to report the synthesis of 3,4-dichloro-5-aminopyridazine (VIII) prepared by another route in connection with the structure of major product obtained from 3,4,6-trichloropyridazine (I) by heating with glacial acetic acid.[3]

In Part II of this series, preparation of 5,6- or 4,6-dichloro-3-pyridazinol (3,4- or 3,5-dichloro-6-pyridazone) (III) having m.p. 203~204° from the reaction of (I) with glacial acetic acid was described.



Replacement of the chlorine in 4- or 5-position of this compound (III) with an amino group yielded a product (IV) of m.p. 278~280°, which gave 3,6-dichloro-4-aminopyridazine (II) by chlorination with phosphoryl chloride in a sealed tube. Furthermore, catalytic reduction of (IV) presents a convenient method for preparing 5-amino-3-pyridazinol (V).[4] Accordingly, the structures of (III) and (IV) were confirmed as 5,6-dichloro-3-pyridazinol and 5-amino-6-chloro-3-pyridazinol, respectively.

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* Schowa-machi, Nagasaki (倉石 典).

[1] Part VI: This Bulletin, **6**, 551 (1958).

[2] Part I: *Ibid.*, **4**, 497 (1956).

[3] Part II: *Ibid.*, **5**, 376 (1957).

[4] Part V: *Ibid.*, **6**, 331 (1958).

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