iii) Reaction with Piperidine : A mixture of 1.0 g. of (IV) and 1.6 g. of piperidine was refluxed for 3 hr., excess of piperidine was distilled off under a reduced pressure, and the residue was dissolved in benzene. This solution was washed with 10% NaOH solution, dried over Na_2SO_4, and benzene was evaporated. The residue was distilled under a reduced pressure and 0.6 g. (63%) of a liquid of b.p_3 170~178° was obtained. Its picrate of m.p. 171~172° showed no depression in m.p. on admixture with the picrate of 4-piperidino-6-methylpyrimidine.

iv) Reaction with Morpholine : A mixture of 1.1 g. of (IV) and 1.6 g. of morpholine was refluxed for 2 hr. and the reaction mixture was treated as above. Low-pressure distillation of the oily product thereby obtained afforded 0.8 g. of a liquid, b.p_{30} 160~173°. This could not be separated into definite substances by redistillation and the whole was therefore derived to the picrate. Recrystallization from MeOH afforded 1.4 g. (58%) of a picrate of m.p. 168°, undepressed by admixture with the picrate of 4-morpholino-6-methylpyrimidine (XIII).

Concentration of the recrystallization mother liquor gave 0.5 g. (20%) of a picrate melting at 172~174°, identical with the picrate of (IV).

v) Reaction with Aniline : A mixture of 1 g. of (IV) and 3 g. of aniline was refluxed for 2 hr. Low-pressure distillation of the oily product thereby obtained gave 0.7 g. of the recovered (IV), b.p_{30} 165~175°, forming a picrate of m.p. 172~174°.

vi) Reaction with Cyclohexylamine : A mixture of 1 g. of (IV) and 3 g. of cyclohexylamine was refluxed for 2 hr. and 0.75 g. of the starting material, b.p_{30} 165~173°, was recovered by low-pressure distillation. The product formed a picrate of m.p. 172~174°.

Summary

Reaction of anionoid reagents with 2-phenoxy-6-methylpyrimidine (IV) and its N-oxide (III) was carried out to examine the reactivity of the phenoxyl in 4-position. It was found that there is no great difference in the reactivity of the phenoxyl group between (III) and (IV) but the phenoxyl in these compounds were substituted more easily than that in 4-phenoxypyridine. During the course of this reaction, 4-phenylthio- (VII), 4-piperidino- (VIII), and 4-morpholino-6-methylpyrimidine 1-oxide (IX), which cannot be prepared by the direct N-oxide formation reaction of the corresponding tertiary bases, were obtained.

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94. Hiroshi Yamanaka* : Reaction of 2-Cyanopyrimidine Derivatives with Nucleophilic Reagents.

(*Shizuoka College of Pharmacy*)

As reported earlier, the structure of 4-alkoxy-6-methylpyrimidine-2-carbonitrile, prepared by the Reissert reaction of 4-alkoxy-6-methylpyrimidine 1-oxide, was determined through treatment of the nitrile with sodium alkoxide to derive it to 2,4-dialkoxy-6-methylpyrimidine and its admixture with an authentic specimen prepared by another route.[1] Such properties of the nitrile group in 2-position of the pyrimidine ring was discovered on treatment of 4-hydroxy-6-methylpyrimidine-2-carboxamide[2] (I) with phosphoryl chloride. In this case, (I) and phosphoryl chloride were reacted at 90°, the reaction product obtained after conventional treatment was purified by chromatography through alumina, and 4-chloro-6-methylpyrimidine-2-carbonitrile (II) and 4-chloro-6-methylpyrimidine-2-carboxamide (III) were obtained. The structure of (II) and (III) was evidenced by their

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1) H. Yamanaka : This Bulletin, **6**, 633(1958).

2) *Idem* : *Ibid.*, **7**, 158(1959).

elemental analytical values but in order to ascertain further, (II) was treated with sodium methoxide in methanol. Unexpectedly, however, the product thereby obtained was not 4-methoxy-6-methylpyrimidine-2-carbonitrile (IV), m.p. 97~99°, but 2,4-dimethoxy-6-methylpyrimidine (V), m.p. 66~68°. It was further found that (IV) could be obtained by carrying out the reaction by gradual addition of 1 mole of sodium methoxide. These facts indicated that the cyano group in 2-position of the pyrimidine ring possesses a fair amount of nucleophilic activity, though smaller than that of the chlorine in 4-position.

Since the example of cyano group with such reactivity in other aromatic heterocyclic compounds is limited to the report on 2,5-dimethyl-3,6-dicyanopyrazine[3] (VI), various reactions were carried out on pyrimidine derivatives possessing a cyano group in 2- or 4-position as a means of elucidating the nature of the cyano group.

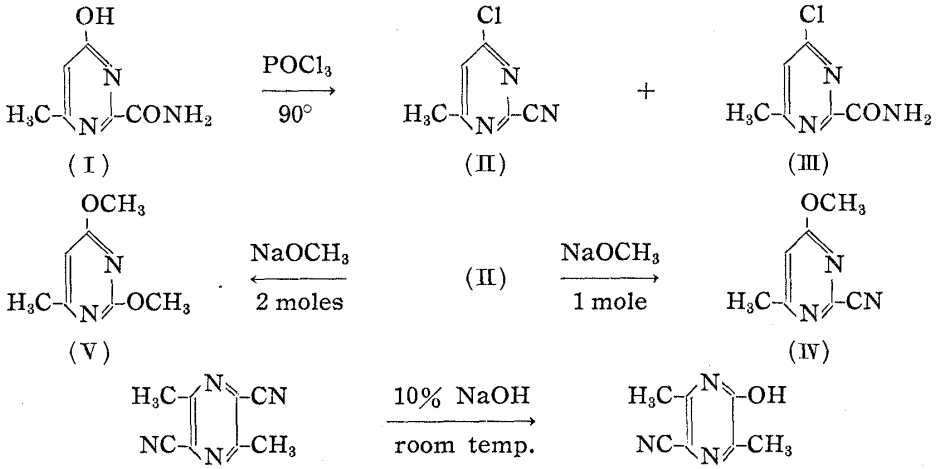


Chart 1.

I. Reaction of Primary Alkoxide Ion

The cyano group in 2- or 4-position of the pyrimidine ring is quite easily substituted with a primary alkoxide ion by reaction at the boiling point of the corresponding alcohols and alkoxylated derivatives are obtained in a good yield. In the case of 2,6-dimethylpyrimidine-4-carbonitrile (XIII), however, 2,6-dimethylpyrimidine-4-carboxamide (XV) was formed as a by-product besides 2,6-dimethyl-4-methoxypyrimidine (XIV) by reaction with sodium methoxide.

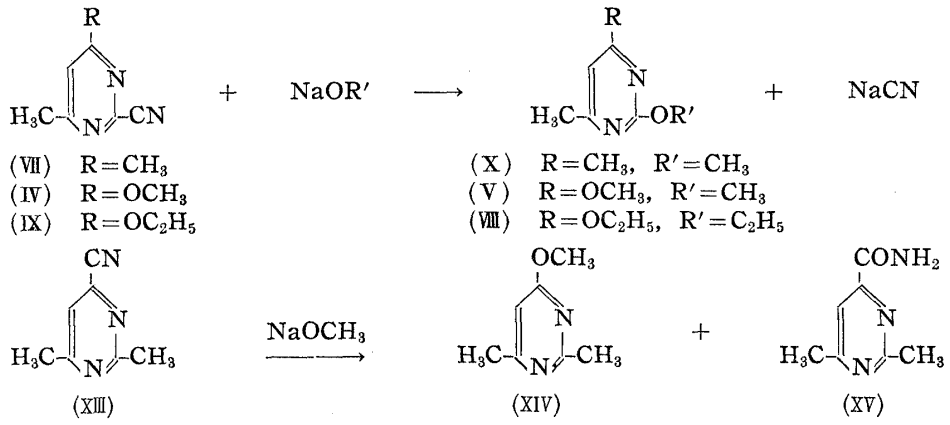


Chart 2.

II. Comparison of the Reactivity of Primary, Secondary, and Tertiary Alkoxide Ions

In order to make comparative examination of the reactivity of alkoxide ions in transiting from primary to secondary or tertiary alkyls, reaction of normal, secondary,

3) E. Golombok, F.S. Spring: J. Chem. Soc., **1949**, 1364.

and tertiary butoxide with 4-butoxy-6-methylpyrimidine-2-carbonitrile (XVI) in corresponding alcohols was carried out at the boiling temperature of respective alcohols. In the case of normal butoxide ion, the reaction was the same as in the foregoing experiments and only 2,4-dibutoxy-6-methylpyrimidine (XVII) was formed in 90% yield. In the case of secondary butoxide, the yield or 2,4-di-*sec*-butoxy-6-methylpyrimidine (XVIII) decreased to 60% and 4-*sec*-butoxy-6-methylpyrimidine-2-carboxamide (XIX) was formed in 24% yield as a by-product. In the case of tertiary butoxide, the majority of the reactant underwent resinification and the total yield became lower, 40% of 2,4-dibutoxy-6-methylpyrimidine (XX) and 15% of 4-butoxy-6-methylpyrimidine-2-carboxamide (XXI) being formed. These facts have shown that the reactivity of the alkoxide ion in this reaction decreases in the order of primary, secondary, and tertiary alkyls.

The structure of (XVIII) was identified with an authentic sample prepared from 2,4-dichloro-6-methylpyrimidine (XXII) and that of (XIX) by its elementary analytical values and non-agreement with 4-butoxy-6-methylpyrimidine-2-carbonitrile. Both (XX) and (XXI) are considered to be a mixture of isomers arising from the butoxyl in 4-position but isolation of isomeric components has not succeeded. The foregoing results indicate that the substitution reaction of 2-cyano group is accompanied by concurrent exchange of alkoxyl group in the 4-position. Reaction of (XVI) with a methoxyl ion affords 2,4-dimethoxy-6-methylpyrimidine (V) and 2-methoxy-4-butoxy-6-methylpyrimidine (XXIII).

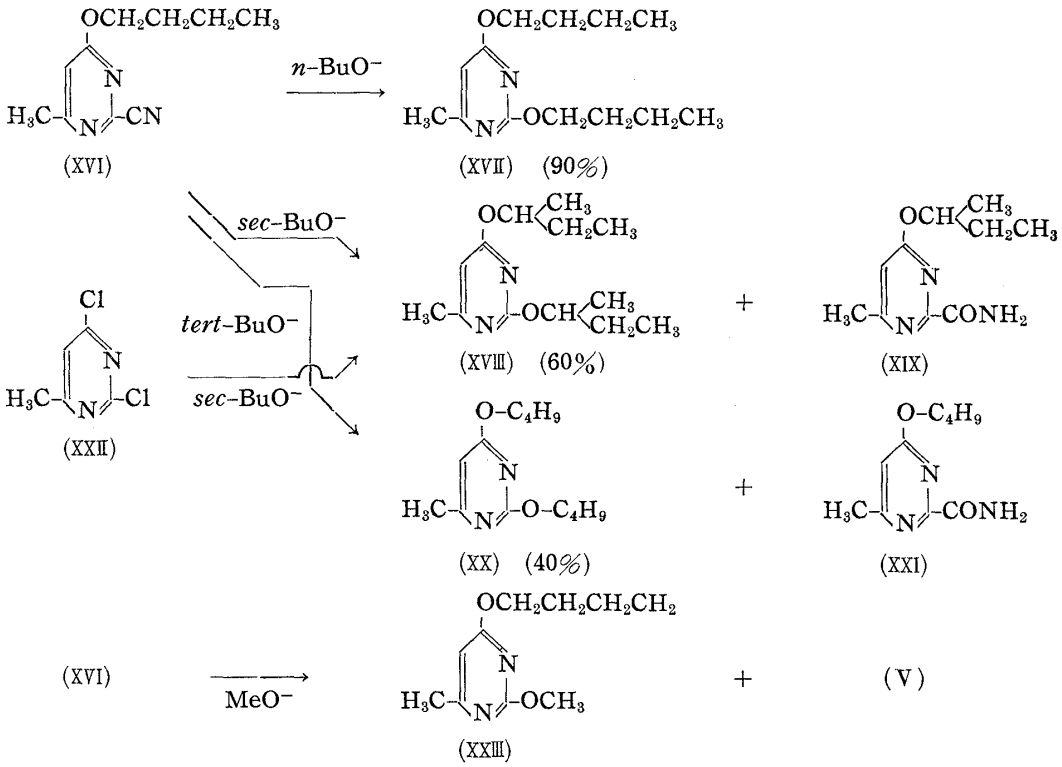
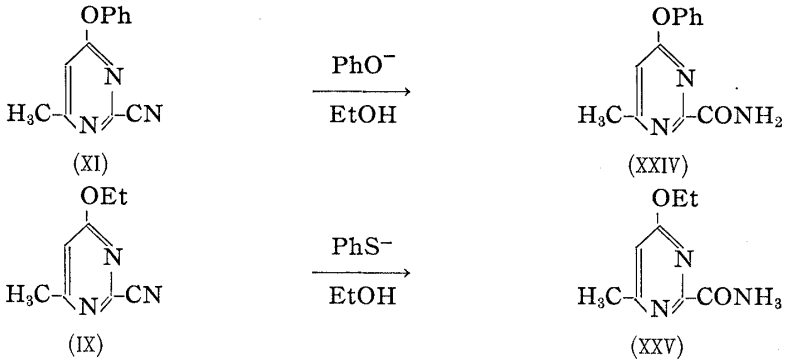


Chart 3.

III. Reaction with Other Anionoid Reagents

In contrast to the comparatively smooth progress of a substitution of alkoxide ion with the cyano group at 2-position in the pyrimidines, reaction with phenoxide or thiophenoxide ion in ethanol, at the boiling point of the alcohol, failed to effect substitution of the cyano group and acid amide was formed in almost quantitative yield. Application of acid chloride to (IV) ended in recovery of the starting material.

In these reactions, formation of (XXIV) and (XXV) would seem to be the result of hydrolysis due to unwarranted inclusion of water in the reaction system but, since the yield



of (XXIV) and (XXV) is almost quantitative and the presence of cyano ion or 2-ethoxy compound was not proved in the reaction system, hydrolysis does not seem to be possible.

IV. Assumption of Reaction Mechanism

The reactions described in the foregoing I to III can be classified roughly into (i) exchange of cyano with alkoxyl group and (ii) decomposition of the cyano group into carboxamide.

(i) The carbon atoms in the 2- and 4-positions of pyrimidine ring have small electron density due to overlapping of the resonance effect of the two ring-nitrogen atoms. Such tendency is further enhanced by the bonding of a radical like cyano with strong electron-attraction. Consequently, this position is liable to anionoid attack and, as shown in Chart 4, the substituted compound (a-2) is formed via the intermediate complex of (a-1) type, similar to the sequence proposed by Bunnett[4] for the reaction of 2,4-dinitro-1-chlorobenzene with methoxide ion.

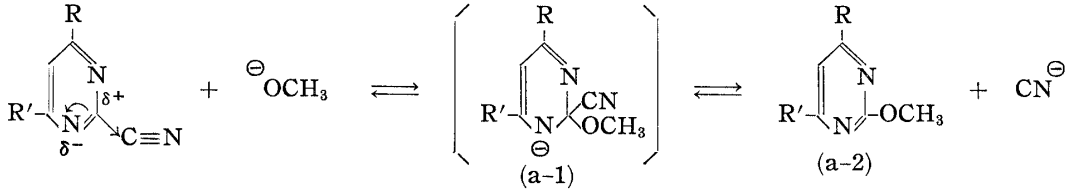


Chart 4.

(ii) In the reaction with phenoxide or thiophenoxide ion, this ion is assumed to attack the triple bond between carbon and nitrogen in the cyano group rather than the ring-carbon atom to which the cyano group is attached.*1 As a result, as shown in Chart 5, the sequence of reactions results in the formation of (b-1) which, via (b-2),

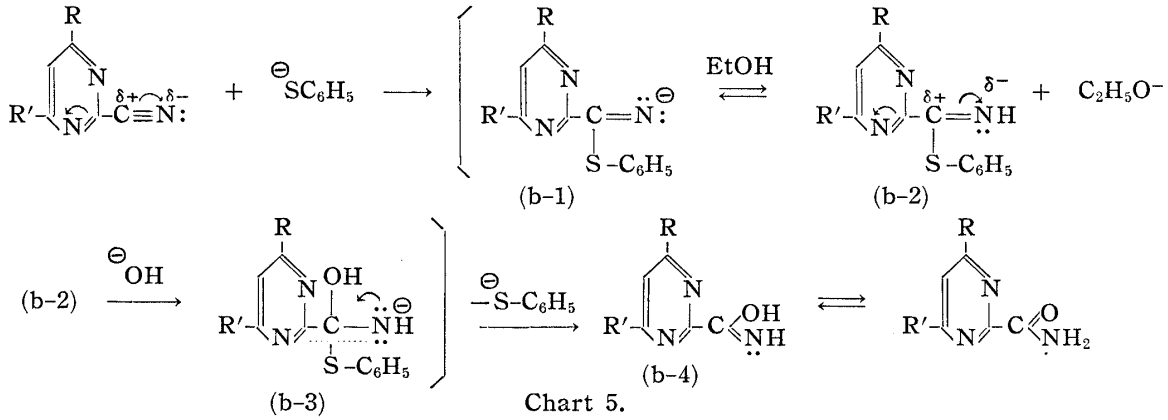


Chart 5.

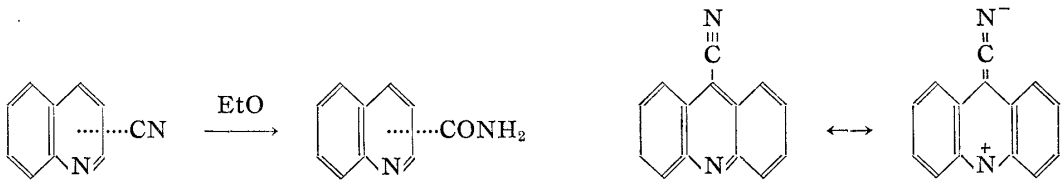
*1 Such difference in the nature of reagents is probably due to the strength of the reagent or spatial size of the reagent but such points cannot be discussed with experimental data now available.

4) J.F. Bunnett, R.Z. Zahler: Chem. Revs., **49**, 273(1951); J.F. Bunnett, *et al.*: J. Am. Chem. Soc., **79**, 385(1957).

converts to (b-3) by the action of hydroxyl ion from water added at the time of after-treatment, with subsequent liberation of thiophenoxide ion to form the aicd amide (b-4).

V. Comparison with Cyano Group of Other Aromatic Heterocycles

Reaction of sodium ethoxide with 2-cyanoquinoline (XXVI), 4-cyanoquinoline (XXVII), and 9-cyanoacridine (XXX) does not result in the occurrence of (i) type reaction observed with pyrimidines and the (ii) type reaction occurs solely to afford the corresponding acid amide, although the starting material is recovered in the case of (XXX). This seems to suggest that the carbon atom in 2- or 4-position of a quinoline ring is not subject to polar effect strong enough to cause the reaction of (i) type. It was concluded that in the case of (XXX), the triple-bond character of the cyano group in its 9-position has been lost due to the large contribution of resonance structure (XXXb) and the starting material was recovered.



The author expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, to Dr. T. Ukai, the Dean of this College, and to Prof. E. Hayashi of this College for their kind and unfailing guidance throughout the course of this work. He is indebted to Miss Y. Saito of the Central Analysis Room of this College for elemental analyses reported herein.

Experimental

Reaction of Phosphoryl Chloride with 4-Hydroxy-6-methylpyrimidine-2-carboxamide (I)—A mixture of 0.5 g. of (I) in 6 cc. of $POCl_3$ was warmed for 15 min. on a boiling water bath by which the crystals dissolved completely. Excess $POCl_3$ was distilled off under a reduced pressure, the residue was poured on crushed ice, and this was extracted with benzene. The extract solution was dried over Na_2SO_4 and passed through alumina column. Evaporation of benzene from the effluent left white crystals which were recrystallized from petr. ether to 0.35 g. of white needles, m.p. 65°. *Anal.* Calcd. for $C_6H_4N_3Cl$ (4-Chloro-6-methylpyrimidine-2-carbonitrile): C, 46.79; H, 2.61; N, 27.30. Found: C, 47.00; H, 2.62; N, 26.78.

The alumina column was then eluted with MeOH and evaporation of MeOH from the effluent left orange crystals. The residue was dissolved in acetone, discolored with activated carbon, and residual crystals were recrystallized from benzene to 0.1 g. of white needles, m.p. 177~178°. *Anal.* Calcd. for $C_6H_6ON_3Cl$ (4-Chloro-6-methylpyrimidine-2-carboxamide): C, 42.10; H, 3.53; N, 24.48. Found: C, 42.45; H, 3.50; N, 24.39.

Reaction of Sodium Methoxide with 4-Chloro-6-methylpyrimidine-2-carbonitrile (II)—i) Reaction with 2 moles of MeONa: To a solution of 0.1 g. of metallic Na dissolved in 10 cc. of MeOH, 0.37 g. of (II) was added and the mixture was refluxed for 1 hr. MeOH was distilled off under a reduced pressure, a small amount of water was added to the residue, and the oily substance that separated out was taken up in ether. Evaporation of ether after drying over K_2CO_3 afforded colorless oil which underwent crystallization on being stimulated. Recrystallization from petr. ether afforded 0.2 g. of 2,4-dimethoxy-6-methylpyrimidine (V) of m.p. 66~68°, undepressed on admixture with an authentic sample.

ii) Reaction with 1 mole of MeONa: A solution of 0.045 g. of metallic Na dissolved in 5 cc. of MeOH was added slowly into a solution of 0.37 g. of (II) dissolved in 5 cc. of MeOH and the whole was refluxed gently for 30 min. after completion of the addition. MeOH was distilled off under a reduced pressure, water was added to the residue, and the oily substance that separated out, which soon crystallized, was extracted with ether. Evaporation of ether from the extract left white crystals which were recrystallized from petr. ether to 0.2 g. of white needles, m.p. 97~99°, undepressed on admixture with 4-methoxy-6-methylpyrimidine-2-carbonitrile (IV) prepared through another route.

Reaction of Sodium Methoxide with 4.6-Dimethylpyrimidine-2-carbonitrile (VII)—To a solution of 50 mg. of metallic Na dissolved in 15 cc. of MeOH, 150 mg. of (VII) was added and the mixture was refluxed for 2 hr. on a boiling water bath. MeOH was distilled off under a reduced pressure, a small

amount of water was added to the residue, and this was extracted with ether. Evaporation of ether afforded a low-melting substance, m.p. 34~37°, which formed a picrate of m.p. 137~138° from MeOH, undepressed on admixture with the picrate of 4,6-dimethyl-2-methoxypyrimidine (X).

The aqueous solution left after extraction with ether was extracted with several portions of $CHCl_3$ but no crystalline product was obtained.

Reaction of Sodium Methoxide with 4-Methoxy-6-methylpyrimidine-2-carbonitrile (IV)—Details of this experiment has already been described.[1]

Reaction of Sodium Methoxide with 2,6-Dimethylpyrimidine-4-carbonitrile*[2] (XIII)—A mixture of 0.4 g of (XIII) in a solution of 0.15 g. of metallic Na dissolved in 5 cc. of MeOH was refluxed for 2 hr. on a boiling water bath. MeOH was distilled off under a reduced pressure, water was added to the residue, and this was extracted thoroughly with $CHCl_3$. The extract was dried over Na_2SO_4, evaporated, and the residue was dissolved in benzene. This benzene solution was passed through a chromatographic column of alumina and elution of the column with benzene afforded 0.2 g. of an oily product whose picrate of m.p. 121~122°, as recrystallized from benzene, showed no depression of m.p. on admixture with the picrate of 2,6-dimethyl-4-methoxypyrimidine (XIV).

Elution of the alumina column with MeOH afforded 0.07 g. of white prisms, m.p. 184~185°, undepressed on admixture with 2,6-dimethylpyrimidine-4-carboxamide (XV).

Reaction of Sodium Butoxide with 4-Butoxy-6-methylpyrimidine-2-carbonitrile (XVI)—i) Reaction with *n*-BuONa : A mixture of 4.0 g. of (XVI) in a solution of 0.8 g. of metallic Na dissolved in 30 cc. of *n*-BuOH was refluxed for 1 hr. and *n*-BuOH was distilled off under a reduced pressure. Water was added to the residue, this solution was extracted with benzene, and benzene layer was dried over Na_2SO_4. Evaporation of benzene left an oil which was distilled under a reduced pressure and 4.5 g. (90%) of colorless, translucent liquid of $b.p_{7\sim8}$ 145~147°, n_D 1.4785, was obtained. *Anal.* Calcd. for $C_{13}H_{22}O_2N_2$ (2,4-Dibutoxy-6-methylpyrimidine) : C, 65.51; H, 9.31; N, 11.76. Found : C, 65.69; H, 9.10; N, 11.64.

ii) Reaction with *sec*-BuONa : To a solution of 0.6 g. of metallic Na dissolved in 30 cc. of *sec*-BuOH, 3.0 g. of (XVI) was added and the mixture was refluxed for 2 hr. The reaction mixture was treated as in the case of reaction with *n*-BuONa and distillation of the final residual oil under a reduced pressure afforded 2.3 g. (60%) of colorless liquid, $b.p_7$ 126~127°, n_D 1.4755, and 1.0 g. of a viscous liquid, $b.p_7$ 180°. *Anal.* Calcd. for $C_{13}H_{22}O_2N_2$ (2,4-Di-*sec*-butoxy-6-methylpyrimidine) : C, 65.51; H, 9.31; N, 11.76. Found : C, 65.70; H, 9.17; N, 11.63.

The picrate of the former melted at 98~99°, as recrystallized from hydr. EtOH, alone and in admixture with the picrate, m.p. 98~99°, of (XVIII) prepared from 2,4-dichloro-6-methylpyrimidine.

The viscous liquid of $b.p_7$ 180° underwent crystallization on being stimulated and afforded 0.8 g. (24%) of needles, m.p. 78~79°, as recrystallized from benzene-petr. ether mixture. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$ (4-*sec*-Butoxy-6-methylpyrimidine-2-carboxamide) : C, 57.40; H, 7.23; N, 20.08. Found: C, 57.47; H, 7.61; N, 19.74. The admixture of this substance with 4-butoxy-6-methylpyrimidine-2-carboxamide, m.p. 83~84°, showed depression of m.p. to 55~65°.

iii) Reaction with *tert*-BuONa : A mixture of 3.0 g. of (XVI) in a solution of 0.6 g. of metallic Na dissolved in 60 cc. of *tert*-BuOH with warming was refluxed for 1.5 hr., by which the solution rapidly colored reddish brown. *tert*-BuOH was distilled off under a reduced pressure, water was added to the residue, and this was extracted with benzene. After drying over Na_2SO_4, the benzene solution was passed through an alumina layer and the residue from its effluent was distilled under a reduced pressure, affording 1.5 g. (40%) of a liquid of $b.p_7$ 131~136°. The liquid was redistilled for analysis to collect a fraction of $b.p_7$ 131~132°, n_D 1.4761. It failed to form a picrate. *Anal.* Calcd. for $C_{13}H_{22}O_2N_2$ (2-*tert*-Butoxy-4-butoxy-6-methylpyrimidine) : C, 65.51; H, 9.31; N, 11.76. Found : C, 65.45; H, 9.43; N, 11.94.

The alumina column was further eluted with MeOH and low-pressure distillation of the residue therefrom afforded 0.5 g. of a viscous liquid boiling out at around 180°. The liquid underwent crystallization on being stimulated but recrystallized product failed to show any distinct melting point.

Reaction of Sodium Methoxide with (XVI)—A mixture of 1.5 g. of (XVI) added to a solution of 0.4 g. of metallic Na dissolved in 30 cc. of MeOH was refluxed for 1 hr. on a boiling water bath, MeOH was distilled off under a reduced pressure, and water and benzene were added to the residue. This was extracted 3 times with 10% HCl and 1.5 g. of a basic liquid was obtained. This was fractionated by low-pressure distillation into two substances. One was a substance of $b.p_{30}$ ca. 100° that crystallized, m.p. 63~65°. Its recrystallization from petr. ether afforded crystals of m.p. 65~67°, undepressed on admixture with 2,4-dimethoxy-6-methylpyrimidine (V). Yield, 0.8 g.

The other fraction was a liquid of $b.p_{30}$ 130~140° which did not crystallize but formed a crystal-

*[2] This experiment has already been reported (H. Yamanaka : This Bulletin, **6**, 638(1958)) but later studies revealed the formation of (XV) as a by-product and the data are corrected herein.

line picrate of m.p. 98~99° as recrystallized from EtOH. Yield, 0.5 g. *Anal.* Calcd. for $C_{10}H_{16}O_2N_2 \cdot C_6H_3O_7N_3$ (2-Methoxy-4-butoxy-6-methylpyrimidine picrate): C, 45.18; H, 4.50; N, 16.47. Found: C, 45.35; H, 4.30; N, 16.55.

Preparation of 2,4-Di-*sec*-butoxy-6-methylpyrimidine (XVIII)—A mixture of 2.0 g. of 2,4-dichloro-6-methylpyrimidine (XXII) added to a solution of 1.0 g. of metallic Na dissolved in 30 cc. of *sec*-BuOH was refluxed for 1 hr., *sec*-BuOH was distilled off under a reduced pressure, and water was added to the residue. This was extracted with benzene and residue from the benzene extract was distilled under a reduced pressure, affording 2.4 g. (82%) of a colorless, translucent liquid, b.p_8 128~129°, n_D 1.4755. Picrate, m.p. 98~99°.

Reaction of Sodium Phenoxide with 4-Phenoxy-6-methylpyrimidine-2-carbonitrile (XI)—To a solution of 0.35 g. of metallic Na dissolved in 5 cc. of dehyd. EtOH, 3.0 g. of phenol was added, the mixture was refluxed for 5 min., cooled, and 2.0 g. of (XXIII) was added. The mixture was refluxed for 1 hr., EtOH was distilled off under a reduced pressure, water was added to the residue, and this was extracted with benzene. The benzene extract was washed twice with 8% NaOH solution, dried over Na_2SO_4, and passed through an alumina column. Evaporation of benzene from the effluent did not leave any residue. Elution of the almina layer with MeOH and evaporation of the solvent from the effluent gave 1.7 g. (80%) of white prisms, m.p. 150°, as recrystallized from dil. MeOH, which showed no depression on admixture with authentic 4-phenoxy-6-methylpyrimidine-2-carboxamide (XXIV).

Reaction of Sodium Thiophenoxide with 4-Ethoxy-6-methylpyrimidine-2-carbonitrile (IX)—A mixture of 2.2 g. of thiophenol added to a solution of 0.23 g. of metallic Na dissolved in 7 cc. of dehyd. EtOH was refluxed for 5 min., cooled, and 0.8 g. of (IX) was added. This mixture was refluxed for 2 hr., EtOH was distilled off under a reduced pressure, water was added to the residue, and this was extracted with benzene. The benzene layer was washed thoroughly with 8% NaOH solution, dried over Na_2SO_4, and passed through a column of alumina. Evaporation of solvent from the effluent left 0.2 g. of oily substance which gradually crystallized, m.p. 60°. It was positive to S test by fusion with Na but negative to N, and was assumed to be a diphenyl disulfide.

Elution of the alumina column with MeOH afforded 0.8 g. of white prisms, m.p. 120~123°, as recrystallized from benzene, which was identified by admixture with 4-ethoxy-6-methylpyrimidine-2-carboxamide (XXV).

Reaction of Phosphoryl Chloride with 4-Methoxy-6-methylpyrimidine-2-carbonitrile (IV)—A mixture of 1.0 g. of (IV) in 5 cc. of $POCl_3$ was refluxed for 2 hr., $POCl_3$ was distilled off under a reduced pressure, and the residue was poured on ice. The crystals that precipitated out were taken up in ether and the ether extract afforded 0.8 g. of the recovered (IV), m.p. 97~99°, as recrystallized from petr. ether.

Reaction of Sodium Ethoxide with 2-Cyanoquinoline (XXVI)—A mixture of 1.5 g. of (XXVI) added to a solution of 0.5 g. of metallic Na dissolved in 30 cc. of dehyd. EtOH was refluxed for 2 hr., EtOH was distilled off under a reduced pressure, and water was added to the residue. The crystals that separated out were collected by filtration and gave 0.5 g. of pale yellow needles, m.p. 205°. Its analytical values suggested the molecular formula of $(C_{10}H_6N_2)_3 \cdot 2H_2O$ but its structure still remains obscure. *Anal.* Found: C, 73.13; H, 4.30; N, 16.96.

The filtrate obtained after removal of above crystals was extracted with a large quantity of benzene and 0.5 g. of crystals, m.p. 123~126°, was obtained. There was no depression of m.p. on its admixture with quinoline-2-carboxamide (XXVIII).

Reaction of Sodium Ethoxide with 4-Cyanoquinoline (XXVII)—A mixture of 0.7 g. of (XXVII) added to a solution of 0.2 g. of metallic Na dissolved in 15 cc. of dehyd. EtOH was refluxed for 2.5 hr., EtOH was distilled off under a reduced pressure, and water was added to the residue. The crystals that separated out were collected by filtration, washed with benzene, and the filtrate was extracted with benzene. Combined filtrate and washings was dried over Na_2SO_4 and benzene was evaporated, leaving some crystals. Its solution in benzene was passed through a column of alumina and 0.3 g. of (XXVII), m.p. 100°, was recovered from its effluent.

The crystals collected as above were recrystallized from water to 0.35 g. of white needles, m.p. 174~176°, undepressed on admixture with quinoline-4-carboxamide (XXIX).

Reaction of Sodium Ethoxide with 4-Cyanoacridine (XXX)—A mixture of 0.17 g. of (XXX) added to a solution of 0.1 g. of metallic Na dissolved in 15 cc. of dehyd. EtOH was refluxed for 2 hr. and the mixture was allowed to cool, from which some pale yellow needle crystals precipitated out. The crystals were collected by filtration and 0.1 g. of (XXX), m.p. 182~183°, was recovered. Concentration of the filtrate afforded another crop of 0.05 g. of (XXX).

Summary

Since the reaction of sodium methoxide with 4-chloro-6-methylpyrimidine-2-carbonitrile afforded 2,4-dimethoxy-6-methylpyrimidine, the cyano group in 2- and 4-positions of the pyrimidine ring is fairly active to nucleophilic reagents. Reaction with 2-cyanopyrimidine derivatives showed that the substitution of cyano group with alkoxide ion decreased in the order to primary, secondary, and tertiary alkyls. This reaction did not take place when the alkoxide ion was replaced with phenoxide or thiophenoxide ion, forming acid amide alone. Application of sodium ethoxide to 2-cyanoquinoline, 4-cyanoquinoline, and 4-cyanoacridine failed to produce any ethoxylated derivatives.

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95. Toyokazu Kishi, Mitsuko Asai, Toru Masuda, and Satoru Kuwada : Application of Chromatography. XXXIX.*1 Biosynthesis of Riboflavin. (3).

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One of the present authors (Masuda)[1] once presumed the mechanism of the biosynthesis of riboflavin by *Eremothecium ashbyii* to be as shown in Chart 1. Katagiri, *et al.*[2] and the present authors[3] later made it clear that riboflavin (IV) can be readily prepared from 6,7-dimethylribolumazine (III) by the action of the enzyme of *Er. ashbyii*. As reported in the previous paper*1 the authors synthesized 4-ribitylamino-5-aminouracil (II) as an intermediate of (III) or 6-methyl-7-hydroxyribolumazine and isolated it as crystalline hydrochloride and hydrosulfite. In the present work, an attempt was made on the synthesis of riboflavin (IV) from (II) via (III) by the action of the above-mentioned enzyme.

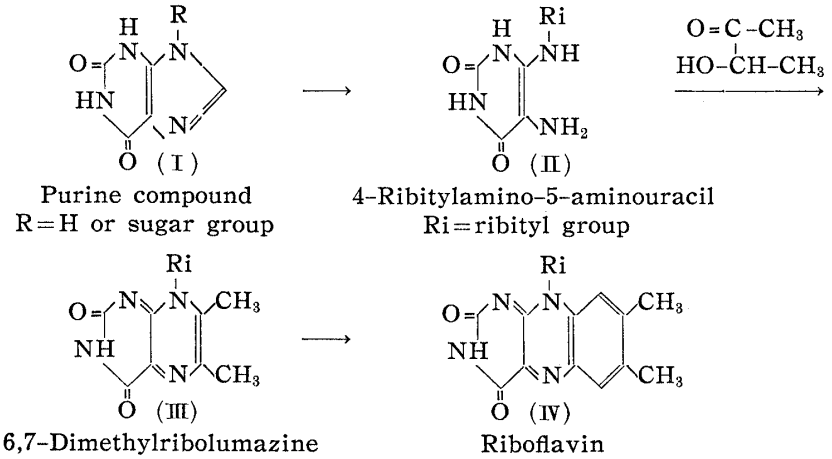

Chart 1.

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*1 Part XXXVIII : This Bulletin, **7**, 366(1959).
*2 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (貴志豊和, 浅井満子, 増田 亨, 桑田 智).
1) T. Masuda : This Bulletin, **5**, 136(1957).
2) H. Katagiri, I. Takeda, K. Imai : J. Vitaminology (Japan), **4**, 285(1958).
3) S. Kuwada, T. Masuda, T. Kishi, M. Asai : This Bulletin, **6**, 618(1958).