UDC 547.853.4'562.1.07

93. Hiroshi Yamanaka*1 : On the Reaction of 4-Phenoxy-6-methylpyrimidine 1-Oxide with Nucleophilic Reagents.

(*Shizuoka College of Pharmacy*)

In 1945, Ochiai and Itai[1] reported the reaction of 4-phenoxypyridine 1-oxide (I) and 4-phenoxyquinoline 1-oxide (II) with anionoid reagents carried out in order to examine reactivity of the phenoxyl group in the 4-position. It was shown that the application of anionoid reagent such as piperidine and morpholine resulted in substitution even at 180~200° and the corresponding 4-substituted compounds are obtained in a good yield. It was pointed out that the characteristics of this reaction is the fact that whereas the N-oxide group is retained in (I), that of (II) is reduced.

On the other hand, the phenoxyl group in 2- or 4-position of a pyrimidine ring is likely to show a fair activity toward anionoid reagents due to the resonance of two nitrogen atoms in the ring and a report endorsing this assumption has also appeared.[2]

With consideration of these facts, reactivity of 4-phenoxy-6-methylpyrimidine 1-oxide[3] (III) to anionoid reagents was examined in comparison with that of 4-phnoexy-6-methylpyrimidine (IV). At the same time, experiments were also carried out in order to prepare N-oxides of several pyrimidine derivatives which cannot be synthesized by the usual procedure of N-oxide formation from the original base.

Reaction of (III) with excess of sodium methoxide in methanol, excess of sodium ethoxide in ethanol, or excess of sodium phenyl sulfide in ethanol respectively afforded 4-methoxy- (V), 4-ethoxy- (VI), and 4-phenylthio-6-methylpyrimidine 1-oxide (VII), each in a good yield. The use of excess alkali in these reactions did not cause coloration of the reaction solution or decrease of the yield and these facts indicate that N-oxides of pyrimidine series are comparatively stable to alkali.*2

Application of piperidine to (III) at its boiling temperature affords 4-piperidino-6-methylpyrimidine 1-oxide (VIII) in a good yield but the same application of morpholine gives only a small amount of 4-morpholino-6-methylpyrimidine 1-oxide (IX) and a fair amount of the deoxygenated 4-morpholino-6-methylpyrimidine (XIII) is obtained. When the latter reaction is carried out at 100° for 4 hours, (IX) is obtained in the main and (XIII) is practically nil. Catalytic reduction of (VIII) over Raney nickel catalyst results in absorption of one mole of hydrogen and 4-piperidino-6-methylpyrimidine (XII) is obtained, identical with a sample prepared by another route.[4]

While substitution reaction with the foregoing reagents occurs smoothly, reaction of (III) with aniline and cyclohexylamine, at the boiling temperature of these reagents, fails to cause substitution at 4-position and results in decomposition of (III) in the former case and recovery of (III) in the latter.

Reaction of the same reagents on (IV) under approximately the same conditions, carried out for the sake of comparison, gave similar results. Reaction of (IV) with sodium

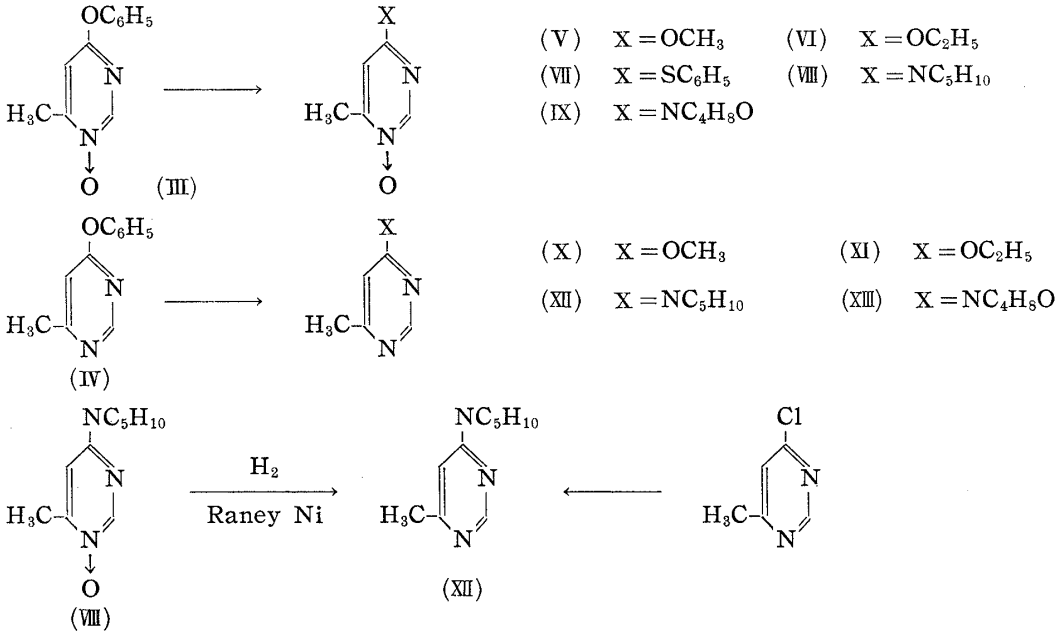
---

*1 Present address : Pharmaceutical Institute, Medical Faculty, Tohoku University. Kita-4-banchō, Sendai (山中 宏).

*2 The N-oxides of pyrimidine series are liable to be ring-cleaved by acids. For example, refluxing of 4-benzyloxy-6-methylpyrimidine N-oxide with 10% hydrochloric acid results in decomposition to ammonium chloride.

1) E. Ochiai, T. Itai, K. Yoshino : Proc. Imp. Acad. (Tokyo), **20**, 141(1945); T. Itai : Yakugaku Zasshi, **65A**, (No. 9—10), 8(1945).
2) T. Matsukawa, K. Shirakawa : Yakugaku Zasshi, **71**, 1313(1951).
3) H. Yamanaka : This Bulletin, **6**, 633(1958).
4) N.B. Chapman, C.W. Rees : J. Chem. Soc., **1954**, 1192.

methoxide, sodium ethoxide, piperidine, and morpholine respectively afforded 4-methoxy- (X), 4-ethoxy- (XI), 4-piperidino- (XII), and 4-morpholino-6-methylpyrimidine (XIII), but the starting material was recovered in the case of aniline and cyclohexylamine.



From the foregoing experimental results, following conclusions are drawn : (i) The phenoxyl group in 4-position of the pyrimidine ring, irrespective of the presence or absence of N-oxide group, is more reactive to anionoid reagents than the phenoxyl in (I) and (II). (ii) The N-oxide group in such pyrimidine ring does not exhibit polar effect on the reactivity of phenoxyl group in the 4-position of the pyrimidine ring to such an extent that it can be detected by this kind of experiment. (iii) Reduction of the N-oxide group does not occur during the course of this reaction when the reaction temperature is limited to below 100°. Preparation of the compounds (VII), (VIII), and (IX) are considered to be impossible through direct N-oxide formation from their tertiary bases.

The writer expresses his deep gratitude to Prof. E. Ochiai of the University of Tokyo, 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 also indebted to Miss. Y. Saito of the Central Analysis Room of this College for elemental analyses.

Experimental

Reaction of 4-Phenoxy-6-methylpyrimidine 1-Oxide (III) and Sodium Alkoxide—i) Reaction with NaOMe : To a solution of 0.06 g. of metallic Na dissolved in 10 cc. of dehyd. MeOH, 0.5 g. of (III) was added and the mixture was refluxed on a boiling water bath for 1 hr. MeOH was distilled off under a reduced pressure, a small amount of water was added to the residue, and this was extracted with $CHCl_3$. The $CHCl_3$ extract was washed twice with 8% NaOH solution, dried over anhyd. Na_2SO_4, and the solvent was evaporated, leaving 0.35 g. of a slightly orange crystals. Recrystallization from benzene afforded 0.32 g. of white plates, m.p. 134.5~136°, underessed on admixture with (V) prepared through another route.[3]

ii) Reaction with NaOEt : To a solution of 0.06 g. of metallic Na dissolved in 10 cc. of dehyd. EtOH, 0.5 g. of (III) was added and the mixture was treated as in the case of reaction with NaOMe. Extraction with $CHCl_3$ afforded 0.35 g. of white plates, m.p. 120~121°, undepressed on admixture with (VI) prepared by another route.[3]

iii) Reaction with $NaSC_6H_5$: To a solution of 0.1 g. of metallic Na dissolved in 2 cc. of dehyd. EtOH, 0.8 g. of freshly distilled thiophenol was added and the mixture was warmed for 15 min. on a boiling water bath. To this solution, 0.6 g. of (III) was added and the whole was refluxed for 2 hr. EtOH was distilled off under a reduced pressure, the residue was extracted with $CHCl_3$, and the $CHCl_3$ layer was washed twice with 10% NaOH solution. The organic solvent layer was then extracted with 10% HCl and the acid extract was neutralized with K_2CO_3 with cooling from the outside. The

oil that separated out was extracted with $CHCl_3$, the extract was dried over Na_2SO_4, and the solvent was evaporated, leaving 0.6 g. of colorless oil. The oil was chilled and the crystalline solid that formed was recrystallized from petr. ether-benzene mixture to 0.5 g. (77%) of 4-phenylthio-6-methylpyrimidine 1-oxide (VII) as white needles, m.p. 107~108°. *Anal.* Calcd. for $C_{11}H_{10}ON_2S$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.81; H, 4.51; N, 12.71.

Reaction of (III) with Piperidine—A mixture of 1.0 g. of (III) and 3 g. of piperidine was refluxed for 2 hr., by which the reaction mixture colored slightly orange. Excess of piperidine was distilled off under a reduced pressure, $CHCl_3$ was added to the residue, and $CHCl_3$ solution was washed twice with 10% NaOH solution. Evaporation of $CHCl_3$ after drying over Na_2SO_4 left 1 g. of an oily substance which crystallized on standing. The crystalline residue was dissolved in $CHCl_3$ and the solution was passed through a short column of alumina to effect discoloration. The residue obtained from the effluent was dissolved in hot benzene, the solution was cooled, and hydrous ether was added to precipitate crystals. 4-Piperidino-6-methylpyrimidine 1-oxide (VIII) was obtained as white needles, m.p. 87~88°. Yield, 0.9 g. (80%). *Anal.* Calcd. for $C_{10}H_{15}ON_3 \cdot 2H_2O$: C, 52.38; H, 8.35; N, 18.33. Found: C, 52.37; H, 8.40; N, 18.96.

Reaction of (III) with Morpholine—i) Reaction at Boiling Temperature of Morpholine: A mixture of 1.5 g. of (III) and 5 cc. of morpholine was refluxed for 2 hr., excess of morpholine was distilled off under a reduced pressure, and the residue was dissolved in $CHCl_3$. The solution was washed twice with 10% NaOH solution, dried over Na_2SO_4, and $CHCl_3$ was evaporated, leaving 1 g. of a mixture of liquid and crystals. This residue was submitted to chromatography through alumina as $CHCl_3$ solution and 0.7 g. of a liquid was obtained from the first eluate, and 0.15 g. of crystals from the following eluate. The liquid formed a picrate of m.p. 168°, identical with the picrate of 4-morpholino-6-methylpyrimidine (XIII). The crystalline residue was recrystallized from a mixture of hydrous ether and benzene in the same way as for (VIII) and white needles, m.p. 116~117°, were obtained. *Anal.* Calcd. for $C_9H_{13}O_2N_3 \cdot H_2O$ (4-Morpholino-6-methylpyrimidine 1-oxide): C, 50.69; H, 7.09; N, 19.60. Found: C, 50.63; H, 7.06; N, 19.60.

ii) Reactin on a Boiling Water Bath: A mixture of 0.8 g. of (III) in 4 cc. of morpholine was heated on a boiling water bath for 4 hr. with occasional shaking, excess of morpholine was distilled off under a reduced pressure, and the residue was treated as above. The crude crystals thereby obtained were washed with ether and recrystallized from a mixture of hydrous ether and benzene, as for (VIII), to 0.4 g. (47%) of (IX) as white needles, m.p. 116~117°.

Evaporation of the solvent from the ether washing left only a trace of orange-colored oily substance and presence of (XIII) was not detected.

Reaction of (III) with Aniline—A mixture of 1 g. of (III) and 3 cc. of aniline was refluxed for 1 hr., when the reation mixture colored dark brown comparatively rapidly. Aniline was distilled off under a reduced pressure, the residue was extracted with $CHCl_3$, and the extract was washed with 10% NaOH. After drying over Na_2SO_4, the $CHCl_3$ solution was passed through an alumina column and only a small amount of light brown oil was obtained, no crystalline product being produced.

Reaction of (III) with Cyclohexylamine—A mixture of 1 g. of (III) and 3 cc. of cyclohexylamine was refluxed for 2 hr. and excess of cyclohexylamine was distilled off under a reduced pressure. Addition of 20% HCl to the residue separated 1 g. of white crystals, m.p. 192~194°(decomp.). This substance was decomposed with 10% Na_2CO_3 and extracted with $CHCl_3$, from which (III), m.p. 120°, was recovered. Prolongation of the reaction time to 15 hr. of refluxing resulted in gradual blackening of the reaction mixture and the majority underwent resinification. After-treatment of this mixture neither afforded the recovered starting material nor any crystalline product.

Catalytic Reduction of 4-Piperidino-6-methylpyrimidine 1-Oxide (VIII)—A solution of 0.6 g. of (VIII) dissolved in 10 cc. of MeOH, added with Raney Ni catalyst prepared from 1 g. of Al-Ni (1:1) alloy, was submitted to reduction at ordinary temperature and pressure. The reduction stopped after rapid (ca. 2 min.) absorption of 1 mole (ca. 59 cc.) of H_2. After removal of the catalyst by filtration, MeOH was evaporated from the filtrate, the residue was dissolved in benzene, and the solution was dried over anhyd. K_2CO_3. Evaporation of benzene left 0.4 g. of an oily substance which formed a picrate of m.p. 172°, undepressed on admixture with the picrate of 4-piperidino-6-methylpyrimidine (XII).

Reactions of 4-Phenoxy-6-methylpyrimidine (IV)—i) Reaction with NaOMe: To a solution of 0.5 g. of metallic Na dissolved in 10 cc. of MeOH, 1.8 g. of (IV) was added and the mixture was treated in approximately the same way as for (III). Benzene extract afforded 0.9 g. (75%) of an oily substance which formed a picrate of m.p. 117°, showing no depression on admixture with the picrate of 4-methoxy-6-methylpyrimidine (X).

ii) Reaction with NaOEt: To a solution of 0.5 g. of metallic Na dissolved in 20 cc. of dehyd. EtOH, 1.8 g. of (IV) was added and the mixture was treated as above. Benzene extract afforded 1 g. (75%) of 4-ethoxy-6-methylpyrimidine (XI), proved as its picrate of m.p. 101~104° by admixture with an authentic specimen.

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.

(Received December 16, 1958)

UDC 547.853.7.07

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

* Present Address : Pharmaceutical Institute, Medical Faculty, Tohoku University. Kita-4-bancho, Sendai (山中 宏).

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

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