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Studies on Pyrimidine Derivatives. XXII.[1] Site-selective Oxidation of Dimethylpyrimidines with Selenium Dioxide to Pyrimidine-monoaldehydes

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The oxidation of 2,4-dimethylquinoline and its 1-oxide with an equimolecular amount of selenium dioxide in boiling dioxane afforded 4-methylquinoline-2-carbaldehyde and its 1-oxide, respectively. This oxidation was applicable to the selective preparation of pyrimidine-4-carbaldehydes from dimethylpyrimidines. In case of pyrimidine derivatives, the presence of an N-oxide group facilitated the oxidation, but the isolated yields of the pyrimidinecarbaldehyde N-oxides were unsatisfactory, because of their instability.

Keywords——2,4-dimethylquinoline; dimethylpyrimidine; selenium dioxide, site-selective reaction; quinoline-4-carbaldehyde; quinoline-4-carbaldehyde N-oxide; pyrimidine-4-carbaldehyde; pyrimidine-4-carbaldehyde N-oxide

Previously, we reported that the oxidation of 2,4-dimethylpyrimidines with a limited amount of selenium dioxide in boiling pyridine and the subsequent esterification of the crude products afforded methyl 2-methylpyrimidine-4-carboxylates as sole products.[2] In the present paper, we describe the generality of this site-selective oxidation and the synthesis of pyrimidine-4-carbaldehydes using the same reagent.

First, the generality of the reaction was examined with 2,4-dimethylquinoline (**1**) as a representative dimethyl-N-heteroaromatic. The oxidation of **1** with an equimolecular amount of selenium dioxide in boiling pyridine, followed by esterification with methanol and thionyl chloride, gave methyl 4-methylquinoline-2-carboxylate (**2**). The purity of the methyl ester (**2**) was checked by gas-chromatographic analysis, but the presence of methyl 2-methylquinoline-4-carboxylate (**4**) or dimethyl quinoline-2,4-dicarboxylate (**5**) was not detected. Sodium borohydride reduction of **2** gave 4-methylquinoline-2-methanol (**3**), which was identical with an authentic sample prepared from 4-methylquinoline (**6**) according to the known procedure.[3]

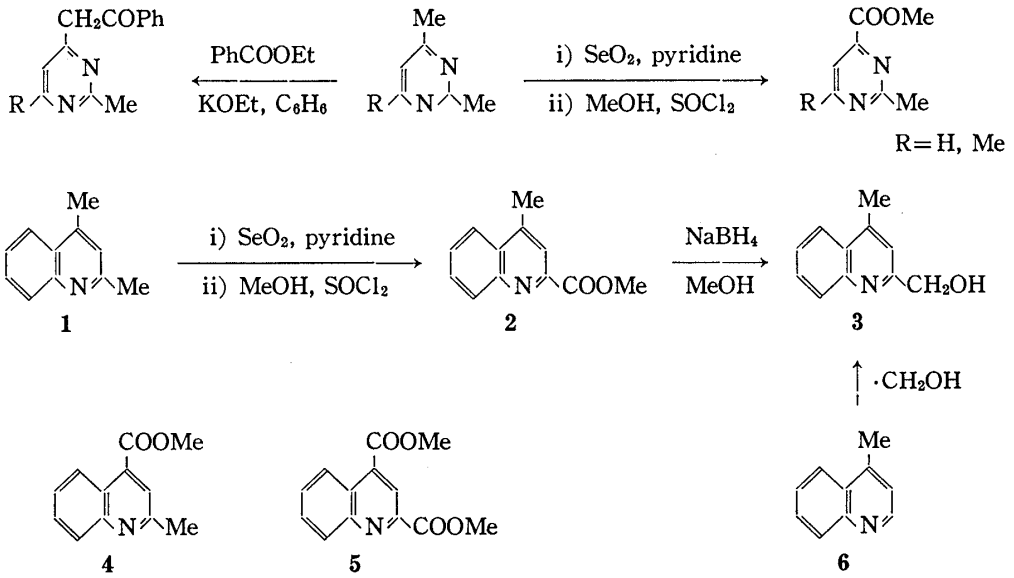

Chart 1

The oxidation of **1** clearly shows that selenium dioxide selectively attacks a methyl group in the neighborhood of a ring nitrogen atom. In 2,4-dimethylpyrimidines the methyl groups are both located at the α-position to a ring nitrogen atom, although they are not equivalent. In this case, selenium dioxide first attacks the more active methyl group. In connection with this, the nitrosation with ethyl nitrite,[4] acylation with ethyl benzoate,[5] and condensation with benzaldehyde[6] of 2,4-dimethylpyrimidines are known to give products in which the 2-methyl group is intact. Accordingly, the formation of methyl 4-methylquinoline-2-carboxylate observed in the present investigation is not inconsistent with that of methyl 2-methylpyrimidine-4-carboxylates described in the preceding paper.[2]

Next, when 2,4-dimethylquinoline (**1**) was treated with the same reagent in dioxane under reflux, 4-methylquinoline-2-carboxylate (**7**) was obtained in 70% yield, instead of the carboxylic acid. For comparison with the above reaction, 2,4-dimethylquinoline 1-oxide (**8**) was then treated with selenium dioxide in dioxane, and 4-methylquinoline-2-carbaldehyde 1-oxide (**9**) was obtained in 97% yield under rather mild conditions. The hydrogenation of **9** over Raney nickel, as well as the sodium borohydride reduction of **9** gave 4-methylquinoline-2-methanol 1-oxide in 79% yield. Accordingly, the introduction of an N-oxide group seems to activate a neighboring methyl group.

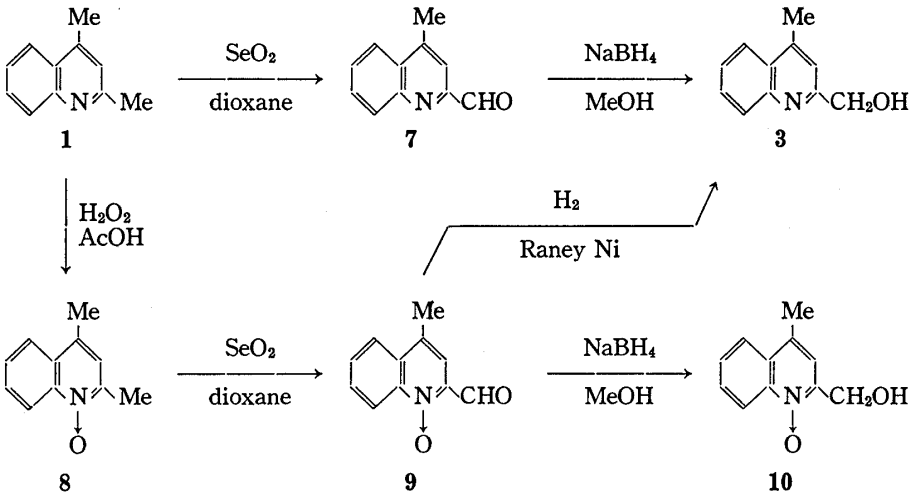

Chart 2

Simple procedures for the preparation of pyrimidine-4-carbaldehydes have not yet been well explored,[7] though several of their acetals were synthesized by ring closure reactions using appropriately modified β-dicarbonyl compounds.[8] From this point of view, selenium dioxide oxidation of 2,4-dimethyl-6-phenylpyrimidine (**11**) and 4,6-dimethyl-2-phenylpyrimidine (**14**) was investigated next. When **11** was treated with a limited amount of selenium dioxide in boiling dioxane, 2-methyl-6-phenylpyrimidine-4-carbaldehyde (**12**) was obtained as expected. In accord with the results obtained previously, the relative reactivity of 2- and 4-methyl groups on pyrimidine ring was not affected by the presence of the 6-phenyl group, so that this finding appears to be a general feature. Quantitative conversion of this product (**12**) into 2-methyl-6-phenylpyrimidine-4-methanol (**13**), which was unequivocally synthesized,[9] clearly confirmed the structure of the aldehyde (**12**).

Clear site-selectivity in the oxidation of 2,4-dimethylpyrimidines was found, as described above, but stoichiometric selectivity in the oxidation of dimethylpyrimidines containing two equivalent methyl groups appeared to be incomplete. Namely, the oxidation of 4,6-dimethyl-2-phenylpyrimidine (**14**) with an equimolecular amount of selenium dioxide gave 43% of the monoaldehyde (**15**) together with 11% of the dialdehyde (**16**). When two equimolecular amounts of selenium dioxide was used, **16** was obtained in 45% yield.

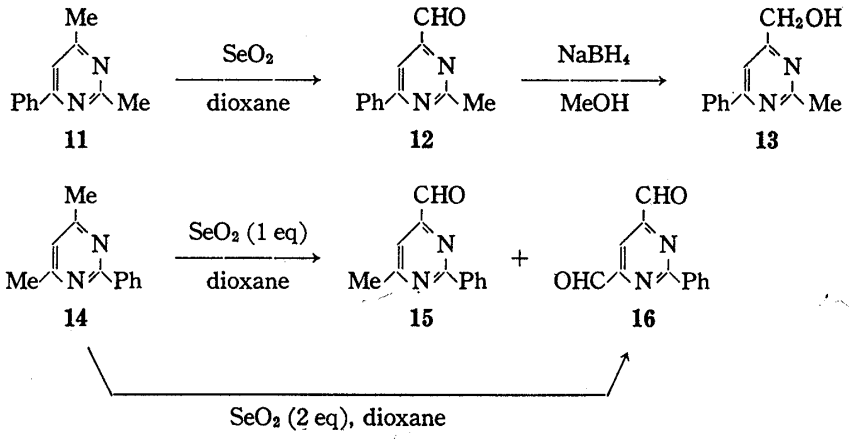

Chart 3

The introduction of an N-oxide group was not attractive in the case of pyrimidine derivatives. Although 2,4-dimethyl-6-phenylpyrimidine 3-oxide (**17**) was easily oxidized under the same conditions to give 2-methyl-6-phenylpyrimidine-4-carbaldehyde 3-oxide (**18**), the yield of **18** did not exceed the yield of **12** (90%) from **11**. Since product **18** is too unstable to isolate in a pure form, its structure was proved by catalytic hydrogenation of the crude product over Raney nickel giving known 2-methyl-6-phenylpyrimidine-4-methanol (**19**).[9] 4,6-Dimethyl-2-phenylpyrimidine 1-oxide (**20**) was oxidized under similar conditions to give a monoaldehyde N-oxide (**21**), as an unstable product. In this case, the corresponding dialdehyde N-oxide (**22**) was not isolated. In order to confirm the structure of the monoaldehyde N-oxide (**21**), this compound was transformed into 4-acetoxymethyl-6-methyl-2-phenylpyrimidine 3-oxide (**24**) *via* 6-methyl-2-phenylpyrimidine-4-methanol 3-oxide (**23**) by sodium borohydride reduction of **21** and subsequent acetylation. In general, the structure of pyrimidine mono-N-oxides can be elucidated by taking their proton magnetic resonance (PMR) spectra in the presence of a shift reagent.[10] The structure **21** was supported by the results of such an experiment. The above observation suggests that an N-oxide group facilitates the oxidation of an α-methyl group. However, the synthesis of 2,4-dimethyl-6-phenylpyrimidine 1-oxide, an isomer of **17**, was found to be so difficult that further investigation on role of N-oxide groups was abandoned for the present.

In order to provide a method of monomethylpyrimidine with selenium dioxide in boiling dioxane is under investigation.

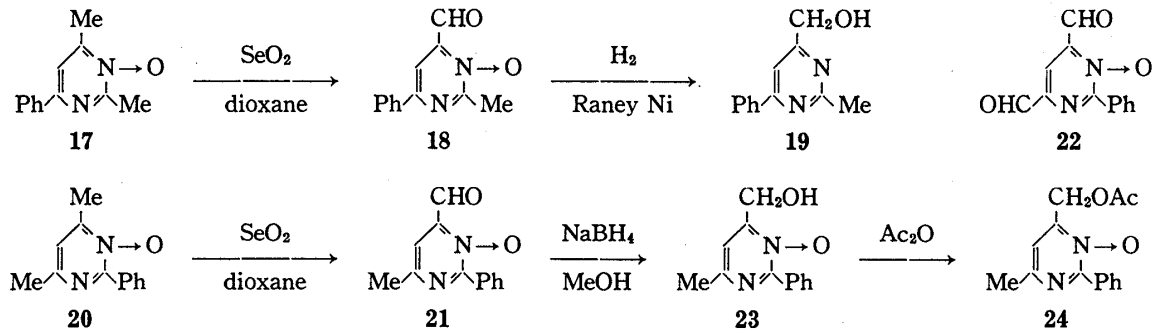

Chart 4

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. PMR spectra were obtained with a Hitachi-Perkin-Elmer R-20 spectrometer.

Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an interna standard. The following abbreviations are used: s=singlet and m=multiplet.

Methyl 4-Methylquinoline-2-carboxylate (2)——Selenium dioxide (2.80 g, 25 mmol) was added portionwise to a pyridine (20 ml) solution of 2,4-dimethylquinoline (3.6 g, 23 mmol) at 90°C over a period of 20 min and then the mixture was heated at 90°C for 1.5 h. After removal of the precipitated Se by filtration, 3 N NaOH (10 ml) was added to the filtrate and the mixture was concentrated under reduced pressure. The residue was treated with active charcoal in 3 N HCl and the 3 N HCl solution was concentrated under reduced pressure to dryness. Thionyl chloride (5 ml) was added to an MeOH (50 ml) solution of the residue and the mixture was stirred at room temperature for 38 h. After removal of the solvent, the residue was made alkaline with 1 N $NaHCO_3$ and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 140—150°C (1 mmHg), which immediately solidified. Recrystallization from hexane gave colorless needles, mp 105—107°C. IR ν_{max}^{KBr} cm^{-1}: 1706. PMR ($CDCl_3$): 2.77 (3H, s), 4.08 (3H, s), 7.57—8.50 (5H, m). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.28; H, 5.41; N, 6.86.

Reduction of 1 with $NaBH_4$——A mixture of 1 (500 mg, 2.48 mmol) and $NaBH_4$ (940 mg, 24.8 mmol) in MeOH (10 ml) was refluxed for 1.5 h. After removal of the solvent by evaporation, H_2O was added to the residue and the mixture was extracted with $CHCl_3$. The crude product was recrystallized from diisopropyl ether to give colorless needles, mp 77—79°C, which were identical with an authentic specimen[3] of 4-methylquinoline-2-methanol (3). Yield 240 mg (55%).

4-Methylquinoline-2-carbaldehyde (7)——A mixture of 1 (515 mg, 3.28 mmol) and SeO_2 (400 mg, 3.6 mmol) in dioxane (15 ml) was refluxed for 2.5 h. The precipitated Se was filtered off and then the dioxane was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. The crude product was recrystallized from hexane to give colorless needles, mp 76—78°C. Yield 392 mg (70%). IR ν_{max}^{KBr} cm^{-1}: 1703. PMR ($CDCl_3$): 2.75 (3H, s), 7.57—8.37 (5H, m), 10.13 (1H, s). *Anal.* Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.84; H, 5.38; N, 7.95.

Reduction of 7 with $NaBH_4$——A mixture of 7 (1.71 g, 10 mmol) and $NaBH_4$ (190 mg, 5 mmol) in MeOH (20 ml) was stirred for 5 min at room temperature. After removal of the solvent by evaporation, the residue was dissolved in 3 N HCl and washed with $CHCl_3$. The aqueous layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The crude product was recrystallized from hexane to give colorless needles, mp 81—82°C, which were identical with an authentic specimen[3] of 4-methylquinoline-2-methanol (3). Yield 1.4 g (81%).

4-Methylquinoline-2-carbaldehyde 1-Oxide (9)——A mixture of 2,4-dimethylquinoline 1-oxide (8) (524 mg, 3 mmol) and SeO_2 (366 mg, 3.3 mmol) in dioxane (15 ml) was refluxed for 1 h. The precipitated Se was filtered off and then the solvent was removed. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. The crude product was recrystallized from AcOEt to give yellow needles, mp 175—176°C. Yield 550 mg (97%). IR ν_{max}^{KBr} cm^{-1}: 1681, 1212. PMR ($CDCl_3$): 2.66 (3H, s), 7.23—8.27 (4H, m), 8.60—9.00 (1H, m), 10.82 (1H, s). This compound was converted to the oxime, mp 231—232°C dec.), which was recrystallized from MeOH to give yellow scales. *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.34; H, 4.87; N, 13.68.

Hydrogenation of 9 over Raney Ni——A mixture of 9 (935 mg, 5 mmol) and W-2 Raney Ni (1 ml) in MeOH (50 ml) was hydrogenated under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The residue was recrystallized from hexane to give colorless needles, mp 81—82°C, which were identical with an authentic specimen[3] of 4-methylquinoline-2-methanol (3). Yield 600 mg (70%).

4-Methylquinoline-2-methanol 1-Oxide (10)——A mixture of 9 (549 mg, 2.93 mmol) and $NaBH_4$ (114 mg, 3 mmol) in MeOH (20 ml) was stirred at room temperature for 5 min. After removal of the solvent, H_2O was added to the residue and the precipitated solid was filtered off, washed with H_2O, and dried under reduced pressure. Recrystallization from diisopropyl ether gave colorless needles, mp 182.5—183°C. Yield 453 mg (79%). IR ν_{max}^{KBr} cm^{-1}: 3150, 1206. PMR (CF_3COOH): 3.10 (3H, s), 5.60 (2H, s), 7.90—8.80 (5H, m). *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.55; H, 5.83; N, 7.22.

2-Methyl-6-phenylpyrimidine-4-carbaldehyde (12)——A mixture of 2,4-dimethyl-6-phenylpyrimidine (11) (651 mg, 3.53 mmol) and SeO_2 (392 mg, 3.53 mmol) in dioxane (20 ml) was refluxed for 5 h. After removal of the precipitated Se by filtration, the solvent was evaporated to dryness. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. The crude product was recrystallized from hexane to give colorless needles, mp 63—64°C. Yield 631 mg (90%). IR ν_{max}^{KBr} cm^{-1}: 1712. PMR ($CDCl_3$): 2.89 (3H, s), 7.38—7.63 (3H, m), 7.99 (1H, s), 8.03—8.28 (2H, m), 10.03 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.83; H, 5.22; N, 13.95.

2-Methyl-6-phenylpyrimidine-4-methanol (13)——A mixture of 12 (240 mg, 1.2 mmol) and $NaBH_4$ (50 mg, 1.3 mmol) in MeOH (10 ml) was stirred at room temperature for 5 min. After removal of the solvent, H_2O was added to the residue and the mixture was extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography using $CHCl_3$ and $CHCl_3$: AcOEt (7: 3) as eluants. The $CHCl_3$: AcOEt (7: 3) eluates gave colorless needles, mp 94—96°C, which were recrystallized from hexane. Yield 229 mg (93%). This compound was identical with an authentic specimen.[9]

Oxidation of 4,6-Dimethyl-2-phenylpyrimidine (14) with SeO_2——A mixture of **14** (536 mg, 2.91 mmol) and SeO_2 (339 mg, 3 mmol) in dioxane (8 ml) was refluxed for 5 h. After removal of the precipitated Se by filtration, the solution was evaporated to dryness. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. The first fraction gave colorless prisms (**15**), mp 80—81°C, which were recrystallized from hexane. Yield 246 mg (43%). IR ν_{max}^{KBr} cm^{-1}: 1711. PMR ($CDCl_3$): 2.68 (3H, s), 7.37—7.67 (4H, m), 8.40—8.67 (2H, m), 10.10 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.79; H, 5.11; N, 14.14.

The second fraction gave a yellow solid which was dissolved in ether and washed with 1 N HCl. Concentration of the ether layer gave colorless needles (**16**), mp 133—135°C, which were recrystallized from diisopropyl ether. IR ν_{max}^{KBr} cm^{-1}: 1722. NMR ($CDCl_3$): 7.37—7.70 (3H, m), 8.07 (1H, s), 8.40—8.73 (2H, m), 10.14 (2H, s). *Anal.* Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.01; H, 3.91; N, 12.99.

2-Phenylpyrimidine-4,6-dicarbaldehyde (16)——A mixture of **14** (318 mg, 1.7 mmol) and SeO_2 (414 mg, 3.74 mmol) in dioxane (10 ml) was refluxed for 5 h. The precipitated Se was filtered off, and the filtrate was evaporated to dryness. The residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. The crude product was recrystallized from diisopropyl ether to give colorless needles, mp 133—135°C. Yield 166 mg (45%).

2-Methyl-6-phenylpyrimidine-4-carbaldehyde 3-Oxide (18)——A mixture of 2,4-dimethyl-6-phenylpyrimidine 3-oxide (**17**) (308 mg, 1.54 mmol) and SeO_2 (170 mg, 1.54 mmol) in dioxane (10 ml) was refluxed for 5 h. The precipitated Se was filtered off, and the filtrate was evaporated to dryness. The residue was treated with $HONH_2 \cdot HCl$–AcONa in the usual manner to give the oxime. Recrystallization from EtOH gave yellow needles, mp 205—206°C. Yield 218 mg (62%). IR ν_{max}^{KBr} cm^{-1}: 2600—3000 (broad), 1230. PMR (CF_3COOH): 3.10 (3H, s), 7.40—7.80 (3H, m), 8.10—8.45 (3H, m), 8.65 (1H, s). *Anal.* Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.83; H, 4.90; N, 18.15.

Hydrogenation of 18 over Raney Ni——A mixture of **17** (454 mg, 2.27 mmol) and SeO_2 (264 mg, 2.38 mmol) in dioxane (14 ml) was refluxed for 2 h. The precipitated Se was filtered off, and the filtrate was evaporated to dryness. A mixture of the residue and W-2 Raney Ni (2 ml) in EtOH (30 ml) was hydrogenated at atmospheric pressure. The catalyst was filtered off and the solvent was distilled off. The residue was purified by SiO_2 column chromatography using $CHCl_3$ and $CHCl_3$: AcOEt (7: 3) as eluants. The $CHCl_3$: AcOEt (7: 3) eluate gave colorless needles (**19**), mp 94—96°C, which were recrystallized from hexane. Yield 303 mg (67%). This compound was identical with an authentic specimen[9] of 2-methyl-6-phenylpyrimidine-4-methanol.

6-Methyl-2-phenylpyrimidine-4-carbaldehyde 3-Oxide (21)——A mixture of 4,6-dimethyl-2-phenylpyrimidine 1-oxide (**20**) (535 mg, 2.67 mmol) and SeO_2 (311 mg, 2.8 mmol) in dioxane (16 ml) was refluxed for 1 h. The precipitated Se was filtered off, and filtrate was evaporated to dryness. The residue was converted to the oxime in the usual manner to afford yellow needles, mp 215—216°C, which were recrystallized from EtOH. Yield 475 mg (78%). IR ν_{max}^{KBr} cm^{-1}: 2550—3000 (broad), 1220. PMR (CF_3COOH): 2.90 (3H, s), 7.50—7.75 (3H, m), 8.00—8.20 (3H, m), 8.67 (1H, s). *Anal.* Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.12; H, 5.00; N, 18.30.

6-Methyl-2-phenylpyrimidine-4-methanol 3-Oxide (23)——A mixture of **20** (506 mg, 2.53 mmol) and SeO_2 (294 mg, 2.66 mmol) in dioxane (15 ml) was refluxed for 5 h. The precipitated Se was filtered off, and the filtrate was evaporated to dryness. A mixture of the residue and $NaBH_4$ (60 mg, 1.59 mmol) in MeOH (20 ml) was stirred at room temperature for 5 min. Water was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using AcOEt as an eluant. The crude product was recrystallized from C_6H_6 to give colorless needles, mp 132—138°C. Yield 335 mg (61%). IR ν_{max}^{KBr} cm^{-1}: 3330, 3200, 1222. PMR ($CDCl_3$): 2.56 (3H, s), 4.79 (3H, s, 1H is disappeared by adding D_2O), 7.19 (1H, s), 7.37—7.58 (3H, m), 8.30—8.50 (2H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.59; H, 5.52; N, 12.77.

4-Acetoxymethyl-6-methyl-2-phenylpyrimidine 3-Oxide (24)——A mixture of **23** (52.9 mg, 0.245 mmol) and Ac_2O (24.1 μl, 0.257 mmol) in $CHCl_3$ (1 ml) was allowed to stand at room temperature for 60 h. The solvent was removed, and the residue was purified by SiO_2 preparative thin-layer chromatography using $CHCl_3$–MeOH (9: 1) as a developing solvent to give yellow leaflets, mp 96—97°C. Yield 49.6 mg (79%). IR ν_{max}^{KBr} cm^{-1}: 1748, 1236. NMR ($CDCl_3$): 2.24 (3H, s), 2.58 (3H, s), 5.39 (2H, s), 7.11 (1H, s), 7.32—7.68 (3H, m), 8.33—8.68 (2H, m). PMR of **24** adding $Eu(fod)_3$ (0.162 mol equivalent) in $CDCl_3$: 2.49 (3H, s), 2.59 (3H, s), 6.83 (2H, s), 7.43 (1H, s), 7.50—7.77 (3H, m), 9.33—9.67 (2H, m). *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.40; N, 10.85. Found: C, 64.81; H, 5.56; N, 10.58.

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References and Notes

1) Part XXI: H. Yamanaka, S. Ogawa, and S. Konno, *Chem. Pharm. Bull.*, **29**, 98 (1981).
2) T. Sakasai, T. Sakamoto, and H. Yamanaka, *Heterocycles*, **13**, 235 (1979).

3) W. Bratti, G.P. Gardini, F. Minisci, F. Bertini, R. Galli, and M. Perchinunno, *Tetrahedron*, **27**, 3655 (1971).
4) H. Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, *Chem. Pharm. Bull.*, **25**, 1821 (1977).
5) H. Yamanaka, H. Abe, and T. Sakamoto, *Chem. Pharm. Bull.*, **25**, 3334 (1977).
6) H. Yamanaka, unpublished data.
7) *a*) D.J. Brown, "The Pyrimidines," in "The Chemistry of Heterocyclic Compounds," ed. by A. Weissberger, Interscience Pub., New York, 1962; *b*) *Idem*, "The Pyrimidines Supplement I," in "The Chemistry of Heterocyclic Compounds," ed. by A. Weissberger and E.C. Taylor, Wiley-Interscience, New York, 1970.
8) *a*) H. Bredereck, R. Sell, and F. Effenberger, *Chem. Ber.*, **97**, 3407 (1964); *b*) T.B. Johnson and E.F. Schroeder, *J. Am. Chem. Soc.*, **53**, 1989 (1931); *c*) A. Burger, T.B. Clements, N.D. Dawson, and R.B. Henderson, *J. Org. Chem.*, **20**, 1383 (1955); *d*) T.B. Johnson and L.A. Mickeska, *J. Am. Chem. Soc.*, **42**, 2349 (1920).
9) T. Sakamoto, K. Kanno, T. Ono, and H. Yamanaka, *Heterocycles*, **6**, 525 (1977).
10) T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, *Chem. Pharm. Bull.*, **27**, 2653 (1979).