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Studies on Pyrimidine Derivatives. XVIII.[1] Reaction of Active Methyl Groups on Pyrimidine N-Oxides

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Knoevenagel-type condensation and the Mannich reaction were investigated with various pyridine N-oxides having an active methyl group. For example, 6-methyl-4-phenylpyrimidine 1-oxide (Va) readily reacted with benzaldehyde in an aqueous ethanolic solution of potassium hydroxide, while 4-methyl-6-phenylpyrimidine (IVa) failed to react with benzaldehyde under the same conditions.

When Va was treated with piperidine hydrochloride and paraformaldehyde, bis piperidinomethylation occurred at the 6-methyl group. The product was transformed into 4-phenyl-6-(2-piperidinoethyl)pyrimidine 1-oxide (XXIIa) by treatment with 5% sulfuric acid at 90°.

Keywords——methylpyrimidine N-oxides; Knoevenagel condensation; styrylpyrimidine N-oxides; Mannich reaction; active methyl group

Although pyrimidine N-oxides reacted with morpholine enamines in the presence of benzoyl chloride to introduce a carbon substituent at the 2-position,[3] the reaction of the same N-oxides with active methylene compounds under similar conditions was observed to result in cleavage of the pyrimidine rings.[4] These findings represent a serious limitation of the synthetic utility of N-oxides. Our interest was therefore focussed on the utilization of active methyl groups attached to pyrimidine N-oxides. The present paper deals with the effect of the N-oxide group on the reactivity of methylpyrimidine N-oxides under basic and acidic conditions.

First, the Knoevenagel-type condensation of methylpyrimidine N-oxides with benzaldehyde in an alkaline medium was investigated. When 4,6-dimethylpyrimidine 1-oxide (II)[5] was allowed to stand with benzaldehyde in an aqueous ethanolic solution of potassium hydroxide at room temperature, yellow crystals precipitated and the reaction mixture was almost solidified within 1 hr. The nuclear magnetic resonance (NMR) spectrum of the crude precipitate suggested it to be a mixture of various pyrimidines containing stytyl-type side chains and 2-hydroxyphenethyl-type side chains. Thus, the crude precipitate was treated with phosphorus trichloride to remove the N-oxide group and to convert the side chains to the same type. After this treatment, 4,6-distyrylpyrimidine (III) was isolated as a sole product in 53% yield. The NMR spectrum of III is consistent with a distyryl (*trans*) structure.

The condensation of 4,6-dimethylpyrimidine (I) with benzaldehyde under identical conditions resulted in the complete recovery of the starting materials.[6]

The reaction of 6-methyl-4-phenylpyrimidine 1-oxide (Va)[7] with benzaldehyde appeared simple, and 4-phenyl-6-styrylpyrimidine 1-oxide (VI) was precipitated in 87% yield without

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1) T. Sakasai, T. Sakamoto, and H. Yamanaka, *Heterocycles*, **13**, 235 (1979).
2) Location: *Aobayama, Sendai 980, Japan.*
3) H. Yamanaka, S. Niitsuma, Y. Bannai, and T. Sakamoto, *Chem. Pharm. Bull.*, **23**, 2591 (1975).
4) H. Yamanaka, T. Sakamoto, Y. Bannai, and S. Ogawa, *Chem. Pharm. Bull.*, **26**, 3404 (1978).
5) R. Hunt, J. McOmie, and E. Sayer, *J. Chem. Soc.*, **1959**, 525.
6) In general, styrylpyrimidines can be synthesized by the thermal condensation of methylpyrimidines with benzaldehyde in the presence of zinc chloride. S. Gabriel and J. Colman, *Chem. Ber.*, **36**, 3379 (1903).
7) H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).

contamination by a hydroxyphenethyl-type by-product. The removal of the N-oxide group from VI was successfully accomplished by treatment of VI with phosphorus trichloride, and 4-phenyl-6-styrylpyrimidine (VII) was obtained in 85% yield. The exhaustive catalytic reduction of VI over Ranay nickel afforded 4-phenethyl-6-phenylpyrimidine (VIII) in good yield, although the reduction of VI with a limited amount of hydrogen failed to give VII or 6-phenethyl-4-phenylpyrimidine 1-oxide in pure form.

The effect of the N-oxide group on active methyl groups was also seen in the reaction of 4-methyl-6-phenylpyrimidine (IVa); no condensation product was obtained under the same conditions.

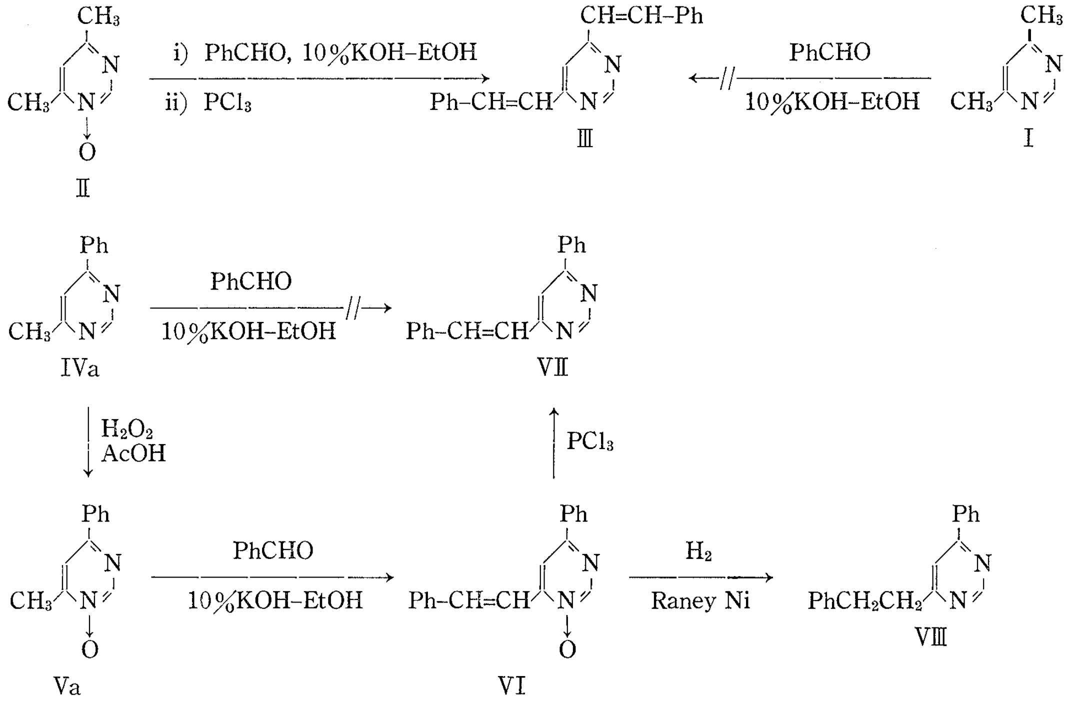

Chart 1

In comparison with Va, 2-methyl-4-phenylpyrimidine 1-oxide (IX) seems to be less reactive. In this case, purification of the precipitate by column chromatography afforded 4-phenyl-2-styrylpyrimidine 1-oxide (X) in 18% yield and 2-(2-hydroxyphenethyl)-4-phenylpyrimidine 1-oxide (XI) in 20% yield, together with the recovery of the starting material (IX) in 12% yield.

In order to compare the reactivities of different methyl groups in a single molecule, the reaction of 2,6-dimethyl-4-phenylpyrimidine 1-oxide (XII)[8] with benzaldehyde was investigated. After treatment of the crude product with phosphorus trichloride as in the case of II, 2-methyl-4-phenyl-6-styrylpyrimidine (XIII) was obtained in 43% yield. However, the corresponding positional isomer, 6-methyl-4-phenyl-2-styrylpyrimidine, was not isolated.

The NMR spectrum of XIII was insufficient to locate the styryl group, although the spectral data indicate a *trans* olefin structure. Thus, authentic XIII was unequivocally synthesized from 4-iodo-2-methyl-6-phenylpyrimidine (XIV) using the cross-coupling reaction with styrene.[9] The identity of the two compounds were confirmed by comparison of their melting points and spectral data.

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8) T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, *Chem. Pharm. Bull.*, **27**, 2653(1979).
9) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **27**, 193 (1979).

Similar results were obserbed in the reaction of 2,4,6-trimethylpyrimidine 1-oxide (XV)[10] with benzaldehyde. Namely, the condensation of XV with excess benzaldehyde (3 mol equivalent) followed by deoxygenation with phosphorus trichloride afforded 2-methyl-4,6-distyrylpyrimidine (XVI) as a main product (17%), together with a small amount (5%) of 2,4,6-tristyrylpyrimidine (XVII). The structure of the main product was supported by the result of catalytic reduction of XVI, giving 2-methyl-4,6-diphenethylpyrimidine (XVIII). Compound XVIII was identical with an authentic sample prepared from 4,6-diiodo-2-methylpyrimidine (XIX) *via* 2-methyl-4,6-diphenylethynylpyrimidine (XX).[11]

Like I and IVa, 2-methyl-4-phenyl-, 2,6-dimethyl-4-phenyl-, and 2,4,6-trimethylpyrimidine were found not to react with benzaldehyde under the conditions used.

On the basis of the results described above, the following conclusions seem reasonable.
1) The introduction of an N-oxide group into pyrimidine rings considerably stimulates Knoevenagel-type condensation of the active methyl groups.
2) Higher reactivity of 4-(and 6) methyl groups than of 2-methyl groups in polymethylpyrimidines[12] is still retained in the presence of an N-oxide group.

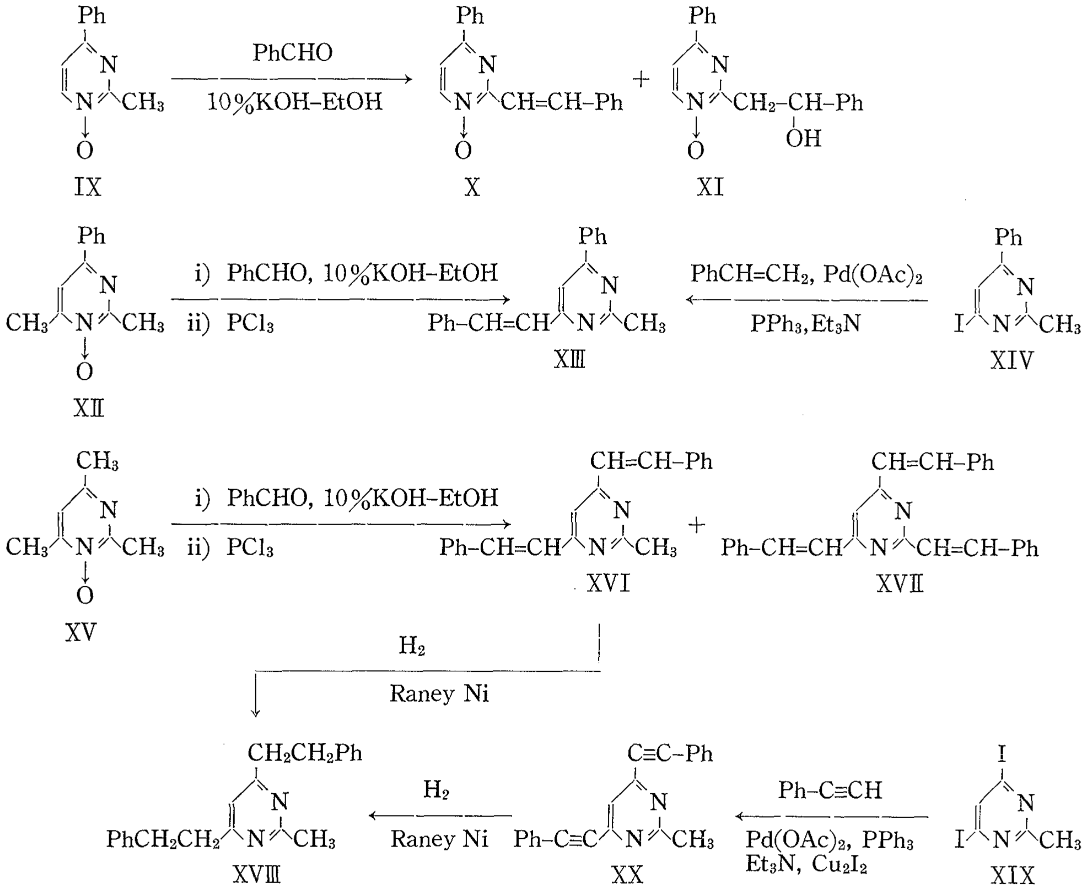

Chart 2

Next, the Mannich reaction[13] of methylpyrimidine N-oxides was investigated. When Va was refluxed in ethanol with piperidine hydrochloride and paraformaldehyde for 4 hr, colorless prisms of XXIa, $C_{23}H_{32}N_4O$, were obtained as a free base in 31% yield together with

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10) R.H. Wiley and S.C. Slaymaker, *J. Am. Chem. Soc.*, **79**, 2233 (1957).
11) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **26**, 3843 (1978).
12) H. Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, *Chem. Pharm. Bull.*, **25**, 1821 (1977).
13) C.G. Overberger and I.C. Kogon, *J. Am. Chem. Soc.*, **76**, 1879 (1954).

the starting material (34%). The elemental analysis and the spectral data show the product to be the bis-Mannich base of Va. On treatment with 5% sulfuric acid at 90° for a short time, XXIa was transformed into 4-phenyl-6-(2-piperidinoethyl)pyrimidine 1-oxide (XXIIa) in 83% yield. Catalytic reduction of XXIa and XXIIa over Raney nickel gave rise to the corresponding tertiary bases (XXIIIa and XXIVa, respectively) in almost quantitative yields. On heating XXIIIa in 5% sulfuric acid, elimination of piperidine from the side chain took place and 4-phenyl-6-(1-piperidinomethylvinyl)pyrimidine (XXV) was isolated. In this case, however, the presence of XXIVa in the reaction mixture was not observed.

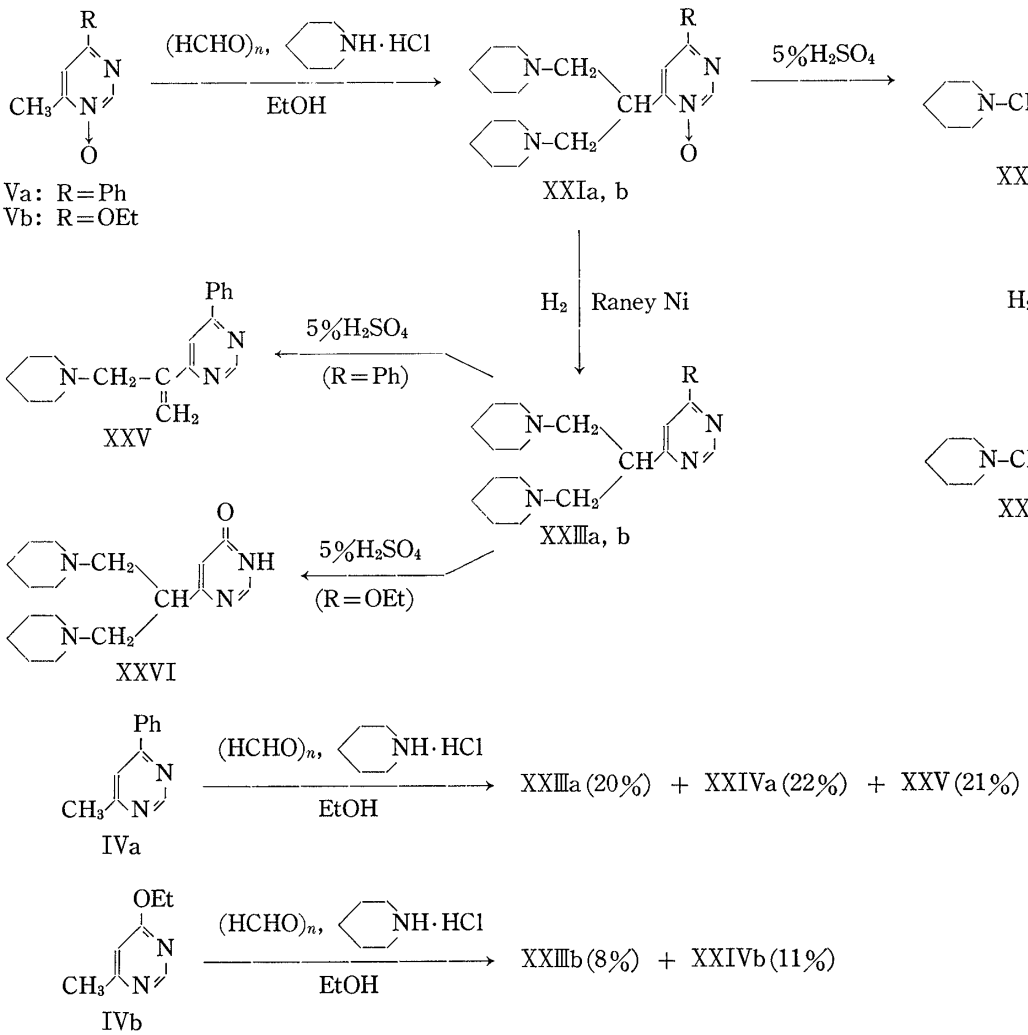

Chart 3

Similar results were obtained from the Mannich reaction of 4-ethoxy-6-methylpyrimidine 1-oxide (Vb),[14] as shown in Chart 3. Unlike the acid hydrolysis of XXIIIa, that of XXIIIb cleaved the ether linkage at the 4-position to give the 4-pyrimidinone (XXVI). The corresponding tertiary bases (IVa, b) underwent the Mannich reaction in essentially the same way as Va, b. For example, IVa reacted with piperidine hydrochloride and paraformaldehyde to give XXIIIa, XXIVa, and XXV, in similar yields. Since the separation of these compounds was complicated, the yields given in Chart 3 were determined by gas-liquid chromatographic analysis. The structures of all the products obtained by these Mannich reactions are supported by their spectral data and elemental analysis data.

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[14] H. Yamanaka, *Chem. Pharm. Bull.*, **6**, 633 (1958).

Accordingly, in weakly acidic media, the presence of an N-oxide group seems to have little effect on the activity of methyl groups, although such media were experimentally convenient for the isolation of the product. Further experiments were not carried out, because pyrimidine N-oxides are known[15] to be unstable in strongly acidic media.

Experimental[16]

4,6-Distyrylpyrimidine (III)——Benzaldehyde (4.24 g, 0.04 mol) and 10% KOH (3 ml) were added to a solution of 4,6-dimethylpyrimidine 1-oxide (II)[5] (1.24 g, 0.01 mol) in EtOH (3 ml). The mixture was stirred at room temperature for 1 hr. Pale yellow crystals precipitated from the mixture were filtered off, washed with water and dried completely. The precipitates and PCl_3 (6 ml) were dissolved in $CHCl_3$ (50 ml) and the resulting solution was heated under reflux for 1 hr. After removal of the solvent, the residue was made alkaline with 20% K_2CO_3 and extracted with $CHCl_3$. Crystals obtained from the $CHCl_3$ extract were recrystallized from AcOEt to give 1.50 g (53%) of III, mp 166—168°, as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 980. NMR ($CDCl_3$): 7.03 (2H, d, $J=16$ Hz), 7.20—7.77 (11H, m), 7.91 (2H, d, $J=16$ Hz), 9.12 (1H, s). *Anal.* Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.54; H, 5.45; N, 9.48.

4-Phenyl-6-styrylpyrimidine 1-Oxide (VI)——Benzaldehyde (0.57 g, 0.0054 mol) and 10% KOH (2 ml) were added to a solution of 6-methyl-4-phenylpyrimidine 1-oxide (Va)[7] (0.50 g, 0.0027 mol) in EtOH (2 ml). The mixture was stirred at room temperature for 1 hr. The precipitates were filtered off and washed with water. Recrystallization from MeOH gave 0.64 g (87%) of VI, mp 196—197°, as yellow needles. IR$\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1250, 980. NMR ($CDCl_3$): 7.20—7.90 (10H, m) 7.90—8.20 (3H, m), 9.05 (1H, s). *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.59; H, 5.09; N, 10.29.

4-Phenyl-6-styrylpyrimidine (VII)——PCl_3 (1 ml) was added to a solution of VI (0.3 g, 0.0011 mol) in $CHCl_3$ (5 ml) and the mixture was heated under reflux for 1 hr. After removal of the solvent, the residue was made alkaline with 30% K_2CO_3. The solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was recrystallized from ether to give 0.24 g (85%) of VII, mp 129—130° (lit.[17] mp 128—130°), as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 995. NMR ($CDCl_3$): 7.12 (1H, d, $J=16$ Hz), 7.28—8.30 (12H, m), 9.20 (1H, s).

4-Phenethyl-6-phenylpyrimidine (VIII)——Raney Ni (1.0 g, wet weight) was added to a solution of VI (0.5 g, 0.0018 mol) in MeOH (60 ml). The mixture was shaken under an H_2 stream (1 atm) at room temperature. When H_2 absorption ceased (87 ml), the catalyst was removed by filtration. Removal of the solvent from the filtrate afforded crude crystals. Recrystallization from petr. ether gave 0.46 g (97%) of VIII, mp 72—74°, as colorless prisms. NMR ($CDCl_3$): 3.10 (4H, s), 7.25 (5H, s), 7.40—7.70 (4H, m), 7.90—8.20 (2H, m), 9.23 (1H, s). *Anal.* Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20: N, 10.76. Found: C, 83.15; H, 6.42; N, 10.88.

2-Methyl-4-phenylpyrimidine 1-Oxide (IX)——A mixture of *m*-chloroperbenzoic acid (2.1 g, 0.012 mol) and 2-methyl-4-phenylpyrimidine[18] (2.0 g, 0.012 mol) in CH_2Cl_2 (25 ml) was allowed to stand overnight at room temperature. The reaction mixture was washed with 30% K_2CO_3. After removal of the solvent, the residual crystals were recrystallized from benzene to give 0.65 g (30%) of IX, mp 153—154°, as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1280. NMR ($CDCl_3$): 2.77 (3H, s), 7.40—7.70 (4H, m), 7.90—8.20 (2H, m), 8.38 (1H, d, $J=7$ Hz). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.02; H, 5.25; N, 15.08.

From the mother liquor of the recrystallization, 2-methyl-4-phenylpyrimidine was recovered in 30% yield.

Reaction of 2-Methyl-4-phenylpyrimidine 1-Oxide (IX) with Benzaldehyde——Benzaldehyde (0.57 g, 0.0054 mol) and 10% KOH (2 ml) were added to a solution of IX (0.5 g, 0.0027 mol) in EtOH (2 ml). The mixture was stirred at room temperature for 1 hr, then extracted with $CHCl_3$ (30 ml). The extract was washed with 20% HCl. After removal of the solvent, the residue was applied to an alumina column and eluted stepwise with $CHCl_3$ and MeOH. From the $CHCl_3$ fraction, yellow needles of 4-phenyl-2-styrylpyrimidine 1-oxide (X) were obtained. Recrystallization from ether afforded 0.13 g (18%), mp 139—140.5°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1270, 980. NMR ($CDCl_3$): 7.20—7.90 (9H, m), 8.00—8.20 (4H, m), 8.36 (1H, d, $J=7$ Hz). *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.90; H, 5.16; N, 10.30.

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15) T. Kato, H. Yamanaka, and N. Yasuda, *J. Org. Chem.*, 32, 3593 (1967).

16) All melting points are uncorrected. Infrared (IR) spectra measurements were performed with a JASCO IRA-1 spectrometer. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are given as ppm downfield from tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, and b=broad.

17) V.F. Sedova and V.P. Mamaev, *Azotsoderzhashchie Geterotsikly*, **1967**, 349 [*Chem. Abstr.* **70**, 87722*d* (1969)].

18) *a*) F. Wunder, *Diplomarb. Techn. Hochschule Stuttgart*, 1957; *b*) H. Bredereck, F. Effenberger, and H.J. Treiber, *Chem. Ber.*, **96**, 1505 (1963).

From the MeOH fraction, colorless prisms of 2-(2-hydroxy-2-phenylethyl)-4-phenylpyrimidine 1-oxide (XI) were obtained. Recrystallization from AcOEt gave 0.16 g (20%), mp 142.5—143.5°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3240, 1270. NMR ($CDCl_3$): 3.40—3.82 (2H, m), 5.20—5.70 (2H, m, 1H was exchangeable with D_2O), 7.10—7.70 (9H, m), 7.80—8.10 (2H, m), 8.38 (1H, d, $J=7$ Hz). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.19; H, 5.59; N, 9.57.

From the 20% HCl layer, IX was recovered in 12% yield.

Reaction of 2,6-Dimethyl-4-phenylpyrimidine 1-Oxide (XII)[8] **with Benzaldehyde**——A mixture of XII (0.50 g, 0.0025 mol), benzaldehyde (0.53 g, 0.005 mol), and 10% KOH (1 ml) in EtOH (4 ml) was stirred as described above. Pale yellow crystals precipitated from the mixture were filtered off and washed with water. After removing the water completely, the precipitates were dissolved in $CHCl_3$ (20 ml) with PCl_3 (3 ml). The resulting solution was heated under reflux for 1 hr. After removing the solvent under reduced pressure, the residue was made alkaline with 15% K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residue was purified by silica gel column with benzene. Recrystallization from hexane gave 0.29 g (43%) of 2-methyl-4-phenyl-6-styrylpyrimidine (XIII), mp 88—89°, as colorless needles. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 970. NMR ($CDCl_3$): 2.78 (3H, s), 7.05 (1H, d, $J=16$ Hz), 7.25—8.30 (12H, m). *Anal.* Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.90; H, 5.63; N, 10.39.

4-Iodo-2-methyl-6-phenylpyrimidine (XIV)——4-Chloro-2-methyl-6-phenylpyrimidine[19] (20 g, 0.1 mol) was shaken occasionally at room temperature with 57% HI (50 ml) for 2 days. The precipitate was filtered off and dissolved in water. The solution was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with aqueous $NaHSO_3$. After removal of the solvent, the residue was distilled under reduced pressure to give 16 g (55%) of XIV, bp 170° (2 mmHg), mp 73.5—74.5°. NMR ($CDCl_3$): 2.70 (3H, s), 7.30—7.70 (3H, m), 7.90—8.20 (3H, m). *Anal.* Calcd for $C_{11}H_9N_2I$: C, 44.62; H, 3.06; N, 9.46. Found: C, 44.85; H, 3.00; N, 9.23.

2-Methyl-4-phenyl-6-styrylpyrimidine (XIII) from XIV——A mixture of XIV (2.0 g, 0.0067 mol), styrene (3.0 g, 0.032 mol), $Pd(OAc)_2$ (60 mg), triphenylphosphine (120 mg), and trimethylamine (1.0 g) was heated in a sealed tube at 120° for 7 hr under an N_2 atmosphere. The reaction mixture was poured into 30% K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the extract was applied to a silica gel column and eluted stepwise with benzene and ether. The ethereal eluate was concentrated to give a residue. The residue was purified by vacuum distillation and subsequent recrystallization from hexane to give 0.4 g (22%) of XIII, bp 150—160° (1 mmHg), mp 87.5—89°, as colorless needles.

The melting point of a mixture of this compound with the sample prepared above showed no depression, and their IR spectra were also identical.

Reaction of 2,4,6-Trimethylpyrimidine 1-Oxide (XV)[10] **with Benzaldehyde**——Benzaldehyde (1.17 g, 0.011 mol) and 10% KOH (1 ml) were added to a solution of XV (0.5 g, 0.0036 mol) in EtOH (4 ml). The mixture was stirred at room temperature for 1 hr. It was then neutralized with 10% HCl and evaporated to dryness under reduced pressure. The residue was extracted with $CHCl_3$. After concentrating the $CHCl_3$ layer to 20 ml, PCl_3 (2 ml) was added. The solution was heated under reflux for 1 hr, then the solvent was evaporated off under reduced pressure. The residue was poured into 30% K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residue was applied to a silica gel column and eluted stepwise with benzene and ether. The benzene eluate gave colorless needles of 2,4,6-tristyrylpyrimidine (XVII), which were recrystallized from benzene–hexane, mp 197—199° (lit.[20] mp 199—200°). The yield was 0.09 g (5%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 980. NMR ($CDCl_3$): 6.80—7.72 (19H, m), 7.88 (2H, d, $J=16$ Hz), 8.10 (1H, d, $J=16$ H z).

The ethereal eluate gave colorless needles of 2-methyl-4,6-distyrylpyrimidine (XVI) which were recrystallized from AcOEt, mp 176—178°. The yield was 0.21 g (17%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 980. NMR ($CDCl_3$): 2.74 (3H, s), 7.20 (2H, d, $J=16$ Hz), 7.82 (2H, d, $J=16$ Hz), 7.05—7.65 (11H, m). *Anal.* Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.89; H, 6.08; N, 9.63.

2-Methyl-4,6-diphenethylpyrimidine (XVIII)——1) A mixture of XVI (60 mg, 0.0002 mol) and Raney Ni (0.2 g) in MeOH (10 ml) was shaken under an H_2 stream (1 atm) at room temperature. When H_2 absorption ceased (12 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residual oil was distilled under reduced pressure to give 55 mg (90%) of XVIII, bp 143—145° (1 mmHg), mp 50—52°. NMR ($CDCl_3$): 2.70 (3H, s), 2.95 (8H, s), 6.61 (1H, s), 7.20 (10H, s). *Anal.* Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.41; H, 7.26; N, 9.63.

2) From 2-methyl-4,6-diphenylethynylpyrimidine (XX)[11] (0.3 g, 0.001 mol) and Raney Ni (0.3 g), XVIII was obtained by a procedure similar to that used for the reduction of XVI. The yield was 0.28 g (91%).

The melting point of a mixture of the product with the sample prepared above showed no depression, and their IR spectra were also identical.

Mannich Reaction of Va[7]——Paraformaldehyde (6.00 g) and piperidine hydrochloride (7.30 g, 0.06 mol) were added to a solution of Va (5.58 g, 0.03 mol) in abs. EtOH (100 ml). After refluxing the mixture for

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19) CIBA Ltd. *Fr.* 1, 396, 684, *April*, 23, 1965; *Chem. Abstr.*, **63**, 9965e. (1965).

20) H. Kondo and K. Yanai, *J. Pharm. Soc. Japan*, **57**, 747 (1937).

2 hr with stirring, paraformaldehyde (6.00 g) and piperidine hydrochloride (7.30 g, 0.06 mol) were added, and the mixture was heated for an additional 2 hr, then concentrated to give the residue. The residue was made alkaline with 30% K_2CO_3 and extracted with $CHCl_3$. The crude product obtained from the extract was applied to an alumina column and eluted with ether. The first fraction gave colorless prisms of 4-phenyl-6-bis(piperidinomethyl)methylpyrimidine 1-oxide (XXIa), which were recrystallized from benzene–petr. ether, mp 139—141°. The yield was 3.58 g (31%). IR ν_{max}^{KBr} cm^{-1}: 3060, 2940, 2860, 2760, 1250. NMR ($CDCl_3$): 1.20—1.90 (12H, m), 2.20—2.60 (8H, m), 2.76 (4H, d, $J=7$ Hz), 3.85—4.40 (1H, m), 7.50—7.70 (3H, m), 7.77 (1H, s), 8.00—8.30 (2H, m), 9.12 (1H, s). *Anal.* Calcd for $C_{23}H_{32}N_4O$: C, 72.59; H, 8.48; N, 14.73. Found: C, 72.64; H, 8.63; N, 14.68.

From the second fraction, 1.88 g (34%) of Va was recovered.

Mannich Reaction of 4-Ethoxy-6-methylpyrimidine 1-Oxide (Vb)[14]——An ethanolic (100 ml) solution of paraformaldehyde (12.00 g), piperidine hydrochloride (14.60 g, 0.12 mol), and Vb (4.62 g, 0.03 mol) was treated according to the procedure adopted for the Mannich reaction of Va. The crude product was purified by column chromatography (Al_2O_3: benzene–AcOEt). The benzene fraction gave colorless needles of 4-ethoxy-6-bis(piperidinomethyl)methylpyrimidine (XXIb) which were recrystallized from benzene–petr. ether, mp 156—158°. The yield was 4.7 g (45%). IR ν_{max}^{KBr} cm^{-1}: 3040, 2950, 2850, 2780, 1235. NMR (CCl_4): 1.20—1.80 (15H, m), 2.20—2.65 (12H, m), 3.60—4.10 (1H, m), 4.32 (2H, q, $J=7$ Hz), 6.52 (1H, s), 8.42 (1H, s). *Anal.* Calcd for $C_{19}H_{32}N_4O_2$: C, 65.48; H, 9.26; N, 16.08. Found: C, 65.35; H, 9.34; N, 15.89.

From the AcOEt fraction, 0.5 g (11%) of Vb was recovered.

Acid Hydrolysis of XXIa——A solution of XXIa (1.00 g, 0.0026 mol) in 5% H_2SO_4 (20 ml) was heated at 87—90° for 6.5 hr. The reaction temperature must be kept below 90°. The solution was then made alkaline with saturated K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residual crystals were recrystallized from petr. ether to give 0.62 g (83%) of 4-phenyl-6-(2-piperidinoethyl)pyrimidine 1-oxide (XXIIa), mp 74—76°, as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3060, 2940, 2860, 2800, 1250. NMR (CCl_4): 1.40—1.90 (6H, m), 2.30—2.65 (4H, m), 2.65—3.20 (4H, m), 7.40—7.70 (3H, m), 7.86 (1H, s), 7.95—8.20 (2H, m), 8.92 (1H, s). *Anal.* Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 72.34; H, 7.48; N, 14.69.

Acid Hydrolysis of XXIb——A solution of XXIb (1.40 g, 0.004 mol) in 5% H_2SO_4 (20 ml) was heated at 77—79° for 3 hr. The solution was made alkaline with saturated K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residue was placed on an alumina column and eluted stepwise with ether and AcOEt. The AcOEt fraction gave colorless needles of 4-ethoxy-6-(2-piperidinoethyl)pyrimidine 1-oxide (XXIIb), which were recrystallized from petr. ether, mp 115—116°. The yield was 0.32 g (32%). IR ν_{max}^{KBr} cm^{-1}: 3040, 2990, 2940, 2850, 2780, 1240. NMR ($CDCl_3$): 1.20—1.80 (9H, m), 2.20—2.60 (4H, m), 2.60—3.25 (4H, m), 4.35 (2H, q, $J=7$ Hz), 6.80 (1H, s), 8.68 (1H, s). *Anal.* Calcd for $C_{13}H_{21}N_3O_2$: C, 62.12; H, 8.42; N, 16.72. Found: C, 61.93; H, 8.38; N, 16.71.

From the ethereal fraction, XXIb was recovered in 7% yield.

Catalytic Reduction of XXIa——Raney Ni (2.0 g) was added to a solution of XXIa (0.5 g, 0.0013 mol) in abs. MeOH (20 ml) and the resulting mixture was stirred under hydrogen at room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residual oil was kept under reduced pressure (3 mmHg) at *ca.* 50° until it solidified. 4-Phenyl-6-bis(piperidinomethyl)-methylpyrimidine (XXIIIa), mp 63—65°, 0.43 g (90%) was obtained. IR ν_{max}^{neat} cm^{-1}: 3040, 2940, 2845, 2790. NMR ($CDCl_3$): 1.00—1.83 (12H, m), 2.10—2.60 (8H, m), 2.72 (4H, d, $J=7$ Hz), 2.93—3.67 (1H, m), 7.40—7.80 (4H, m), 7.97—8.37 (2H, m), 9.25 (1H, s). *Anal.* Calcd for $C_{23}H_{32}N_4$: C, 75.78; H, 8.85; N, 15.37. Found: C, 75.93; H, 8.96; N, 15.14.

Catalytic Reduction of XXIb——Raney Ni (0.5 g) was added to a solution of XXIb (1.0 g, 0.0029 mol) in MeOH (30 ml) and the resulting mixture was shaken under an H_2 stream (1 atm) at room temperature. When H_2 absorption ceased (68 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residual oil was distilled under reduced pressure to give 0.86 g (90%) of 4-ethoxy-6-bis-(piperidinomethyl)methylpyrimidine (XXIIIb), bp 150—152° (2 mmHg). IR ν_{max}^{neat} cm^{-1}: 2920, 2840, 2780. NMR ($CDCl_3$): 1.20—1.80 (15H, m), 2.10—2.45 (8H, m), 2.60 (4H, d, $J=6$ Hz), 2.75—3.40 (1H, m), 4.40 (2H, q, $J=7$ Hz), 6.56 (1H, s), 8.70 (1H, s). *Anal.* Calcd for $C_{19}H_{32}N_4O$: C, 68.63; H, 9.70; N, 16.85. Found: C, 68.75; H, 9.88; N, 16.80.

Catalytic Reduction of XXIIa——Raney Ni (0.5 g) was added to a solution of XXIIa (0.9 g, 0.0032 mol) in MeOH (20 ml) and the resulting mixture was shaken under an H_2 stream (1 atm) at room temperature. When H_2 absorption ceased (74 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residual oil was distilled under reduced pressure to give 0.75 g (88%) of 4-phenyl-6-(2-piperidinoethyl)pyrimidine (XXIVa), bp 148—150° (4 mmHg). IR ν_{max}^{neat} cm^{-1}: 3060, 2930, 2840, 2800. NMR ($CDCl_3$): 1.40—1.90 (6H, m), 2.30—2.70 (4H, m), 2.70—3.30 (4H, m), 7.40—7.70 (4H, m), 8.00—8.30 (2H, m), 9.18 (1H, s). *Anal.* Calcd for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.07; H, 7.79; N, 15.89.

Catalytic Reduction of XXIIb——Raney Ni (0.5 g) was added to a solution of XXIIb (0.4 g, 0.0016 mol) in MeOH (15 ml) and the resulting mixture was shaken under an H_2 stream (1 atm) at room temperature. When H_2 absorption ceased (43 ml), the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residual oil was distilled under reduced pressure to give 0.34 g (91%) of 4-ethoxy-6-(2-

piperidinoethyl)pyrimidine (XXIVb), bp 114—116° (3 mmHg). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2920, 2840, 2780. NMR ($CDCl_3$): 1.20—1.90 (9H, m), 2.20—2.65 (4H, m), 2.65—3.00 (4H, m), 4.40 (2H, q, $J=7$ Hz), 6.57 (1H, s), 8.66 (1H, s). *Anal.* Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.58; H, 8.98; N, 17.64.

Acid Hydrolysis of XXIIIa——A solution of XXIIIa (0.40 g, 0.0011 mol) in 5% H_2SO_4 (10 ml) was heated at 87—90° for 2 hr. After washing the solution with ether, it was made alkaline with K_2CO_3 and extracted with ether. After removal of the solvent, the residual oil was distilled under reduced pressure to give 0.26 g (85%) of 4-phenyl-6-(1-piperidinomethylvinyl)pyrimidine (XXV), bp 132—134° (3 mmHg). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3060, 2940, 2860, 2800. NMR ($CDCl_3$): 1.30—1.90 (6H, m), 2.30—2.70 (4H, m), 3.45 (2H, s), 5.63 (1H, s), 6.37 (1H, s), 7.40—7.70 (3H, m), 8.00—8.30 (3H, m), 9.20 (1H, s). *Anal.* Calcd for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.14; H, 7.63; N, 15.23.

Acid Hydrolysis of XXIIIb——A solution of XXIIIb (0.50 g, 0.0015 mol) in 5% H_2SO_4 (10 ml) was heated at 77—79° for 3 hr. The solution was made alkaline with K_2CO_3 and extracted with $CHCl_3$. After removal of the solvent, the residual crystals were recrystallized from benzene–petr. ether to give 0.17 g (37%) of 6-bis(piperidinomethyl)methyl-4(3H)-pyrimidinone (XXVI), mp 168—169°. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3020, 2960, 2860, 2800, 1675. NMR ($CDCl_3$): 1.00—1.90 (12H, bs), 1.90—3.30 (13H, m), 6.27 (1H, s), 7.90 (1H, s), 9.90—10.40 (1H, b, exchangeable with D_2O). *Anal.* Calcd for $C_{17}H_{28}N_4O$: C, 67.07; H, 9.27; N, 18.41. Found: C, 67.03; H, 9.16; N, 17.94.

Mannich Reaction of 4-Methyl-6-phenylpyrimidine (IVa)——Paraformaldehyde (1.00 g) and piperidine hydrochloride (1.21 g, 0.01 mol) were added to a solution of IVa (0.85 g, 0.005 mol) in abs. EtOH (20 ml). After refluxing mixture for 2 hr with stirring, paraformaldehyde (1.00 g) and piperidine hydrochloride (1.21 g, 0.01 mol) were added to the mixture. It was heated for an additional 2 hr, and the mixture was then concentrated to give the residue. The residue was made alkaline with 30% K_2CO_3 and extracted with ether. After removal of the solvent, the residual oil was distilled under reduced pressure to give 1.05 g of an oil, bp 150—180° (3 mmHg). Gas-liquid chromatographic analysis (FID; column, 10% SE 30 (1 m); column temperature, 230°; carrier gas (N_2), 60 ml/min) showed the oil to be a mixture of 0.37 g (20%) of XXIIIa, 0.29 g (22%) of XXIVa, and 0.29 g (21%) of XXV.

Mannich Reaction of 4-Ethoxy-6-methylpyrimidine (IVb)——Using the procedure described for IVa, IVb (1.38 g, 0.01 mol) was treated with paraformaldehyde (4.00 g) and piperidine hydrochloride (4.84 g, 0.04 mol) in abs. EtOH (40 ml). The crude product was distilled under reduced pressure to give 0.53 g of an oil, bp 100—160° (3 mmHg). Gas–liquid chromatographic analysis (FID; column, 10% SE 30 (1 m); column temperature, 200°; carrier gas (N_2), 60 ml/min) showed the oil to be a mixture of 0.28 g (8%) of XXIIIb and 0.25 g (11%) of XXIVb.

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