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Studies on Pyrimidine Derivatives. XX.[1] Synthetic Utility of Hydroxymethylpyrimidines and Related Compounds

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The conversion of a hydroxymethyl group at the 2- or 4-position of simple pyrimidines to a chloromethyl, cyanomethyl, ethoxycarbonylmethyl, or formyl group is described. Various pyrimidines having an olefinic side chain were also synthesized *via* the Wittig reagents derived from chloromethylpyrimidines.

Keywords——hydroxymethylation; chloromethylpyrimidine; cyanomethylpyrimidine; pyrimidinecarbaldehyde; Wittig reaction

We have previously reported the preparation of pyrimidine derivatives with a hydroxymethyl group at the 2- or 4-position by means of the homolytic hydroxymethylation of simply alkylated pyrimidines.[3] Since the chemical properties of such pyrimidines have rarely been reported in the literature, our interest was then focussed on the utilization of the hydroxymethylpyrimidines in synthetic purposes. In the present paper, we describe the synthesis of various pyrimidine derivatives containing a carbon side-chain at the above mentioned positions from hydroxymethylpyrimidines.

Firstly, a synthesis starting from 4,6-dimethylpyrimidine-2-methanol (II), which is readily accessible by hydroxymethylation of 4,6-dimethylpyrimidine (I), was investigated. When II was treated with excess phosphoryl chloride in chloroform, 2-chloromethyl-4,6-dimethylpyrimidine (III) was obtained as a colorless solid, though the reaction of II with thionyl chloride failed to give a significant product. Upon heating with sodium cyanide in aqueous ethanol, III was converted into 4,6-dimethylpyrimidine-2-acetonitrile (IV) in satisfactory yield.

The alkylation of IV with benzyl chloride in methanol in the presence of potassium methoxide gave α-benzyl-(4,6-dimethyl-2-pyrimidinyl)acetonitrile (VI) together with a small amount of the dibenzyl derivative (V). In order to prepare VI free of contamination with V, the following reaction sequence was employed. Reaction of IV with benzaldehyde produced α-(4,6-dimethyl-2-pyrimidinyl)cinnamonitrile (VII). Although the spectral data of VII are in accord with its benzylidene structure, the geometrical structure (*E*-form or *Z*-form) with regard to the side-chain double bond has not yet been determined. Catalytic hydrogenation of VII over palladium charcoal afforded VI, as expected.

Hydrogen chloride was passed through a cold ethanolic solution of IV, and the resultant ethyl imidate (X) was hydrolyzed by adding water to give ethyl 4,6-dimethylpyrimidine-2-acetate (XI). However, direct hydrolysis of IV with conc. hydrochloric acid resulted in the formation of 2,4,6-trimethylpyrimidine (IX), probably by decarboxylation of the carboxylic acid intermediate.

Condensation of III with ethyl cyanoacetate under the usual conditions was then examined, and ethyl α-cyano-4,6-dimethylpyrimidine-2-propionate (VIII) was obtained, as expected.

1) Part XIX: T. Sakamoto, H. Yamanaka, A. Shiozawa, W. Tanaka, and H. Miyazaki, *Chem. Pharm. Bull.*, **28**, 1832 (1980).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Sakamoto, K. Kanno, T. Ono, and H. Yamanaka, *Heterocycles*, **6**, 525 (1977).

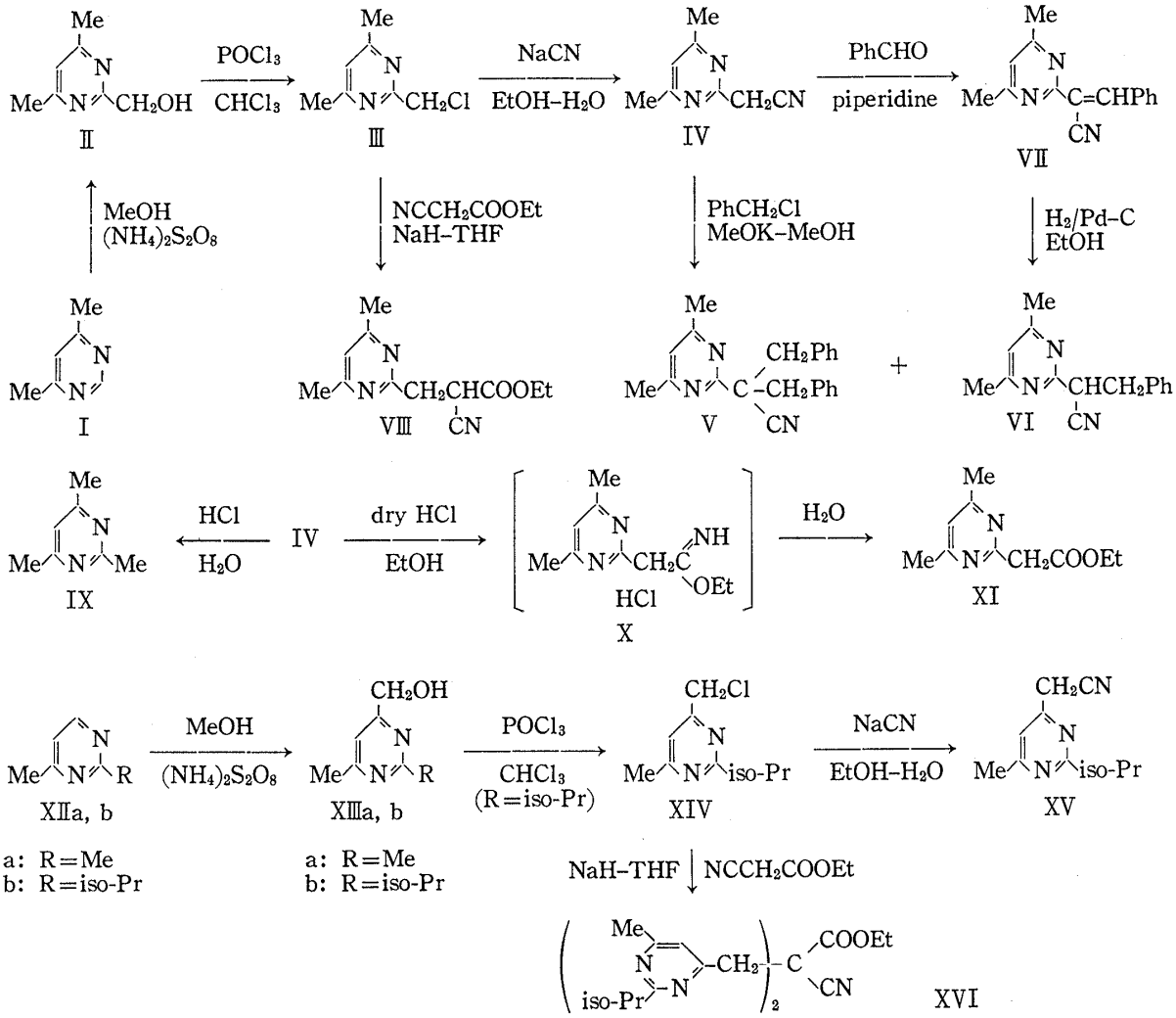

Chart 1

Because of difficulties encountered in transforming 2,6-dimethylpyrimidine-4-methanol (XIIIa) into the 4-chloromethyl derivative, 2-isopropyl-6-methylpyrimidine was employed as starting material for the 4-substituted series. Thus, 2-isopropyl-6-methylpyrimidine-4-methanol (XIIIb) was treated with phosphoryl chloride in chloroform, as for the 2-hydroxymethylpyrimidine, to give the corresponding 4-chloromethylpyrimidine (XIV) in considerable yield. While the cyanation of XIV readily afforded 2-isopropyl-6-methylpyrimidine-4-acetonitrile (XV), the reaction of XIV with ethyl cyanoacetate appeared to be less straightforward. Elemental analysis of the product (XVI) established the molecular fromula to be $C_{23}H_{31}N_5O_2$, and the nuclear magnetic resonance (NMR) spectrum showed the presence of two pyrimidine moieties per molecule. Accordingly, the structure of this product is considered to be ethyl α,α-bis(2-isopropyl-6-methyl-4-pyrimidinylmethyl)cyanoacetate (XVI). The compound corresponding to VIII was not isolated from the reaction mixture.

Secondly, as few papers have been published on the preparation of pyrimidine aldehydes,[4] the conversion of these hydroxymethylpyrimidines into aldehydes was investigated. Thus, when II was oxidized with a limited amount of selenium dioxide in warm dioxane, 4,6-dimethylpyrimidine-2-carbaldehyde (XX) was obtained in satisfactory yield. The presence of an alde-

4) *a*) H. Bredereck, R. Sell, and F. Effenberger, *Chem. Ber.*, **97**, 3407 (1964); *b*) J.L. Wong, M.S. Brown, and H. Rapoport, *J. Org. Chem.*, **30**, 2398 (1965); *c*) E.L. Stogryn, *J. Heterocycl. Chem.*, **11**, 251 (1974); *d*) V.P. Mamaev and E.A. Gracheva, *Khim. Getertsikl. Soedin*, **1969**, 1086 [*C.A.*, **72**, 121474*c* (1970)].

hyde group in XX was confirmed by the NMR spectrum, a positive Fehling's test, and by oxime formation through the usual procedure. Similarly, XIII was oxidized by the same reagent to give 2-isopropyl-6-methylpyrimidine-4-carbaldehyde (XXI).

These aldehydes are stable enough for storage under a ordinary atmosphere.

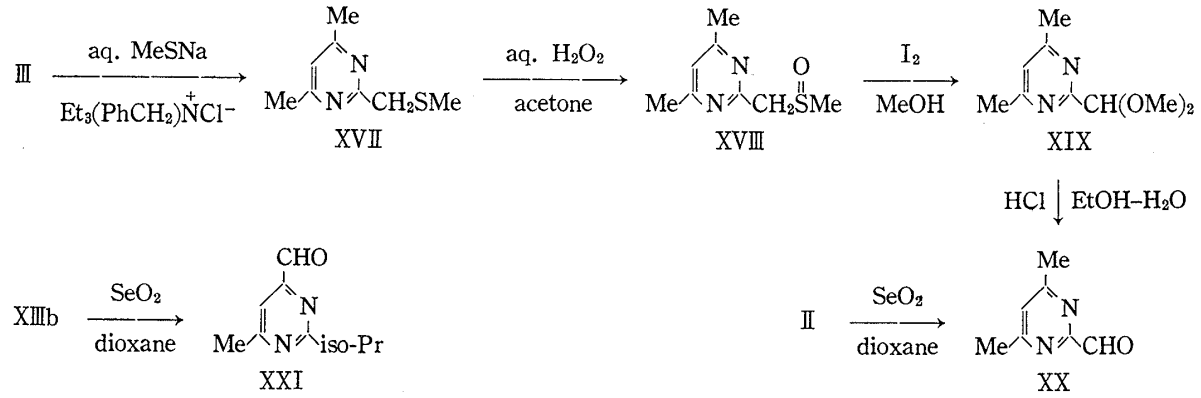

Chart 2

In addition to the above experiments, an alternative preparation of XX through the Pummerer rearrangement was investigated. Namely, III was allowed to stand overnight in a methanolic solution of sodium methanethiolate to give 4,6-dimethyl-2-methylthiomethylpyrimidine (XVII). Controlled oxidation of XVII with hydrogen peroxide afforded the corresponding sulfoxide (XVIII) without formation of any other oxidized product. By means of the usual Pummerer rearrangement procedure, the sulfoxide (XVIII) was treated with

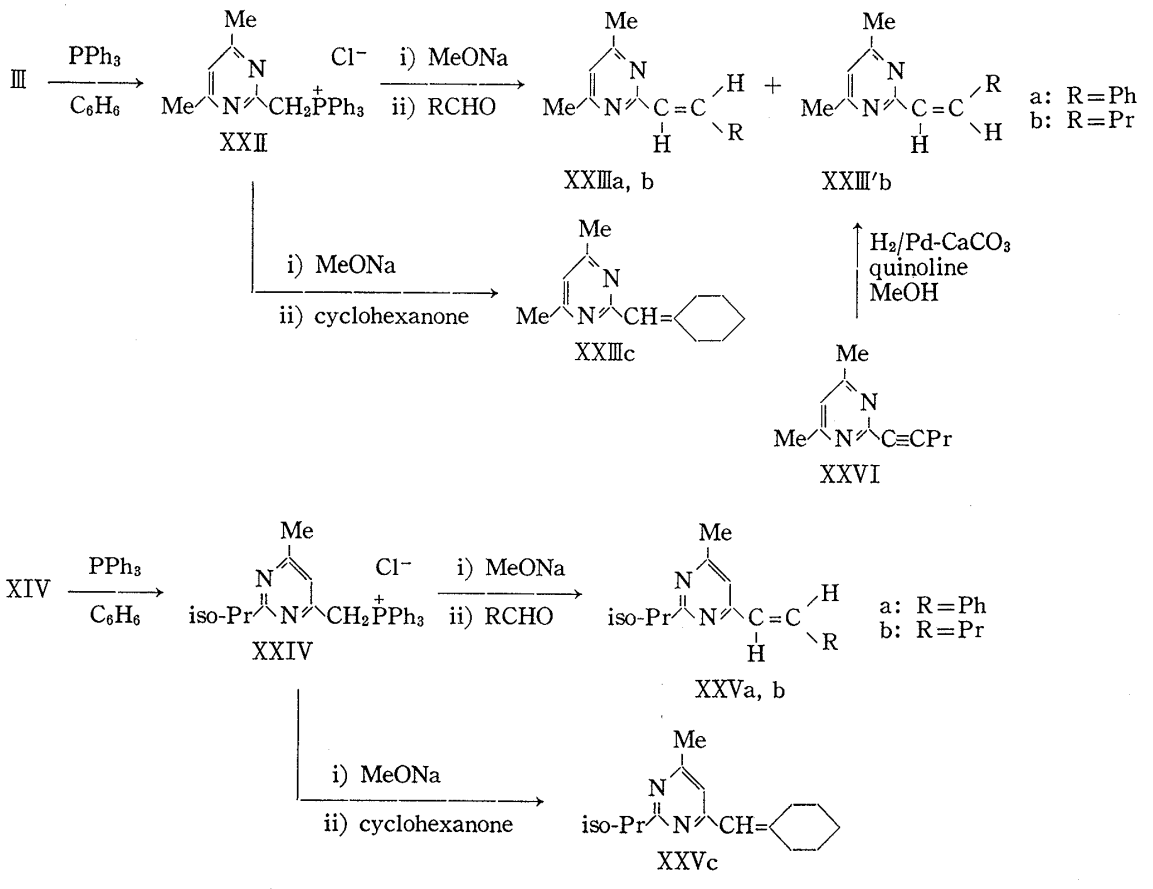

Chart 3

iodine in methanol, and 2-dimethoxymethyl-4,6-dimethylpyrimidine (XIX) was obtained, as expected. Transformation of the acetal group to an aldehyde group was then carried out in the usual manner to give the aldehyde (XX), which was identical with the sample prepared previously. Although this preparation of the aldehyde seems to be rather complicated, the yield in each step was satisfactory.

Finally, preparation of the Wittig reagents from the chloromethylpyrimidines (III, XIV), and the reactions thereof, were examined. For example, III readily reacted with triphenylphosphine to give the corresponding phosphonium salt (XXII). Treatment with sodium methoxide and subsequent reaction with benzaldehyde converted XXII into 4,6-dimethyl-2-*trans*-styrylpyrimidine (XXIIIa). Various pyrimidine derivatives having an olefinic side-chain (XXIIIb, c and XXVa, b, c) were obtained by the same method. In addition to the above results, the reaction of XXII with *n*-butyraldehyde appeared to be noteworthy. Namely, contamination of the *trans* isomer (XXIIIb) with the *cis* isomer (XXIII'b) (62: 38) was confirmed by comparison of the gas chromatogram of the product with that of an authentic sample of XXIII'b, prepared from 4,6-dimethyl-2-(1-pentynyl)pyrimidine (XXVI).

In conclusion, on the basis of the above results, hydroxymethyl- and chloromethylpyrimidines appear to be potentially useful intermediates for the synthesis of various pyrimidine derivatives.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were obtained at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed by ppm downfield from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

4,6-Dimethylpyrimidine-2-methanol (II)——A mixture of 4,6-dimethylpyrimidine (I) (1.08 g, 0.01 mol), H_2O (9 ml), MeOH (18 ml), conc. H_2SO_4 (0.7 ml), and $(NH_4)_2S_2O_8$ (4.56 g, 0.02 mol) was refluxed for 5 hr. The mixture was concentrated under reduced pressure and the residue was diluted with H_2O, made alkaline with K_2CO_3, and then extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless solid, bp 121° (22 mmHg), mp 87—88°. Lit.[5] mp 89°. Yield 1.3 g (93%).

2,6-Dimethylpyrimidine-4-methanol (XIIIa)——A mixture of 2,6-dimethylpyrimidine (XIIa) (2.16 g, 0.02 mol), H_2O (16 ml), MeOH (36 ml), conc. H_2SO_4 (1.4 ml), and $(NH_4)_2S_2O_8$ (9.12 g, 0.04 mol) was refluxed for 2 hr. The solvent was removed under reduced pressure and the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product was sublimed under reduced pressure to give pale yellow needles, mp 108.5—110°. Lit.[5] mp 109—110°. Yield 1.5 g (54%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. NMR ($CDCl_3$): 2.50 (3H, s), 2.70 (3H, s), 4.00 (1H, broad s), 4.70 (2H, s), 7.10 (1H, s).

2-Isopropyl-6-methylpyrimidine-4-methanol (XIIIb)——A mixture of 2-isopropyl-6-methylpyrimidine (XIIb) (5.4 g, 0.04 mol), H_2O (30 ml), MeOH (70 ml), conc. H_2SO_4 (3 ml), and $(NH_4)_2S_2O_8$ (9 g, 0.04 mol) was refluxed for 1 hr. $(NH_4)_2S_2O_8$ (9 g, 0.04 mol) was added to the mixture, and the whole was refluxed for a further 3 hr. After removal of the solvent under reduced pressure, the residue was diluted with H_2O, made alkaline with K_2CO_3, and then extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a pale yellow liquid, bp 135—138° (20 mmHg). Yield 3.3 g (53%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400. NMR ($CDCl_3$): 1.30 (6H, d, J=7 Hz), 2.48 (3H, s), 2.80—3.50 (1H, m), 3.90—4.50 (1H, broad), 4.69 (2H, s), 7.02 (1H, s). *Anal.* Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.45; H, 8.86; N, 17.17.

2-Chloromethyl-4,6-dimethylpyrimidine (III)——A mixture of II (3.8 g, 0.027 mol), $POCl_3$ (15 ml), and $CHCl_3$ (15 ml) was refluxed for 3 hr. The mixture was concentrated under reduced pressure and the residue was poured onto ice, made alkaline with K_2CO_3, and then extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless solid, bp 125—128° (25 mmHg), mp 65—65.5°. Yield 3.9 g (90%). NMR ($CDCl_3$): 2.50 (6H, s), 4.62 (2H, s), 6.95 (1H, s). *Anal.* Calcd for $C_7H_9ClN_2$: C, 53.67; H, 5.80; Cl, 22.64; N, 17.89. Found: C, 53.86; H, 6.00; Cl, 22.84; N, 17.85.

4-Chloromethyl-2-isopropyl-6-methylpyrimidine (XIV)——A mixture of XIIIb (5.4 g, 0.033 mol), $POCl_3$ (15 ml), and $CHCl_3$ (15 ml) was refluxed for 3 hr. The mixture was concentrated under reduced pressure and the residue was poured onto ice, made alkaline with K_2CO_3, and then extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 118—120° (20 mmHg). Yield 5 g (84%). NMR ($CDCl_3$): 1.30 (6H, d, J=7 Hz), 2.50 (3H, s), 2.80—3.50 (1H, m), 4.52 (2H, s), 7.20 (1H, s).

5) D.J. Brown and P. Waring, *Aust. J. Chem.*, **27**, 2251 (1951).

Anal. Calcd for $C_9H_{13}ClN_2$: C, 58.69; H, 7.06; Cl, 19.02; N, 15.22. Found: C, 58.83; H, 7.36; Cl, 18.44; N, 15.41.

4,6-Dimethylpyrimidine-2-acetonitrile (IV)——A mixture of III (5 g, 0.032 mol), NaCN (6.5 g, 0.133 mol), H_2O (3.5 ml), and EtOH (75 ml) was refluxed for 1.5 hr with stirring. After removal of the solvent under reduced pressure, the residue was diluted with H_2O and extracted with ether. The crude product was distilled under reduced pressure to give a colorless solid, bp 102° (3 mmHg), mp 78—79°. Yield 5 g (84%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240. NMR ($CDCl_3$): 2.46 (6H, s), 3.96 (2H, s), 6.95 (1H, s). *Anal.* Calcd for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.20; H, 6.15; N, 29.01.

2-Isopropyl-6-methylpyrimidine-4-acetonitrile (XV)——A mixture of XIV (1 g, 0.005 mol), NaCN (2.1 g, 0.05 mol), H_2O (1 ml), and EtOH (20 ml) was refluxed for 1.5 hr. After removal of the solvent under reduced pressure, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a pale yellow liquid, bp 120—123° (20 mmHg). Yield 0.45 g (48%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240. NMR ($CDCl_3$): 1.30 (6H, d, $J=7$ Hz), 2.50 (3H, s), 2.90—3.50 (1H, m), 3.85 (2H, s), 7.20 (1H, s). *Anal.* Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 67.98; H, 7.84; N, 23.46.

Reaction of IV with Benzyl Chloride——Compound IV (0.9 g, 0.006 mol) and benzyl chloride (0.84 g, 0.007 mol) were added to a solution of KOMe prepared from metallic potassium (0.24 g, 0.006 g atom) and abs. MeOH (4 ml), and the mixture was refluxed for 45 min. After removal of the MeOH under reduced pressure, the residue was made alkaline with 3 N NaOH and extracted with $CHCl_3$. The crude product was purified by Al_2O_3 column chromatography with $CHCl_3$ as an eluant. The first fraction gave colorless scales (VI), mp 119—120°, which were recrystallized from EtOH. Yield. 0.94 g (65%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240. NMR ($CDCl_3$): 2.48 (6H, s), 3.28—3.45 (2H, m), 4.12—4.42 (1H, m), 6.98 (1H, s), 7.32 (5H, s). *Anal.* Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.64; H, 6.22; N, 17.85. The second fraction gave colorless needles (V), mp 138—139°, which were recrystallized from EtOH. Yield 0.11 g (5%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240. NMR ($CDCl_3$): 2.40 (6H, s), 3.10—3.48 (4H, m), 6.81 (1H, s), 7.14 (10H, s). *Anal.* Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.84. Found: C, 80.30; H, 6.60; N, 12.94.

α-(4,6-Dimethyl-2-pyrimidinyl)cinnamonitrile (VII)——A mixture of IV (1.0 g, 0.0068 mol), benzaldehyde (0.72 g, 0.067 mol), piperidine (a few drops), and EtOH (3 ml) was heated at 50° for 2 hr with stirring. The solution was then cooled, and the resulting precipitate was filtered and recrystallized from EtOH to give colorless needles, mp 130—131°. Yield 1.0 g (63%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220. NMR ($CDCl_3$): 2.50 (6H, s), 6.95 (1H, s), 7.40—7.60 (3H, m), 7.90—8.15 (2H, m), 8.65 (1H, s). *Anal.* Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.18; H, 5.60; N, 18.08.

α-(4,6-Dimethyl-2-pyrimidinyl)-β-phenylpropionitrile (VI)——Compound VII (0.5 g, 0.002 mol) was hydrogenated in EtOH (20 ml) over 10% palladium charcoal (2 g) at ordinary pressure. After filtration of the catalyst, the mixture was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give colorless scales, mp 119—120°. Yield 0.46 g (91%).

Ethyl 4,6-Dimethylpyrimidine-2-acetate (XI)——Gaseous HCl was introduced into a solution of IV (1.3 g, 0.09 mol) in abs. EtOH (20 ml) with ice cooling for 30 min. After removal of the EtOH under reduced pressure, the residue was diluted with H_2O. The mixture was stirred at room temperature for 1 hr, made alkaline with K_2CO_3, and extracted with ether. The crude product was distilled under reduced pressure to give a colorless solid, bp 95—96° (5 mmHg), mp 65—66°. Yield 1.4 g (82%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750. NMR ($CDCl_3$): 1.26 (3H, t, $J=7$ Hz), 2.46 (6H, s), 3.93 (2H, s), 4.20 (2H, q, $J=7$ Hz), 6.92 (1H, s). *Anal.* Calcd for $C_9H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.85; H, 7.29; N, 14.60.

Hydrolysis of IV——A mixture of IV (2.7 g, 0.018 mol), EtOH (20 ml), and conc. HCl (50 ml) was refluxed for 8 hr. After removal of the solvent, the residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid (IX), bp 82° (33 mmHg). Yield 1.3 g (59%). This compound was identical with 2,4,6-trimethylpyrimidine (IX).

Ethyl α-Cyano-4,6-dimethylpyrimidine-2-propionate (VIII)——Ethyl cyanoacetate (1.39 g, 0.012 mol) was added dropwise to a stirred and ice-cooled suspension of 50% NaH (0.58 g, 0.012 mol) in dry THF (20 ml) and the mixture was stirred for 0.5 hr. A solution of III (1.56 g, 0.01 mol) in dry THF (10 ml) was added to this mixture, and the whole was refluxed for 3 hr. After removal of the THF under reduced pressure at room temperature, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with AcOEt as an eluant. Distillation of the crude product under reduced pressure gave a pale yellow liquid, bp 140—145° (2 mmHg). Yield 0.4 g (17%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1750. NMR ($CDCl_3$): 1.45 (3H, t, $J=7$ Hz), 2.45 (6H, s), 3.60 (2H, d, $J=7$ Hz), 4.15—4.60 (3H, m), 7.00 (1H, s). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.44; N, 18.03. Found: C, 61.89; H, 6.63; N, 18.21.

Ethyl α,α-Bis(2-Isopropyl-6-methyl-4-pyrimidinylmethyl)cyanoacetate (XVI)——Ethyl cyanoacetate (1.36 g, 0.012 mol) was added dropwise to a stirred and ice-cooled suspension of 50% NaH (0.58 g, 0.012 mol) in dry THF (20 ml) and the mixture was stirred for 0.5 hr. A solution of XIV (1.84 g, 0.01 mol) in dry THF (10 ml) was added dropwise to this mixture, and the whole was refluxed for 3 hr. After removal of the THF under reduced pressure at room temperature, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with AcOEt as an eluant. Recrystallization

from hexane gave colorless needles, mp 98—99.5°. Yield 0.5 g (24%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2350, 1750. NMR ($CDCl_3$): 1.25—1.50 (15H, m), 2.50 (6H, s), 2.90—3.40 (2H, m), 3.45 (2H, s), 3.50 (2H, s), 4.30 (2H, q, J= 7 Hz), 7.00 (2H, s). *Anal.* Calcd for $C_{23}H_{31}N_5O_5$: C, 67.45; H, 7.63; N, 17.10. Found: C, 67.82; H, 7.83; N, 17.26.

4,6-Dimethylpyrimidine-2-carbaldehyde (XX)——A mixture of II (1.38 g, 0.01 mol), SeO_2 (0.6 g, 0.005 mol), and dry dioxane (20 ml) was refluxed for 1 hr. The resulting selenium was filtered off, and the dioxane was removed from the filtrate under reduced pressure. The residue was diluted with H_2O and the mixture extracted with $CHCl_3$. The crude product was recrystallized from hexane to give colorless needles, mp 88—89°. Lit.[4d] mp 89—90°. Yield 0.66 g (49%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740. NMR ($CDCl_3$): 2.62 (6H, s), 7.25 (1H, s), 10.08 (1H, s).

2-Isopropyl-6-methylpyrimidine-4-carbaldehyde (XXI)——A mixture of XIIIb (1 g, 0.006 mol), SeO_2 (0.33 g, 0.003 mol), and dry dioxane (15 ml) was stirred at room temperature for 3 hr. The resulting selenium was filtered off, and the dioxane was removed from the filtrate under reduced pressure. The residue was diluted with H_2O and the mixture extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a pale yellow liquid, bp 100—102° (20 mmHg). Yield 0.55 g (55%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. NMR ($CDCl_3$): 1.40 (6H, d, J=7 Hz), 2.63 (3H, s), 2.80—3.50 (1H, m), 7.52 (1H, s), 10.01 (1H, s). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.85; H, 7.50; N, 16.92.

4,6-Dimethyl-2-pyrimidinylmethyl Methyl Sulfide (XVII)——Benzyltriethylammonium chloride (0.8 g) and 15% aq. MeSNa (46.7 ml) were added to a solution of III (7.83 g, 0.05 mol) in C_6H_6 (40 ml). After being stirred at 70° for 22 hr, the mixture was extracted with C_6H_6. Removal of the C_6H_6 under reduced pressure gave a colorless liquid, bp 111° (4 mmHg). Yield 7.32 g (78%). NMR ($CDCl_3$): 2.18 (3H, s), 2.47 (6H, s), 3.84 (2H, s), 6.93 (1H, s). *Anal.* Calcd for $C_8H_{12}N_2S$: C, 57.10; H, 7.14; N, 16.65; S, 19.06. Found: C, 57.32; H, 7.23; N, 16.66; S, 19.03.

4,6-Dimethyl-2-pyrimidinylmethyl Methyl Sulfoxide (XVIII)——Aqueous (30%) H_2O_2 (4.53 g, 0.04 mol) was added to a solution of XVII/(6.73 g, 0.04 mol) in acetone (50 ml) and the mixture was allowed to stand at room temperature for 4 days. Aq. (30%) H_2O_2 (0.34 g, 0.01 mol) was added, and the whole was then allowed to stand for a further 3 days at room temperature. Water was added and the mixture was concentrated under reduced pressure, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with acetone as an eluant. Recrystallization from ether gave colorless prisms, mp 73—75.5°. Yield 6.36 g (86%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1060. NMR ($CDCl_3$): 2.45 (6H, s), 2.71 (3H, s), 4.27 (2H, broad s), 6.98 (1H, s). *Anal.* Calcd for $C_8H_{12}N_2OS$: C, 52.15; H, 6.56; N, 15.20; S, 17.40. Found: C, 52.05; H, 6.64; N, 15.03; S, 17.70.

2-Dimethoxymethyl-4,6-dimethylpyrimidine (XIX)——A mixture of XVIII (2.76 g, 0.015 mol), I_2 (7.61 g, 0.03 mol), and MeOH (50 ml) was refluxed for 6 hr. After neutralization with aq. K_2CO_3, the mixture was evaporated to dryness under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. Na_2SO_3 and dried over Na_2SO_4. The crude product was distilled under reduced pressure to give a pale yellow liquid, bp 118—120° (7 mmHg). Yield 2.22 g (81%). NMR ($CDCl_3$): 2.50 (6H, s), 3.47 (6H, s), 5.39 (1H, s), 7.03 (1H, s). *Anal.* Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.20; H, 8.06; N, 15.40.

Hydrolysis of XIX——Conc. HCl (0.12 ml) was added to a solution of XIX (1.46 g, 0.008 mol) in 50% EtOH (12 ml) and the mixture was refluxed for 1 hr. After removal of the solvent under reduced pressure, the residue was made alkaline with K_2CO_3 and the mixture was extracted with $CHCl_3$. The $CHCl_3$ was removed under reduced pressure and the residue was purified by SiO_2 column chromatography with ether: petr. ether (1: 1) as an eluant. Recrystallization from ether–petr. ether gave colorless needles, mp 88—89°. This compound was identical with the sample prepared previously.

(4,6-Dimethyl-2-pyrimidinylmethyl)triphenylphosphonium Chloride (XXII)——A mixture of III (4.70 g, 0.03 mol) and triphenylphosphine (7.87 g, 0.03 mol) in dry C_6H_6 (40 ml) was refluxed for 40 hr with stirring. The resulting precipitate was filtered and washed with ether. Yield 9.9 g (79%).

(2-Isopropyl-6-methyl-4-pyrimidinylmethyl)triphenylphosphonium Chloride (XXIV)——A mixture of XIV (0.9 g, 0.05 mol) and triphenylphosphine (1.3 g, 0.005 mol) in dry C_6H_6 (15 ml) was refluxed for 8 hr with stirring. The resulting precipitate was filtered off and washed with ether. Yield 1.8 g (83%).

General Procedure for the Wittig Reaction of Pyrimidinylmethyltriphenylphosphonium Chloride (XXII and XXIV)——A solution of sodium methoxide, prepared from metallic sodium (92 mg, 0.004 g atom) and abs. MeOH (10 ml), was added to an ice-cooled suspension of pyrimidinylmethyltriphenylphosphonium chloride (0.004 mol) in dry C_6H_6 (10 ml) with stirring. The mixture was stirred for 30 min at room temperature, and then a solutions of aldehyde (0.005 mol) in dry C_6H_6 (10 ml) was added. After being stirred for 8 hr at room temperature, the mixture was extracted with 3 N HCl. The aqueous solution was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The crude product was purified by recrystallization or distillation.

4,6-Dimethyl-2-*trans*-styrylpyrimidine (XXIIIa)——The crude product was obtained from XXII (1.68 g, 0.004 mol) and benzaldehyde (0.53 g, 0.005 mol) according to the general procedure. Recrystallization from petr. ether gave colorless prisms, mp 47—50°. Yield 0.3 g (40%). NMR ($CDCl_3$): 2.45 (6H, s), 6.81 (1H, s), 7.00—7.75 (6H, m), 8.00 (1H, d, J=16 Hz). *Anal.* Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.12; H, 6.68; N, 13.07.

4,6-Dimethyl-2-(1-pentenyl)pyrimidine (XXIIIb)——The crude product was obtained from XXII (1.68 g, 0.004 mol) and *n*-butyraldehyde (0.36 g, 0.005 mol) according to the general procedure. Distillation under reduced pressure gave a colorless liquid, bp 90—95° (3 mmHg). Yield 0.35 g (49%). NMR ($CDCl_3$): 0.98 (3H, t, $J=7$ Hz), 1.20—1.80 (2H, m), 2.00—2.60 (2H, m), 2.45 (6H, s), 6.40—7.50 (3H, m). *Anal.* Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.69; H, 9.29; N, 15.63.

2-Cyclohexylidenemethyl-4,6-dimethylpyrimidine (XXIIIc)——The crude product was obtained from XXII (1.68 g, 0.004 mol) and cyclohexanone (0.50 g, 0.005 mol) according to the general procedure. Distillation under reduced pressure gave a colorless liquid, bp 110—114° (2 mmHg). Yield 0.40 g (49%). NMR ($CDCl_3$): 1.15—2.00 (6H, m), 2.20—3.20 (4H, m), 2.45 (6H, s), 6.35 (1H, s), 6.80 (1H, s). *Anal.* Calcd for $C_{13}H_{18}N_2 \cdot 1/2H_2O$: C, 73.89; H, 9.06; N, 13.26. Found: C, 73.94; H, 8.74; N, 13.28.

2-Isopropyl-6-methyl-2-*trans*-styrylpyrimidine (XXVa)——The crude product was obtained from XXIV (1.8 g, 0.004 mol) and benzaldehyde (0.53 g, 0.005 mol) according to the general procedure. Distillation under reduced pressure gave a colorless liquid, bp 140—145° (2 mmHg). Yield 0.45 g (47%). NMR ($CDCl_3$): 1.40 (6H, d, $J=7$ Hz), 2.50 (3H, s), 2.80—3.50 (1H, m), 7.04 (1H, d, $J=16$ Hz), 7.00 (1H, s), 7.30—7.70 (5H, m), 7.90 (1H, d, $J=16$ Hz). *Anal.* Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.76; H, 7.78; N, 11.60.

2-Isopropyl-6-methyl-4-(1-*trans*-pentenyl)pyrimidine (XXVb)——The crude product was obtained from XXIV (1.80 g, 0.004 mol) and *n*-butylaldehyde (0.36 g, 0.005 mol) according to the general procedure. Distillation under reduced pressure gave a colorless liquid, bp 90—94° (2 mmHg). Yield 0.50 g (72%). NMR ($CDCl_3$): 1.00 (3H, t, $J=6$ Hz), 1.35 (6H, d, $J=7$ Hz), 1.40—2.00 (2H, m), 2.00—2.60 (2H, m), 2.45 (3H, s), 2.80—3.50 (1H, m), 6.40 (1H, d, $J=17$ Hz), 6.75—7.50 (1H, m), 6.90 (1H, s). *Anal.* Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.78; N, 13.71. Found: C, 76.49; H, 10.08; N, 13.62.

4-Cyclohexylidenemethyl-2-isopropyl-6-methylpyrimidine (XXVc)——The crude product was obtained from XXIV (1.80 g, 0.004 mol) and cyclohexanone (0.50 g, 0.005 mol) according to the general procedure. Distillation under reduced pressure gave a colorless liquid, bp 110—113° (2 mmHg). Yield 0.2 g (17%). NMR ($CDCl_3$): 1.35 (6H, d, $J=7$ Hz), 1.50—1.80 (6H, broad s), 2.10—2.40 (2H, broad), 2.43 (3H, s), 2.70—3.00 (2H, broad), 3.00—3.40 (1H, m), 6.13 (1H, s), 6.76 (1H, s). *Anal.* Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.12. Found: C, 78.35; H, 9.62; N, 11.97.

4,6-Dimethyl-2-(1-pentynyl)pyrimidine (XXVI)——A mixture of 4,6-dimethyl-2-iodopyrimidine (2.34 g, 0.01 mol), 1-pentyne (0.75 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (0.07 g, 0.001 mol), CuI (0.0038 g, 0.002 mol), and triethylamine (60 ml) was stirred for 6 hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 108—110° (3 mmHg). Yield 1.3 g (75%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240. NMR ($CDCl_3$): 1.08 (3H, t, $J=7$ Hz), 1.40—2.00 (2H, m), 2.30—2.65 (2H, m), 2.45 (6H, s), 6.95 (1H, s). *Anal.* Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.09; H, 7.61; N, 15.54.

4,6-Dimethyl-2-(1-*cis*-pentenyl)pyrimidine (XXIII'b)——Compound XXVI (1 g, 0.006 mol) was hydrogenated over Pd-$CaCO_3$ (0.1 g) in EtOH (15 ml) containing quinoline (0.1 g) at ordinary pressure. The mixture was shaken with hydrogen until one molecular equivalent had been absorbed. The Pd-$CaCO_3$ was removed by filtration and the EtOH was removed by evaporation under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was distilled under reduced pressure to give a colorless liquid, bp 118—123° (20 mmHg). Yield 0.9 g (89%). NMR ($CDCl_3$): 1.00 (3H, t, $J=7$ Hz), 1.20—1.80 (2H, m), 2.30—3.00 (2H, m), 2.45 (6H, s), 5.90—6.40 (1H, m), 6.55 (1H, d, $J=12$ Hz), 6.80 (1H, s). *Anal.* Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.97; H, 9.19; N, 15.70.

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