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Studies on Pyrimidine Derivatives. XXI.[1] Nucleophilic Substitution of 4-Chloropyrimidines and Related Compounds with Carbanions

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The reaction of 4-chloro-2,6-dimethylpyrimidine 1-oxide (II) with ethyl cyanoacetate and malononitrile under basic conditions gave the expected condensation products, while the reaction of II with methylene ketones failed. On the other hand, 2,6-dimethyl-4-phenylsulfonylpyrimidine (X) smoothly reacted not only with the above active methyl compounds but also with methylene ketones such as acetone, acetophenone and cyclohexanone.

Keywords——nucleophilic substitution; active methylene compounds; 4-phenylsulfonylpyrimidines; 4-acylmethylpyrimidines; aromatic amine N-oxides; peracid oxidation

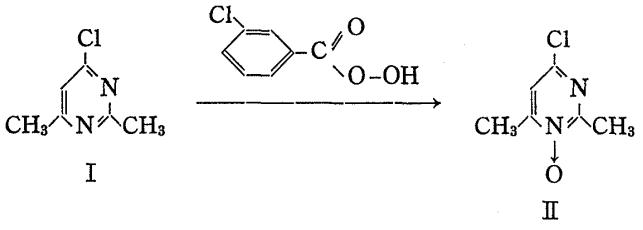
Although 4-chloropyrimidines are useful as synthetic intermediates, good results are not always obtained in the reaction of such pyrimidines with various kinds of active methylene compounds.[2-5] For example, Elderfield *et al.*[6] reported the condensation of 4-chloro-2,6-dimethylpyrimidine (I) with ethyl cyanoacetate to give ethyl α-(2,6-dimethyl-4-pyrimidinyl)-cyanoacetate (Va) in a yield of less than 30%. In the present paper, we describe some methods for the preparation of pyrimidine derivatives containing a carbon-functional group from the title compounds.

First, nucleophilic substitution of 4-chloro-2,6-dimethylpyrimidine 1-oxide (II) with active methylene compounds was investigated, because the introduction of an N-oxide group is known to improve the relative reactivity of a chloro substituent at the active position in six-membered N-heteroaromatics. Namely, Okamoto *et al.*[7] estimated the rate constant of 4-chloroquinoline 1-oxide with piperidine to be about forty times greater than that of 4-chloroquinoline under the same reaction conditions. Similarly, Katritzky *et al.*[8] reported that 2-chloro-4,6-dimethylpyrimidine 1-oxide reacted with imidazole itself to give the 2-(1-imidazolyl)pyrimidine N-oxide in 71% yield.

The oxidation of I with monopermaleic acid has already been reported to give II in 34% yield,[9] but the use of *m*-chloroperbenzoic acid instead of monopermaleic acid gave a rather better result (65%).

When a mixture of equimolar amounts of I and II were allowed to stand with a limited amount of sodium ethoxide in ethanol at room temperature, the ethoxide ion reacted predominantly with the N-oxide (II) to give 4-ethoxy-2,6-dimethylpyrimidine 1-oxide (IV), and the conversion of I into 4-ethoxy-2,6-dimethylpyrimidine (III) was poor. This suggests that the 4-chloro group in the pyrimidine ring, like that in the quinoline ring, was activated by the introduction of an N-oxide group.

Based on the above observations, the reactions of II with ethyl cyanoacetate and malononitrile were investigated in comparison with the reactions of I with the same reagents. As shown in Chart 2 and Table I, the reactions of II under appropriate conditions gave the desired substituted pyrimidine N-oxides (VIa, b) in satisfactory yields. In contrast the reactions of I with ethyl cyanoacetate and malononitrile afforded the corresponding products (Va, b) in yields not exceeding those of VIa, b. The N-oxides were readily deoxygenated with phosphorus trichloride to give Va, b, and the melting point of Va is coincident with the value reported in the literature.[6] However, the synthesis of such pyrimidine derivatives from II



I II

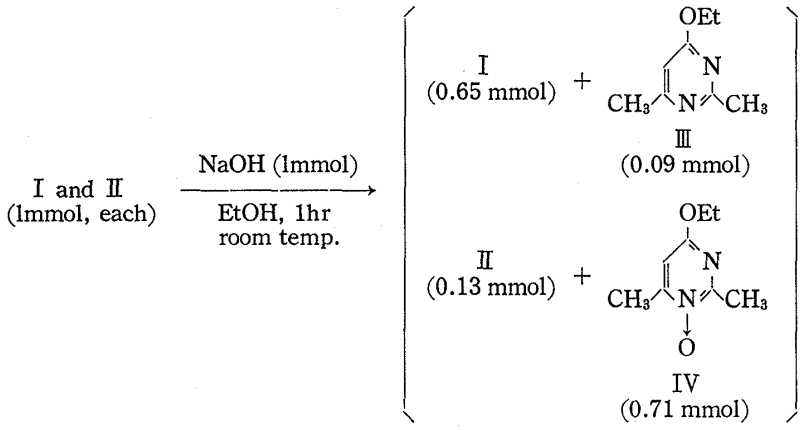
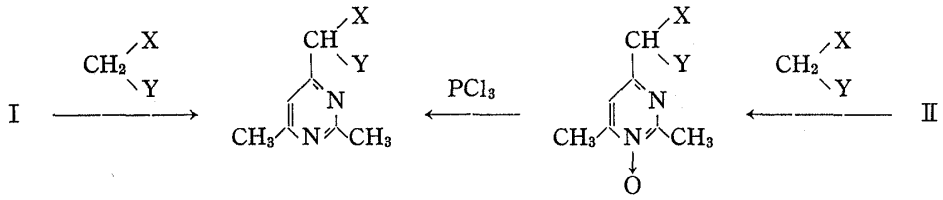


Chart 1



Va, b VIa, b

a: X=CN, Y=COOEt
b: X=Y=CN

Chart 2

seems to be subject to restrictions: namely, the reaction of II with acetone, acetophenone or cyclohexanone resulted in the formation of resinous substance and no identifiable product was obtained.

Thus, our interest was focussed on finding a suitable leaving group on the pyrimidine nucleus for nucleophilic substitution instead of the chloro group. Thus, according to Hayashi's method[10] II was treated with sodium *p*-toluenesulfinate to give 2,6-dimethyl-4-(*p*-toluenesulfonyl)pyrimidine 1-oxide (VII). By the reaction of VII with cyclohexanone in the presence of sodium hydride in tetrahydrofuran, a product of mp 219° (dec.) was obtained. The same compound (VIII) was formed in good yield when II was treated with sodium hydride without adding cyclohexanone. The mass spectrum and the elemental analysis of VIII established its molecular formula to be $C_{19}H_{20}N_4O_4S$. The nuclear magnetic resonance (NMR) spectrum of VIII suggested the presence of four methyl groups and one methylene group in the molecule, showing signals at δ=2.45 (3H, s), 2.48 (3H, s), 2.67 (6H, s), and 4.24 (2H, s) together with signals due to six aromatic ring protons. On the basis of these spectral data, the structure of the product was presumed to be 1,3′-dioxido-6′-(*p*-toluenesulfonyl)-2,2′,6-trimethyl-4,4′-dipyrimidinylmethane (VIII), formed through the self-condensation of VII. Since the 6-methyl group in 2,6-dimethylpyrimidine 1-oxides is known to have higher reactivity than the 2-methyl group in a simple molecule,[11] the above structure seems reasonable.

Table I. Reaction of 4-Chloropyrimidines with Active Methylene Compounds (Yields of Products under Various Reaction Conditions)

Active methylene compounds	Pyrimidines	Products	Yield of products (%) NaH, THF reflux, 24 hr	$NaNH_2$, THF reflux, 24 hr	Na, dioxane reflux, 20 hr	50% NaOH, benzene room temp., 24 hr[a]
$CH_2(CN)COOEt$	I	Va	trace (42)[b]	0 (70)	26 (38)	0 (90)
	II	VIa	55 (0)	0 (38)	26 (0)	26 (0)
$CH_2(CN)_2$	I	Vb	22 (0)	27 (20)	—	0 (86)
	II	VIb	82 (0)	61 (0)		35 (0)

a) In these cases, a phase transfer catalyst, tetrabutylammonium iodide, was added.
b) The figures printed in parenthesis represent percentages of the recovered starting materials.

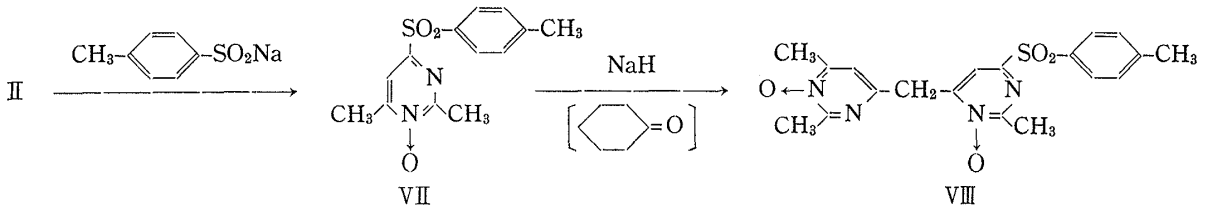


Chart 3

The formation of VIII in the above reaction suggests that the presence of an N-oxide group in VII may be unfavorable influence for the present purpose. In this connection, there are papers[12–18] describing the utility of an arylsulfonyl group attached to N-heteroaromatics other than pyrimidines for nucleophilic substitution.

Thus, 2,6-dimethyl-4-phenylsulfonylpyrimidine (X) was synthesized by the oxidation of 2,6-dimethyl-4-phenylthiopyrimidine (IX) with *m*-chloroperbenzoic acid. The synthesis of X by this route is practical, because I could not react with sodium benzenesulfinate under conditions similar to those used for the convertion of II into VII.

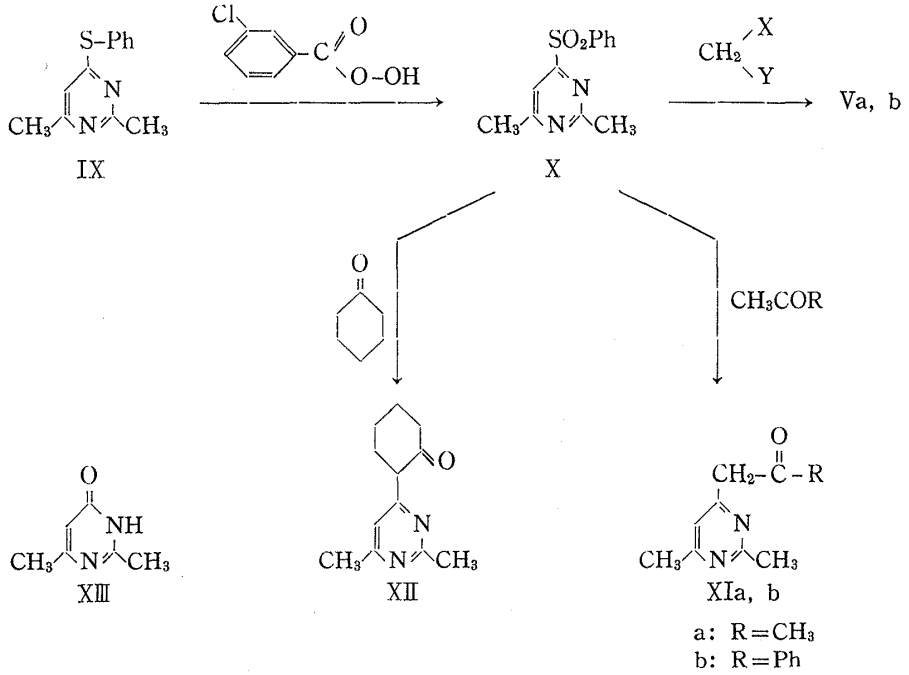


Chart 4

When X was treated with ethyl cyanoacetate and malononitrile in warm tetrahydrofuran in the presence of sodium hydride, Va and Vb were obtained in 75 and 78% yields, respectively. Further, X reacted with monoketones such as acetone, acetophenone and cyclohexanone to give 4-acetonyl-2,6-dimethyl- (XIa), 2,6-dimethyl-4-phenacyl- (XIb), and 2,6-dimethyl-4-(2-oxocyclohexyl)pyrimidine (XII), respectively. In every case a considerable amount of 2,6-dimethyl-4-pyrimidinone (XIII) was obtained as a by-product. The compound XIb was identical with an authentic specimen obtained by the benzoylation of 2,4,6-trimethylpyrimidine.[19] These results are summarized in Chart 4 and Table II. The presence of keto-enol tautomers was observed in the NMR spectra of these products (XIa, b and XII), as in the case of the corresponding 2-isomers. Since analysis of the tautomerism is not essential to this investigation, the findings obtained on the fine structure of the above products will be presented elsewhere.

Table II. Reaction of X with Functionalized Carbanions

	R	Reaction conctions				Product			
		Base	Solvent	Time (hr)	Temp (°C)	No.	mp or bp (°C)	Yield (%)	Yield of XIII (%)
$CH_2<^{X}_{Y}$	COOEt	NaH	THF	1	reflux	Va	171—173	75	—[a]
	CN	NaH	THF	1	reflux	Vb	310 (dec.)	78	—[a]
$CH_2-\overset{O}{\overset{\|}{C}}-R$	CH_3	NaH	THF	1	40	XIa	72—74 (1 mmHg)	53	20
	Ph	NaH	THF	3.5	40	XIb	160—162 (3 mmHg)[b]	35	32
Cyclohexanone	—	NaH	THF	1.5	40	XII	100—102 (3 mmHg)	32	16

a) In these cases the formation of the by-product (XIII) was not observed.
b) The boiling point is in accord with the reported value.

On the basis of these investigations, it can be concluded that, for nucleophilic substitution at the 4-position of a pyrimidine ring with carbanion-like reagents, the utilization of a phenylsulfonyl group is more effective than the activation of a chloro substituent by introducing an N-oxide group.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Mass spectra (MS) were taken with a Hitachi M-52G spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed as ppm downfield from tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and b=broad.

4-Chloro-2,6-dimethylpyrimidine 1-Oxide (II)——A solution of *m*-chloroperbenzoic acid (6.21 g, 0.036 mol) and 4-chloro-2,6-dimethylpyrimidine (I) (4.27 g, 0.03 mol) in CH_2Cl_2 (100 ml) was allowed to stand at room temperature for 2 days. The reaction mixture was washed with 30% K_2CO_3. After removal of the solvent, the residual crystals were recrystallized from hexane to give 3.10 g (65%) of II, mp 99—101° (lit.[10] mp 100—102°), as colorless needles. IR ν_{max}^{KBr} cm^{-1}: 1265. NMR (CCl_4): 2.40 (3H, s), 2.57 (3H, s), 7.24 (1H, s).

Competitive Reaction of 4-Chloro-2,6-dimethylpyrimidine (I) and Its 1-Oxide (II) with Ethoxide Ion——A solution of NaOH (80 mg, 2 mmol) in abs. EtOH (6 ml) was added dropwise to a solution of I (290 mg, 2 mmol) and II (320 mg, 2 mmol) in abs. EtOH (4 ml) at 20—25°. The reaction mixture was stirred for 1 hr at the same temperature, then 10% HCl (4 ml) was added under ice-cooling to neutralize the mixture. The solvent was removed under reduced pressure, and the resulting syrup was made alkaline by adding saturated K_2CO_3 aq. solution. The mixture was exhaustively extracted with $CHCl_3$. A part of the extract was analyzed by gas-chromatography (FID; column, 10% SE-30 (1 m); column temperature, from 90° to 150°; carrier gas (N_2) 60 ml/min, without the addition of an internal standard). The observed mole ratio of I, II, 4-ethoxy-2,6-dimethylpyrimidine (III), and 4-ethoxy-2,6-dimethylpyrimidine 1-oxide (IV) was 0.92: 0.18: 0.12: 1.

The main part of the $CHCl_3$ extract was evaporated to dryness to give the residue, which was chromatographed on an alumina column first with benzene, then with $CHCl_3$. From the $CHCl_3$ eluate, 0.24 g (71%) of IV was obtained as colorless prisms (hexane), mp 102—104°. Based on the above yield, the yields of I, II, III, IV were calculated to be 65, 13, 8, and 71%, respectively.

Reaction of II with Ethyl Cyanoacetate——1) NaH (170 mg, 7 mmol) was added to a solution of ethyl cyanoacetate (680 mg, 6 mmole) in dry THF (20 ml) and the mixture was stirred at room temperature for 10 minutes. Compound II (320 mg, 2 mmol) was added thereto and the mixture was heated under reflux for 24 hr with stirring. A small amount of H_2O was added to the mixture and it was concentrated under reduced pressure. The residue was made acidic with 10% HCl and extracted with $CHCl_3$. After removal of the solvent, the residual crystals were recrystallized from AcOEt to give 260 mg (55%) of ethyl α-(2,6-dimethyl-1-oxido-4-pyrimidinyl)cyanoacetate (VIa), mp 165° (dec.) as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2190, 1660, 1615. NMR (DMSO-d_6): 1.21 (3H, t, J=7 Hz), 2.34 (3H, s), 2.48 (3H, s), 4.10 (2H, q, J=7 Hz), 7.80 (1H, s), 8.50—12.00 (1H, b, exchangeable with D_2O). MS: m/e=235. *Anal.* Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57ε N, 17.86. Found: C, 55.60; H, 5.50; N, 17.53.

2) Na (140 mg, 6 mg·atom) was added to a solution of ethyl cyanoacetate (680 mg, 6 mmol) in dry dioxane (10 ml) and the mixture was heated under reflux for 2 hr with stirring. Compound II (320 mg, 2 mmol) was added thereto and the mixture was heated under reflux for 20 hr with stirring. The reaction mixture was treated according to the procedure used above to give 120 mg (26%) of VIa.

3) A mixture of II (320 mg, 2 mmol), ethyl cyanoacetate (450 mg, 4 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), benzene (10 ml), and 50% NaOH (2 ml) was stirred at room temperature for 1 day. The reaction mixture was treated according to the procedure used above and VIa was obtained. The yield was 120 mg (26%).

General Procedure for the Reaction of 4-Chloropyrimidines with Malononitrile——NaH or $NaNH_2$ (12 mmol) was added to a solution of malononitrile (10 mmol) in dry THF (35 ml) and the mixture was stirred at room temperature for 10 min. A 4-chloropyrimidine (3.5 mmol) was added thereto and the mixture was heated under reflux for 24 hr with stirring. A small amount of H_2O was added to the mixture, and the whole was concentrated under reduced pressure. The residue was made acidic with 10% HCl. The resulting precipitates were filtered and decolorized by treatment with activated charcoal powder. Recrystallization from MeOH or MeOH–AcOEt gave the reaction products.

α-(2,6-Dimethyl-4-pyrimidinyl)malononitrile (Vb)——1) Vb was obtained from NaH (290 mg, 12 mmol), malononitrile (660 mg, 10 mmol), I (500 mg, 3.5 mmol), and dry THF (35 ml) according to the general procedure as pale yellow prisms, mp 310° (dec.). The yield was 130 mg (22%). IR ν_{max}^{KBr} cm^{-1}: 3240, 2200, 2180, 1650, 1620. NMR (CF_3COOH): 2.59 (3H, s), 3.00 (3H, s), 7.18 (1H, s). *Anal.* Calcd for $C_9H_8N_4$: C, 62.77; H, 4.68; N, 32.54. Found: C, 62.67; H, 4.59; N, 32.60.

2) Vb was obtained from $NaNH_2$ (470 mg, 12 mmol), malononitrile (660 mg, 10 mmol), I (500 mg, 3.5 mmol), and dry THF (35 ml) according to the general procedure. The yield was 150 mg (27%). From the 10% HCl layer, I was recovered in 20% yield.

α-(2,6-Dimethyl-1-oxido-4-pyrimidinyl)malononitrile (VIb)——1) VIb was obtained from NaH (170 mg, 7 mmol), malononitrile (400 mg, 6 mmol), II (320 mg, 2 mmol), and dry THF (20 ml) according to the general procedure as colorless prisms, mp 182° (dec.). The yield was 310 mg (82%). IR ν_{max}^{KBr} cm^{-1}: 3400, 2800, 2210, 2180, 1640. NMR (DMSO-d_6): 2.40 (3H, s), 2.49 (3H, s), 6.70 (1H, s), 10.00—11.50 (1H, b, exchangeable with D_2O). *Anal.* Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found: C, 57.68; H, 4.38; N, 29.66.

2) VIb was obtained from $NaNH_2$ (270 mg, 7 mmol), malononitrile (400 mg, 6 mmol), II (320 mg, 2 mmol), and dry THF (20 ml) according to the general procedure. The yield was 230 mg (61%).

3) A mixture of II (320 mg, 2 mmol), malononitrile (260 mg, 4 mmol), tetrabutylammonium iodide (74 mg, 0.2 mmol), benzene (20 ml), and 50% NaOH (2 ml) was stirred at room temperature for 1 day. The aqueous layer was separated and made acidic with 10% HCl. It was evaporated to dryness under reduced pressure and extracted with MeOH. After removal of the solvent, the residue was purified by passing it through a silica gel column ($CHCl_3$: MeOH=4: 1). Recrystallization from MeOH–AcOEt gave 130 mg (35%) of VIb.

Deoxygenation of VIa——PCl_3 (3 ml) was added to a solution of VIa (300 mg, 1.3 mmol) in $CHCl_3$ (20 ml) and the mixture was heated under reflux for 1 hr. After removal of the solvent, 10% HCl (10 ml) was added to the residue. The solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was recrystallized from benzene-hexane to give 200 mg (71%) of ethyl α-(2,6-dimethyl-4-pyrimidinyl)cyanoacetate (Va), mp 172—173° (lit.[7] mp 172.5—173°), as pale yellow needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2200, 1630. NMR ($CDCl_3$): 1.32 (3H, t, J=7 Hz), 2.37 (3H, s), 2.55 (3H, s), 4.25 (2H, q, J=7 Hz), 6.80 (1H, s), 13.00—14.00 (1H, b, exchangeable with D_2O).

The melting point of a mixture of this compound with the sample prepared from I and ethyl cyanoacetate[7] showed no depression, and the IR spectra of the two products were identical.

Deoxygenation of VIb——Finely powdered VI (300 mg, 1.6 mmol) was added to PCl_3 (7 ml) and the mixture was heated under reflux for 1.5 hr. The mixture was evaporated to dryness under reduced pressure, then the residue was washed with Et_2O and recrystallized from MeOH to give 190 mg (69%) of Vb, mp 310° (dec.), as pale yellow prisms.

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

2,6-Dimethyl-4-(*p*-toluenesulfonyl)pyrimidine 1-Oxide (VII)——A mixture of II (3.30 g, 0.021 mol), sodium *p*-toluenesulfinate tetrahydrate (7.50 g, 0.03 mol), and dimethylformamide (30 ml) was heated at 60—70° for 4 hr with stirring. The reaction mixture was poured into H_2O (250 ml) and the resulting precipitates were filtered off. Recrystallization from benzene gave 4.91 g (85%) of VII, mp 178—179°, as pale yellow prisms. IR ν_{max}^{KBr} cm^{-1}: 1350, 1330, 1320, 1280, 1160. NMR ($CDCl_3$): 2.47 (3H, s), 2.58 (3H, s), 2.70 (3H, s), 7.43 (2H, d, $J=8$ Hz), 7.98 (2H, d, $J=8$ Hz), 8.07 (1H, s). *Anal.* Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.27; H, 4.96; N, 9.95.

Reaction of VII in the Presence of NaH——1) NaH (170 mg, 7 mmol) was added to a solution of VII (500 mg, 1.8 mmol) in dry THF (20 ml). The mixture was heated under reflux for 1 hr with stirring. After removal of the solvent under reduced pressure, the residue was made acidic with 10% HCl and extracted with $CHCl_3$. The solvent was removed under reduced pressure and the residual crystals were recrystallized from MeOH to give 260 mg (72%) of 1,3′-dioxido-6′-(*p*-toluenesulfonyl)-2,2′,6-trimethyl-4,4′-dipyrimidinylmethane (VIII), mp 219° (dec.), as pale yellow prisms. IR ν_{max}^{KBr} cm^{-1}: 1330, 1275, 1265, 1160. NMR ($CDCl_3$): 2.45 (3H, s), 2.48 (3H, s), 2.67 (6H, s), 4.24 (2H, s), 7.20—7.60 (3H, m), 7.70—8.20 (3H, m). MS: $m/e=400$. *Anal.* Calcd for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.04; N, 13.99; S, 8.01. Found: C, 56.87; H, 4.94; N, 13.71; S, 7.68.

2) VIII was obtained from NaH (170 mg, 7 mmol), VII (500 mg, 1.8 mmol), dry THF (20 ml), and cyclohexanone (530 mg, 5.4 mmol) according to the procedure used above. The yield was 110 mg (31%).

2,6-Dimethyl-4-phenylthiopyrimidine (IX)——Benzenethiol (5.72 g, 0.052 mol) was added dropwise to a solution of NaOEt [prepared from Na (1.20 g, 0.052 g·atom)] in abs. EtOH (25 ml), and the mixture was heated under reflux for 30 minutes. Compound I (7.50 g, 0.052 mol) was added dropwise thereto and the mixture was heated under reflux for 2 hr with stirring. A small amount of H_2O was added to the mixture and the whole was concentrated under reduced pressure to give the residue. The residue was dissolved in 20% HCl, washed with Et_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. After removal of the solvent, the residual crystals were recrystallized from hexane to give 11.00 g (98%) of IX, mp 78—80°, as colorless prisms. NMR (CCl_4): 2.21 (3H, s), 2.48 (3H, s), 6.32 (1H, s), 7.47 (5H, bs). *Anal.* Calcd for $C_{12}H_{12}N_2S$: C, 66.65; H, 5.59; N, 12.96; S, 14.80. Found: C, 66.46; H, 5.60; N, 13.00; S, 14.66.

2,6-Dimethyl-4-phenylsulfonylpyrimidine (X)——A solution of IX (2.16 g, 0.01 mol) in CH_2Cl_2 (100 ml) was cooled in an ice-bath and *m*-chloroperbenzoic acid (2.93 g, 0.017 mol) was added thereto with stirring. After the mixture had been stirred at room temperature overnight, *m*-chloroperbenzoic acid (0.86 g, 0.005 mol) was added. Stirring was continued for a further 5 hr. The mixture was washed with 30% K_2CO_3. After removal of the solvent, the residue was purified by passing it through an alumina column with Et_2O. Recrystallization from hexane gave 1.63 g (66%) of X, mp 93—94.5°, as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1350, 1320, 1310, 1160. NMR ($CDCl_3$): 2.60 (3H, s), 2.69 (3H, s), 7.40—7.80 (3H, m), 7.82 (1H, s), 8.00—8.30 (2H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.06; H, 4.87; N, 11.29; S, 12.89. Found: C, 57.85; H, 4.82; N, 11.18; S, 12.45.

Reaction of X with Ethyl Cyanoacetate——NaH (170 mg, 7 mmol) was added to a solution of ethyl cyanoacetate (680 mg, 6 mmol) in dry THF (20 ml) and the mixture was stirred at room temperature for 10 minutes. Compound X (500 mg, 2 mmol) was added and the mixture was heated under reflux for 1 hr with stirring. A small amount of H_2O was added, and the mixture was concentrated under reduced pressure to give the residue. The residue was made acidic with 10% HCl and extracted with $CHCl_3$. After removal of the solvent, the residue was purified by passing it through an alumina column with AcOEt. Recrystallization from benzene–hexane gave 330 mg (75%) of Va, mp 172—173°, as pale yellow needles. The melting point of a mixture of this compound with the sample prepared above showed no depression and the IR spectra of the two products were identical.

Reaction of X with Malononitrile——NaH (170 mg, 7 mmol) was added to a solution of malononitrile (400 mg, 6 mmol) in dry THF (20 ml) and the mixture was stirred at room temperature for 10 minutes. Compound X (500 mg, 2 mmol) was added thereto and the mixture was heated under reflux for 1 hr with stirring. A small amount of H_2O was added, and the mixture was concentrated under reduced pressure to give the residue. The residue was made acidic with 10% HCl and the resulting precipitates were filtered off. Recrystallization from MeOH gave 270 mg (78%) of Vb, mp 310° (dec.), as pale yellow prisms. The melting point of a mixture of this compound with the sample prepared above showed no depression and the IR spectra of the two products were identical.

Reaction of X with Acetone——A mixture of X (500 mg, 2 mmol), acetone (2 ml) and NaH (100 mg, 4 mmol) in dry THF (20 ml) was heated at 40° for 1 hr with stirring, then 10% HCl (10 ml) was added and the mixture was concentrated to 10 ml under reduced pressure. The residual mixture was washed with Et_2O, made alkaline with $NaHCO_3$, and extracted with Et_2O.

After removal of the solvent, the residual oil was distilled under reduced pressure to give 190 mg (53%) of 4-acetonyl-2,6-dimethylpyrimidine (XIa), bp 72—74° (1 mmHg). (lit.[21] bp 75—76° (0.5 mmHg)). IR ν_{max}^{neat} cm^{-1}: 1730, 1635. NMR ($CDCl_3$): 2.04 (1.35H, s), 2.24 (1.65H, s), 2.35 (1.35H, s), 2.46 (1.65H, s), 2.53 (1.35H, s), 2.66 (1.65H, s), 3.80 (1.1H, s), 5.18 (0.45H, s), 6.37 (0.45H, s), 6.92 (0.55H, s), 14.50—15.30 (0.45H,

b). The IR spectra of this compound and the sample prepared by an alternative route[20] were identical.

The aqueous layer was concentrated to dryness and extracted with hot $CHCl_3$. The $CHCl_3$ extract gave 50 mg (20%) of 2,6-dimethyl-4-pyrimidinone (XIII).

Reaction of X with Acetophenone——A mixture of X (500 mg, 2 mmol), acetophenone (360 mg, 3 mmol), and NaH (100 mg, 4 mmol) in dry THF (20 ml) was heated at 40° for 3.5 hr with stirring, then 10% HCl (10 ml) was added and the mixture was concentrated to 10 ml under reduced pressure. The residual mixture was washed with Et_2O, made alkaline with $NaHCO_3$, and extracted with Et_2O.

After removal of the solvent, the residual oil was distilled under reduced pressure to give 160 mg (35%) of 2,6-dimethyl-4-phenacylpyrimidine (XIb), bp 160—162° (3 mmHg) (lit.[21] bp 146—150° (0.7 mmHg)). The IR spectra of this compound and the sample prepared by an alternative route[19] were identical. The aqueous layer was concentrated to dryness and extracted with hot $CHCl_3$. The $CHCl_3$ extract gave 80 mg (32%) of XIII.

Reaction of X with Cyclohexanone——A mixture of X (500 mg, 2 mmol), cyclohexanone (290 mg, 3 mmol), and NaH (100 mg, 4 mmol) in dry THF (20 ml) was heated at 40° for 1.5 hr with stirring. The mixture was concentrated to dryness and dissolved in 10% HCl (20 ml). The solution was washed with Et_2O, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. After removal of the solvent, the residue was purified by passing it through an alumina column with Et_2O. Vacuum distillation gave 130 mg (32%) of 2,6-dimethyl-4-(2-oxocyclohexyl)pyrimidine (XII), bp 100—102° (3 mmHg), mp 45—47°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1635. NMR ($CDCl_3$): 1.50—2.00 (4H, m), 2.10—2.70 (4.05H, m), 2.46 (2.85H, s), 2.61 (2.85H, s), 2.69 (0.15H, s), 2.81 (0.15H, s), 6.69 (0.95H, s), 6.92 (0.05H, s), 15.79 (0.95H, s, exchangeable with D_2O). *Anal.* Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.40; H, 7.89; N, 14.00.

The aqueous layer was concentrated to dryness and extracted with hot $CHCl_3$. The $CHCl_3$ extract gave 40 mg (16%) of XIII.

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