Synthesis of Pyrimidine Derivatives by the Reaction of Ketene Dithioacetals with Amides

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Reactions of methyl 2-cyano-3,3-bis(methylthio)acrylate (**1a**) with carboxamides **2a-g** in the presence of sodium hydride in a mixture of benzene and *N,N*-dimethylacetamide took place displacement with the methylthio group to give the corresponding methyl 3-*N*-acylamino-2-cyano-3-(methylthio)acrylates **3a-g** which were readily converted to the corresponding pyrimidine derivatives at reflux in methanol in good yields. Reactions of 2-cyano-3,3-bis(methylthio)acrylonitrile (**1b**) with the carboxamides **2a-f** gave directly pyrimidine-5-carbonitrile derivatives **7a-f**. Ketene dithioacetals **1a,b** smoothly reacted with thioamide **2g** or urea **2h,i** to give the expected pyrimidine derivatives **9,10a,b**. Polyfunctionalized pyrimidines, thus obtained, were also used for the synthesis of fused pyrimidine derivatives.

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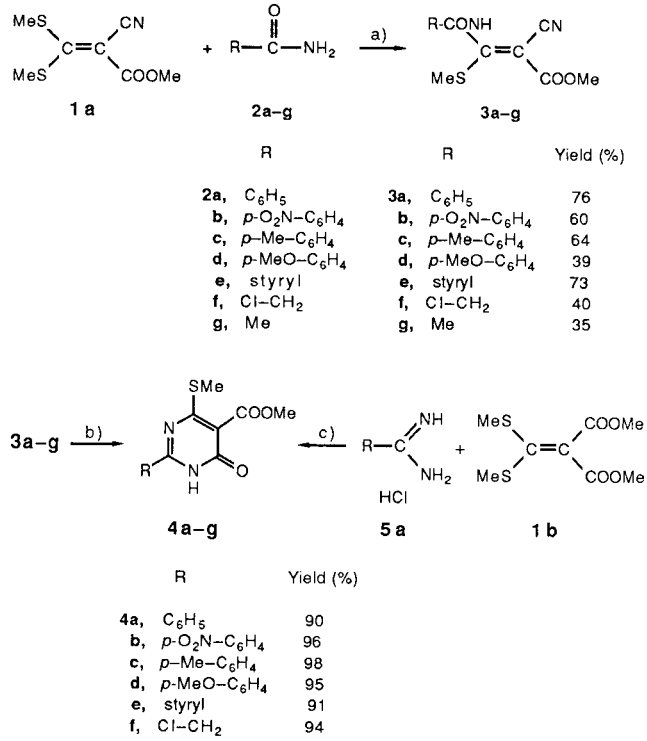
Pyrimidine derivatives, which constitute a partial structure of the purine base and many biologically active compounds, are involved widely in living organisms and have attracted much attention from the view point of medicinal chemistry. The soporific and hypnotic barbiturates and a number of antibacterial and antimalarial drugs also contain pyrimidine rings. Since the direct introduction of some specific substituents into the pyrimidine nucleus is not easy, syntheses directed to the construction of the ring bearing useful functional groups in the first step have been well developed [1-3]. Ketene dithioacetals are also versatile reagents for the preparation of pyrimidine derivatives similar to ethoxymethylene compounds [4-6]. We have found that the synthesis of pyrimidines is generally attained by the condensation reaction of ketene dithioacetals with amidine derivatives in the presence of an appropriate base [7-15]. In our extension of ketene dithioacetals to synthesis, we now wish to report a novel synthesis of functionalized pyrimidine derivatives by the reaction of ketene dithioacetals with carboxamides in the presence of sodium hydride and synthesis of the 6-aminouracil and fused pyrimidine derivatives [16]. In spite of numerous reactions of ketene dithioacetals with nucleophiles such as amines or active methylene compounds, to our knowledge, the reaction with carboxamides has unknown for the purpose of synthesis of heterocycles.

The reaction of methyl 2-cyano-3,3-bis(methylthio)acrylate (**1a**) [17] with benzamide **2a** in the presence of sodium hydride in benzene and *N,N*-dimethylacetamide (1:1) at room temperature for 30 hours gave methyl 3-benzoylamino-2-cyano-3-(methylthio)acrylate (**3a**) in 76% yield. The resulting **3a** was readily converted to methyl 3,4-dihydro-6-methylthio-4-oxo-2-phenylpyrimidine-5-carboxylate (**4a**) at reflux in methanol in 90% yield. The structure of **4a** was confirmed by comparison of its infrared (ir) and nuclear magnetic resonance (nmr) spectral data with those of an authentic specimen prepared by the reaction of methyl 2-methoxycarbonyl-3,3-bis(methylthio)acrylate (**1b**) with benzamidine hydrochloride **5a** in the presence of sodium methoxide. Compounds **3b-g** and **4b-g** were also synthesized by the reaction of **1a** with the corresponding carboxamides **2a-g** in a similar manner to that described for **3a** and **4a**. The reaction mechanism is shown in Chart 2.



a) NaH in benzene + *N,N*-dimethylacetamide at room temperature; b) in MeOH reflux; c) Et_3N, reflux in methanol

Chart 1

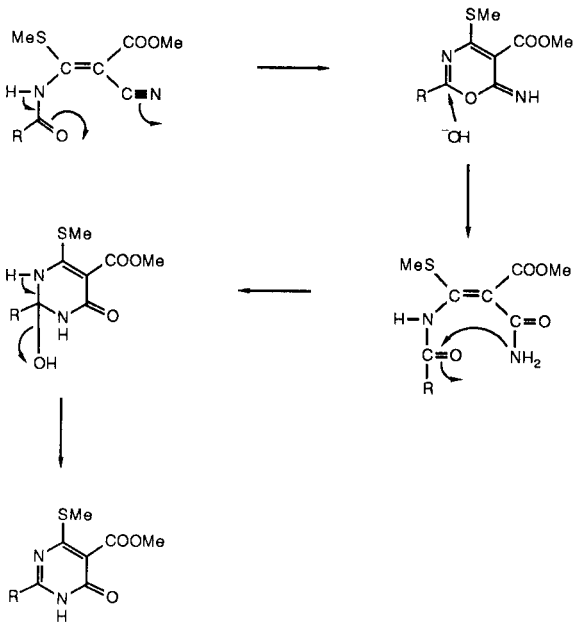
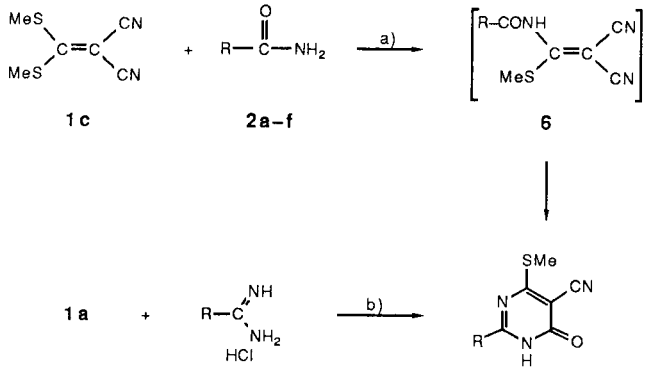


Chart 2

Moreover, the reaction of 2-cyano-3,3-bis(methylthio)-acrylonitrile (**1c**) [17] with carboxamides **2a-g** gave directly the corresponding pyrimidine-5-carbonitriles **7a-f** under the same conditions that described for **3a**. In this reaction, the corresponding intermediates **6** could not be isolated. Compound **7a** and **7f** were also prepared by the reaction of **1a** with benzamidine and acetamidine hydrochlorides, **5a** and **5b** respectively, in the presence of potassium carbonate in *N,N*-dimethylformamide in 89 and 77% yields, respectively.



	R	Yield(%)
7a,	C_6H_5	57 (89)*
b,	p-O_2N-C_6H_4	33
c,	p-Me-C_6H_4	32
d,	p-MeO-C_6H_4	30
e,	styryl	35
f,	Me	18 (77)*

a) NaH, in benzene–*N,N*-dimethylacetamide; b) Et_3N, in ethanol
* From **1a** and **5a,b**

Chart 3

Ketene dithioacetal **1a** also reacted with thioacetamide **2g**, followed by cyclization to yield methyl 2-methyl-4-mercapto-6-methylthiopyrimidine-5-carboxylate (**8**) which could be readily converted to methyl 2-methyl-4,6-bis-(methylthio)pyrimidine-5-carboxylate (**9**) by methylation with dimethyl sulfate in good yield. Under the similar conditions, the reaction of **1a** with urea **2h** or *N*-phenylurea **2i** afforded the corresponding 6-methylthiouracil-5-carbonitrile **10a,b**. In this case, the intermolecular cyclization of the methoxycarbonyl group in ketene dithioacetal with the amido group in urea occurred and the corresponding uracil derivatives were obtained.

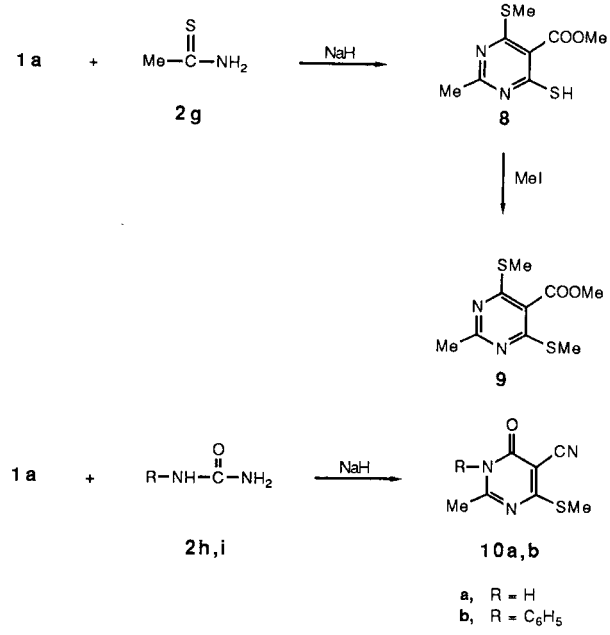


Chart 4

The aminolysis of 2- and 4-(or 6-)alkylthiopyrimidines has hitherto been well documented [2]. Kinetic studies show that 4-(or 6-)methylthiopyrimidines undergo aminolysis more rapidly than the corresponding 2-methylthiopyrimidines [2,3]. In addition, electron-withdrawing substituents such as a 5-nitro- or a carbonyl group increases the rate markedly [1,2,3]. Aminolysis of **4a** with morpholine did not occur, but **7f** reacted with morpholine smoothly at 100° to give 6-morpholinopyrimidine-5-carbonitrile (**12**) in 78% yield.

It is known that nucleophilic displacement of alkylsulfinyl and alkylsulfonyl groups occurs more rapidly than that of alkylthio groups [18]. Treatment of **4a** and **4b** with 30% hydrogen peroxide in acetic acid gave the sulfonyl derivatives **13a** and **13b** in 70 and 52% yields, respectively. In fact, **13a** smoothly reacted with amines such as benzylamine, cyclohexylamine, morpholine, aniline, and *o*-anisidine to give the corresponding 6-aminopyrimidine derivatives **11a-e** which were also obtained by the reaction of **3a** with corresponding amines at 100°.

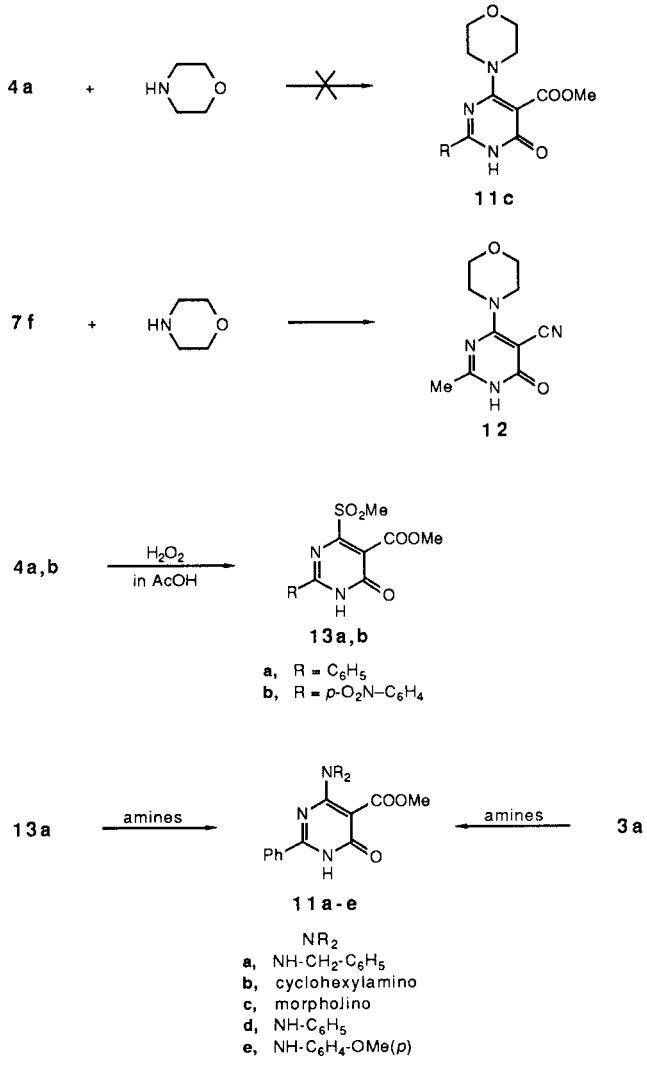


Chart 5

Chloropyrimidines are the most versatile intermediates for the synthesis of pyrimidine derivatives. Aminolysis of halogenopyrimidines is well-known [1,2,3]. However there are few examples of the reaction of halogenopyrimidines with active methylene compounds, such as diethyl malonate, and ethyl cyanoacetate, *etc.* [2,3].

Chlorination of **4a** with phosphorus oxychloride gave 4-chloropyrimidine derivatives **19** though poor yield along with decarboxylation product **20**. Chlorination of **7a** or **7f** occurred smoothly to give the expected products **22a** and **22b** in 90 and 70% yields, respectively. Reactions of **19**, **22a** and **22b** with amines (such as aniline, morpholine, *o*-anisidine) gave the corresponding 6-aminopyrimidine derivatives in good yields.

The reaction of **21a** with active methylene compounds (methyl cyanoacetate, ethyl cyanoacetate, and malononitrile) in the presence of potassium carbonate in dimethyl sulfoxide gave the corresponding displacement products **23a-d** of methylthio group. Because of a methylthio group is involved in reaction products, these pyrimidine derivatives will become useful synthetic intermediates, especially synthesis of 4,6-disubstituted pyrimidines.

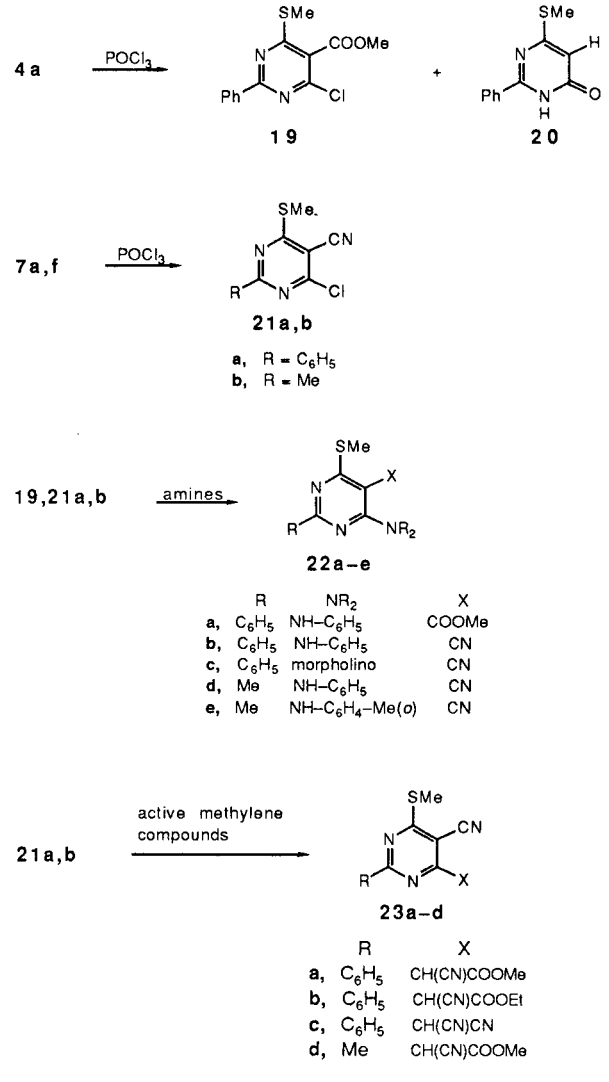


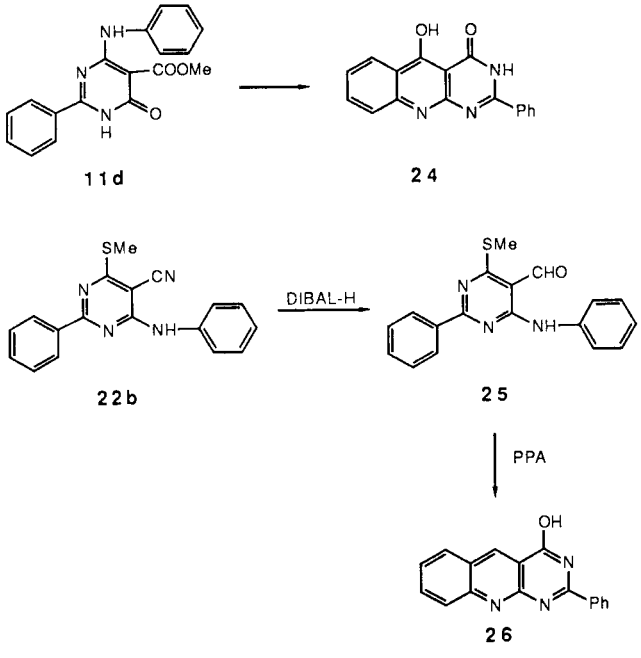
Chart 6

The pyrimidine derivatives, obtained here, are not only interesting from the viewpoint of biological activities but also important and useful as the starting materials for the conversion to other heterocyclic compounds, especially, fused pyrimidine derivatives. At first, we attempted the synthesis of pyrimido[3,4-*b*]quinolines, in general prepared from quinoline and uracil derivatives, which are of interest from various pharmacological activities. Compound **11d** was readily converted to **24** by only heating at 230° in diphenyl ether. On the other hand, compound **26** was obtained from **22b** which was prepared by the treatment at **25** with diisobutylaluminium hydride, followed by

heating in the presence of polyphosphoric acid. 4-Methylthiopyrimido[4,5-*d*]quinoline derivative was not detected in the reaction mixture. This type of cyclization is the common method of the synthesis of pyrimido[4,5-*b*]quinoline derivatives from 5-formyluracil [19].

Next, we examined the synthesis of pyrazolo[4,5-*d*]-pyrimidines which reveal interesting pharmacological activity like allopurinol, 4-hydroxy-1*H*-pyrazolo[3,4-*d*]pyrimidine [20,21]. The reaction of **7a** and **7f** with hydrazine derivatives gave the corresponding pyrazolo[3,4-*d*]pyrimidine derivatives **28a-c** in good yields. Compound **21c** also reacted with phenylhydrazine to give **29** in 65% yield. When **22c** was allowed to react with hydrazine hydrate in methanol at reflux, 4-hydrazino-6-morpholino-2-phenylpyrimidine-5-carbonitrile (**30**) was obtained in 75% yield. In the case of use of excess hydrazine hydrate under the condition at heating at 180°, 3-amino-4-hydrazinopyrazolo-[3,4-*d*]pyrimidine (**32**) was obtained in good yield. These methods were applied to synthesis of 3,4-diaminopyrazolo-[3,4-*d*]pyrimidine derivatives.

Compounds **13** and **21a** were also useful for the synthesis of thieno[2,3-*d*]pyrimidines which shows important pharmacological activity. The reaction of **13a** with methyl thioglycolate in the presence of triethylamine in methanol gave methyl 3,4-dihydroxy-6-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (**32**). In a similar manner, methyl 5-amino-4-methylthio-2-methylthieno[2,3-*d*]pyrimidine-6-carboxylate (**33**) was obtained from **21a** and methyl thioglycolate in good yields.



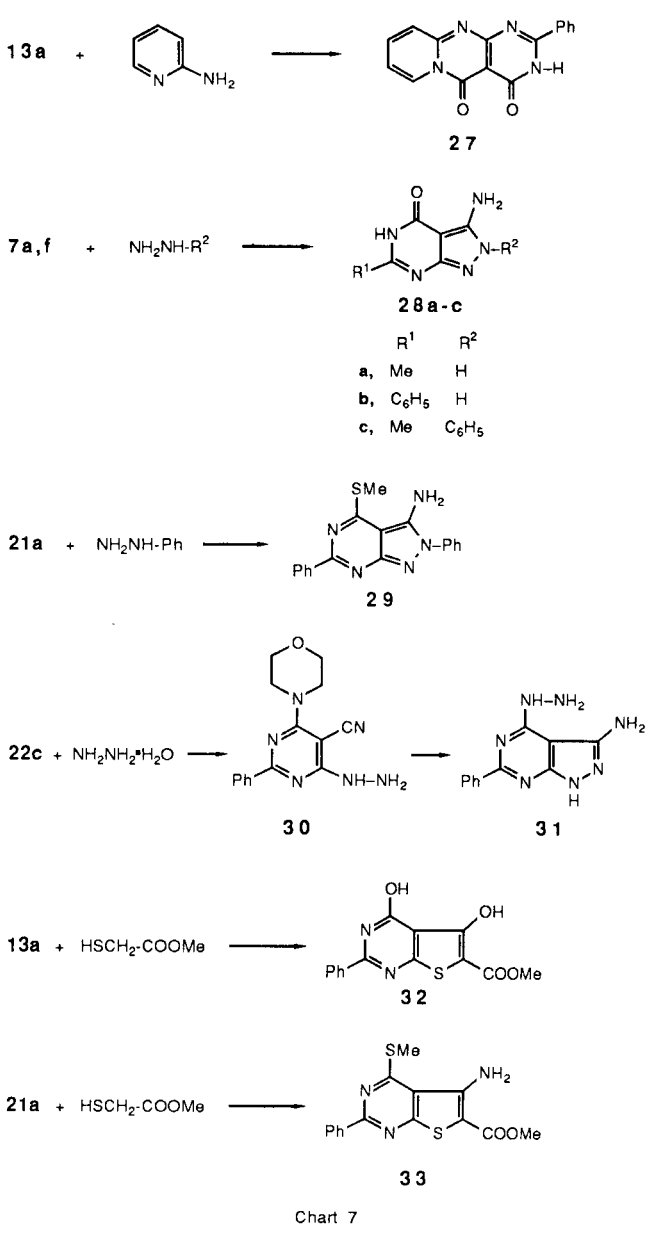


Chart 7

EXPERIMENTAL

All melting points were determined in capillary tubes and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on JASCO IRA-2 spectrometer and ultraviolet (uv) absorption spectra were determined in 95% ethanol on a Hitachi EP-S2 spectrometer. Nuclear magnetic resonance (nmr) spectra were obtained on JNM-PS-100 (100 MHz) and JNM-FX-90Q (90 MHz) spectrometer with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-01SG mass spectrometer.

Methyl 3-*N*-Benzoylamino-2-cyano-3-methylthioacrylate (**3a**).

A mixture of 2.03 g (10 mmoles) of **1a**, 1.21 g (10 mmoles) of benzamide **2a**, 0.96 g (50% in paraffin, 20 mmoles) of sodium hydride, and a solution of 50 ml of benzene and 50 ml of *N*,*N*-dimethylacetamide was stirred at room temperature for 20 hours. The resulting reddish reaction mixture was poured into 100 ml of ice-water. The water layer was acidified with 10% hydrochloric acid. The resulting precipitate was col-

lected by filteration and recrystallized from benzene to give 2.10 g (2.10 mmoles) of colorless needles, mp 137°, in 76% yield; ir (potassium bromide): ν max cm^{-1} 2198 (CN), 1710, 1670 (C=O); uv (ethanol): λ max nm (log ε) 242 (4.07), 278 (4.03), 328 (4.18); ^1H nmr (deuteriochloroform): δ 2.71 (3H, s, SMe), 3.84 (3H, s, OMe), 7.20-8.19 (5H, s, aromatic-H), 12.80 (1H, s, NH).

Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.66; H, 4.34; N, 10.04; S, 11.48.

Methyl 2-Cyano-3-methylthio-3-*N*-*p*-nitrobenzoylaminoacrylate (**3b**).

This compound (1.93 g, 6.0 mmoles) was synthesized in 60% yield from *p*-nitrobenzamide (**2b**) (1.66 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a similar manner to that described for **3a**. An analytical sample was recrystallized from benzene to give tan needles, mp 190°; ir (potassium bromide): ν max cm^{-1} 2202 (CN), 1672 (CO); uv (ethanol): λ max nm (log ε) 212 (4.35), 265 (4.26), 303 (4.35); ^1H nmr (deuteriochloroform): δ 2.73 (3H, s, SMe), 3.87 (3H, s, OMe), 8.00-8.74 (4H, m , aromatic-H).

Anal. Calcd. for $C_{13}H_{11}N_3O_5S$: C, 48.60; H, 3.45; N, 13.08; S, 9.98. Found: C, 48.61; H, 3.41; N, 13.01; S, 9.90.

Methyl 2-Cyano-3-*N*-*p*-methylbenzoylamino-3-methylthioacrylate (**3c**).

This compound (1.86 g, 6.4 mmoles) was synthesized in 64% yield from *p*-methylbenzamide (**2c**) (1.35 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a similar manner to that described for **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 144°; ir (potassium bromide): ν max cm^{-1} 2202 (CN), 1708, 1665 (CO); uv (ethanol): λ max nm (log ε) 241 (4.04), 302 (4.15), 332 (4.18); ^1H nmr (deuteriochloroform): δ 2.45 (3H, s, *p*-Me), 2.65 (3H, s, SMe), 3.85 (3H, s, OMe), 7.30 (2H, d, J = 7.0 Hz, aromatic-H), 7.80 (2H, d, J = 7.0 Hz, aromatic-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 58.20; H, 4.89; N, 9.61; S, 10.70.

Methyl 2-Cyano-3-methylthio-3-*N*-*p*-methoxybenzoylaminoacrylate (**3d**).

This compound (1.19 g, 3.89 mmoles) was synthesized in 39% yield from *p*-methoxybenzamide (**2d**) (1.51 g, 10 mmoles) and **1a** (2.05 g, 10 mmoles) in a similar manner to that described for **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 132°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1688, 1662 (CO); uv (ethanol): λ max nm (log ε) 235 (4.05), 302 (4.24), 330 (4.25); ^1H nmr (deuteriochloroform): δ 2.64 (3H, s, SMe), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 6.95 (2H, d, J = 8.0 Hz, aromatic-H), 7.92 (2H, d, J = 8.0 Hz, aromatic-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.95; H, 4.63; N, 8.94; S, 10.12.

Methyl 2-Cyano-3-methylthio-3-*N*-styrylcarbonylaminoacrylate (**3e**).

This compound (2.20 g, 7.28 mmoles) was synthesized in 73% yield from cinnamide (1.47 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a similar manner to that described for **3a**. An analytical sample was recrystallized from benzene to give yellow plates, mp 157°; ir (potassium bromide): ν max cm^{-1} 2199 (CN), 1718, 1660 (CO); uv (ethanol): λ max nm (log ε) 220 (4.31), 227 (4.22), 285 (4.41), 293 (4.39), 304 (4.38); ^1H nmr (deuteriochloroform): δ 2.68 (3H, s, SMe), 3.87 (3H, s, OMe), 6.60 (1H, d, J = 16.0 Hz, -CH=CH-), 7.83 (1H, d, J = 16.0 Hz, -CH=CH-), 7.46 (5H, m, aromatic-H), 11.40 (1H, bs, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.26; S, 10.60. Found: C, 59.74; H, 4.69; N, 9.26; S, 10.40.

Methyl 3-Chloromethylcarbonylamino-2-cyano-3-methylthioacrylate (**3f**).

This compound (0.99 g, 3.98 mmoles) was synthesized in 40% yield from chloroacetamide (**2f**) (0.93 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a manner similar to that described for **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 124°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1710, 1675 (CO); uv (ethanol): λ max nm (log ε) 265 (3.77), 322 (4.19); ^1H nmr (deuteriochloroform): δ 2.65 (3H, s, SMe), 3.88 (3H, s, OMe), 4.24 (2H, s, $-CH_2-$), 10.40 (1H, bs, NH).

Anal. Calcd. for $C_8H_9ClN_2O_3S$: C, 38.64; H, 3.65; N, 11.20; S, 12.89. Found: C, 38.77; H, 3.64; N, 11.20; S, 12.59.

Methyl 3-Acetylamino-2-cyano-3-methylthioacrylate (**3g**).

This compound (0.749 g, 3.50 mmoles) was synthesized in 35% yield from acetamide (0.59 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a similar manner to that described for **3a**. An analytical sample was recrystallized from benzene to give colorless needles, mp 110°; ir (potassium bromide): ν max cm^{-1} 2201 (CN), 1705, 1688 (CO); uv (ethanol): λ max nm (log ε) 264 (3.85), 324 (4.18); ^1H nmr (deuteriochloroform): δ 2.64 (3H, s, 2-Me or SMe), 2.70 (3H, s, 2-Me or SMe), 4.10 (3H, s, OMe), 9.60 (1H, bs, NH).

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.76; H, 4.65; N, 12.90; S, 15.37.

Methyl 3,4-Dihydro-4-methylthio-2-phenyl-4-oxopyrimidine-5-carboxylate (**4a**).

A solution of 2.76 g (10 mmoles) of **3a** in 100 ml of methanol was refluxed for 20 hours. After removal of the solvent the residue was recrystallized from acetic acid to give 2.48 g (8.98 mmoles) of colorless needles, mp 285°, in 90% yield; ir (potassium bromide): ν max cm^{-1} 1674, 1620 (CO); uv (ethanol): λ max nm (log ε) 219, 257, 306, min, nm 232, 279 (insufficient solubility); ^1H nmr (trifluoroacetic acid): δ 2.70 (3H, s, SMe), 3.99 (3H, s, OMe), 7.27-8.62 (5H, m, aromatic-H).

Anal. Calcd. for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.50; H, 4.41; N, 10.04; S, 11.56.

Methyl 3,4-Dihydro-4-methylthio-2-*p*-nitrophenyl-4-oxopyrimidine-5-carboxylate (**4b**).

This compound (3.08 g, 9.59 mmoles) was synthesized in 96% yield from **3b** (3.21 g, 10 mmoles) in a manner similar to that described for **4a**. An analytical sample was recrystallized from acetic acid to give yellow needles, mp 265°; ir (potassium bromide): ν max cm^{-1} 1685, 1655 (CO); uv (ethanol): λ max nm (log ε) 225 (4.20), 245 (4.27), 272 (4.28), 344 (3.98); ^1H nmr (trifluoroacetic acid): δ 2.83 (3H, s, SMe), 4.03 (3H, s, OMe), 8.40 (4H, s, aromatic-H).

Anal. Calcd. for $C_{13}H_{11}N_3O_5S$: C, 48.60; H, 3.45; N, 13.08; S, 9.98. Found: C, 48.82; H, 3.64; N, 12.79; S, 9.53.

Methyl 3,4-Dihydro-6-methylthio-2-*p*-methylphenyl-4-oxopyrimidine-5-carboxylate (**4c**).

This compound (2.84 g, 7.79 mmoles) was synthesized in 98% yield from **3c** (2.90 g, 10 mmoles) in a manner similar to that described for **4a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 283°; ir (potassium bromide): ν max cm^{-1} 1675, 1633 (CO); uv (ethanol): λ max nm (log ε) 225 (4.28), 265 (4.35), 303 (4.26), 343 (4.12); ^1H nmr (trifluoroacetic acid): δ 2.47 (3H, s, *p*-Me or SMe), 2.71 (3H, s, *p*-Me or SMe), 3.90 (3H, s, OMe), 7.35 (2H, d, J = 8.0 Hz, aromatic-H), 7.85 (2H, d, J = 8.0 Hz, aromatic-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 58.20; H, 4.89; N, 9.61; S, 10.70.

Methyl 3,4-Dihydro-6-methylthio-2-*p*-methoxyphenyl-4-oxopyrimidine-5-carboxylate (**4d**).

This compound (2.91 g, 9.51 mmoles) was synthesized in 95% from **3d** (3.06 g, 10 mmoles) in a manner similar to that described for **4a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 290°; ir (potassium bromide): ν max cm^{-1} 1675, 1633 (CO); uv (ethanol): λ max nm (log ε) 261 (4.60), 329 (3.95); ^1H nmr (trifluoroacetic acid): δ 2.72 (3H, s, SMe), 3.93 (3H, s, OMe), 4.03 (3H, s, OMe), 6.98-8.25 (4H, m, aromatic-H).

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.95; H, 4.63; N, 8.94; S, 10.12.

Methyl 3,4-Dihydro-6-methylthio-2-styryl-4-oxopyrimidine-5-carboxylate (**4e**).

This compound (2.74 g, 9.11 mmoles) was synthesized in 91% yield from **3e** (3.02 g, 10 mmoles) in a manner similar to that described for **4a**.

An analytical sample was recrystallized from acetic acid to give colorless needles, mp 261°; ir (potassium bromide): ν max cm^{-1} 1660, 1633 (CO); uv (ethanol): λ max nm 230, 238 (shoulder), 273, 290 (shoulder), 307 (shoulder), 340 (shoulder); min, nm 248 (insufficient solubility); ^1H nmr (trifluoroacetic acid): δ 2.66 (3H, s, SMe), 3.99 (3H, s, OMe), 6.88 (1H, d, J = 16.0 Hz, -CH=CH-), 8.14 (1H, d, J = 16.0 Hz, -CH=CH-).

Anal. Calcd. for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.26; S, 10.06. Found: C, 59.67; H, 4.67; N, 9.31; S, 10.11.

Methyl 3,4-Dihydro-2-chloromethyl-6-methylthio-4-oxopyrimidine-5-carboxylate (**4f**).

This compound (2.34 g, 9.41 mmoles) was synthesized in 94% yield from **3f** (3.02 g, 10 mmoles) in a manner similar to that described for **4a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 184°; ir (potassium bromide): ν max cm^{-1} 1665 (CO); uv (ethanol): λ max nm (log ϵ) 244 (4.37), 295 (3.84); ^1H nmr (trifluoroacetic acid): δ 2.60 (3H, s, SMe), 3.97 (3H, s, OMe), 4.56 (2H, s, $-CH_2-$).

Anal. Calcd. for $C_8H_9ClN_2O_3$: C, 38.64; H, 3.65; N, 11.38; S, 12.89. Found: C, 38.75; H, 3.66; N, 11.38; S, 13.05.

Synthesis of **4a** by the Reaction of Phenylamidine Hydrochloride (**5a**) with Ketene Dithioacetals **1b**.

A mixture of 1.18 g (5 mmoles) of phenylamidine hydrochloride, 1.18 g (5 mmoles) of dimethyl bis(methylthio)methylene malonate (**1b**), 1.38 g (10 mmoles) of potassium carbonate, and 100 ml of dimethylsulfoxide was heated at 100° for 10 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The resulting precipitate was collected by the filtration and recrystallized from acetic acid to give 1.05 g (3.8 mmoles) of colorless needles, **4a**, mp 285°, in 76% yield.

3,4-Dihydro-6-methylthio-4-oxopyrimidine-5-carbonitrile (**7a**).

A mixture of 1.70 g (10 mmoles) of **1c**, 1.21 g (10 mmoles) of benzamide (**2a**), 0.96 g (50%, 20 mmoles) of sodium hydride, and a solution of 50 ml of benzene and 50 ml of *N,N*-dimethylacetamide was stirred at room temperature for 20 hours. The reaction mixture was poured into 100 ml of ice-water and the water layer was acidified with 10% hydrogen chloride. The resulting precipitate was collected by filtration. A solution of this crude product in 100 ml of methanol was refluxed for 10 hours. After removal of the solvent the residue was recrystallized from acetic acid to give 1.39 g (5.72 mmoles) colorless needles, mp 341°, in 57% yield; ir (potassium bromide): ν max cm^{-1} 2207 (CN), 1655 (CO); uv (ethanol): λ max nm (log ϵ) 254 (4.47), 300 (4.00), 318 (4.02); ^1H nmr (trifluoroacetic acid): δ 2.81 (3H, s, SMe), 7.89-8.37 (5H, m, aromatic-H).

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.25; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.15; H, 3.60; N, 17.44; S, 13.21.

3,4-Dihydro-6-methylthio-2-*p*-nitrophenyl-4-oxopyrimidine-5-carbonitrile (**7b**).

This compound (0.95 g, 3.30 mmoles) was synthesized in 33% yield from *p*-nitrobenzamide (**2b**) (1.66 g, 10 mmoles) and **1c** (1.70 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from acetic acid to give yellow needles, mp 335°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1653 (CO); uv (ethanol): λ max nm (log ϵ) 224 (4.29), 246 (4.06), 270 (4.42), 308 (4.18), 352 (4.04); ^1H nmr (trifluoroacetic acid): δ 2.80-2.90 (3H, m, SMe), 8.17-8.52 (4H, m, aromatic-H).

Anal. Calcd. for $C_{12}H_8N_4O_3S$: C, 50.00; H, 2.80; N, 19.43; S, 11.12. Found: C, 49.86; H, 2.84; N, 19.06; S, 10.99.

3,4-Dihydro-6-methylthio-2-*p*-methylphenyl-4-oxopyrimidine-5-carbonitrile (**7c**).

This compound (0.82 g, 3.19 mmoles) was synthesized in 32% yield from *p*-methylbenzamide (**2c**) (1.35 g, 10 mmoles) and **1c** (1.70 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 315°; ir (potassium bromide): ν max cm^{-1} 2202 (CN), 1656 (CO), uv (ethanol): λ max nm (log ϵ) 216 (4.16), 226 (4.06), 233 (4.00), 255 (4.31), 270 (4.23), 304 (4.20); ^1H nmr (trifluoroacetic acid): δ 2.50 (3H, s, *p*-Me), 2.81 (3H, s, SMe), 7.42 (2H, d, J = 9.0 Hz, aromatic-H), 8.07 (2H, d, J = 9.0 Hz, aromatic-H).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.59; H, 4.32; N, 16.22; S, 12.21.

3,4-Dihydro-6-methylthio-2-*p*-methoxyphenyl-4-oxopyrimidine-5-carbonitrile (**7d**).

This compound (0.82 g, 3.00 mmoles) was synthesized in 30% yield from *p*-methoxybenzamide (1.51 g, 10 mmoles) and **1c** (1.70 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 301°; ir (potassium bromide): ν max cm^{-1} 2201 (CN), 1633 (CO); uv (ethanol): λ max nm (log ϵ) 231 (4.08), 240 (4.11), 255 (4.17), 276 (4.12), 285 (4.16), 318 (4.23); ^1H nmr (trifluoroacetic acid): δ 2.85 (3H, s, SMe), 3.97 (3H, s, OMe), 7.16 (2H, d, J = 9.0 Hz, aromatic-H), 8.20 (2H, d, J = 9.0 Hz, aromatic-H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 56.93; H, 3.86; N, 14.97; S, 12.02.

3,4-Dihydro-6-methylthio-2-styryl-4-oxopyrimidine-5-carbonitrile (**7e**).

This compound (0.94 g, 3.50 mmoles) was synthesized in 35% yield from cinnamide (1.47 g, 10 mmoles) and **1c** (1.70 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from acetic acid to give pale yellow needles, mp 354°; ir (potassium bromide): ν max cm^{-1} 2198 (CN), 1650 (CO); uv (ethanol): λ max nm (log ϵ) 227 (4.31), 268 (4.24), 308 (4.33), 339 (4.37); ^1H nmr (trifluoroacetic acid): 2.77 (3H, s, SMe), 6.83 (1H, d, J = 17.0 Hz, -CH=CH-), 7.50 (5H, m, aromatic-H), 8.18 (1H, d, J = 17.0 Hz, -CH=CH-).

Anal. Calcd. for $C_{14}H_{11}N_3OS$: C, 62.44; H, 4.12; N, 15.60; S, 11.91. Found: C, 62.41; H, 4.19; N, 15.57; S, 11.87.

3,4-Dihydro-2-methyl-6-methylthio-4-oxopyrimidine-5-carbonitrile (**7f**).

This compound (0.33 g, 1.82 mmoles) was synthesized in 18% yield from acetamide (0.59 g, 10 mmoles) and **1c** (1.70 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from benzene-methanol to give colorless needles, mp 307°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 1656 (CO); uv (ethanol): λ max nm (log ϵ) 242 (4.28), 282 (3.91), 311 (3.84); ^1H nmr (trifluoroacetic acid): δ 2.66 (3H, s, 2-Me), 2.73 (3H, s, SMe).

Anal. Calcd. for $C_7H_7N_3OS$: C, 62.44; H, 4.12; N, 15.60; S, 11.91. Found: C, 62.29; H, 4.19; N, 15.56; S, 11.74.

Reaction of **1a** with Amidine Derivatives.

A solution of 0.85 g (5 mmoles) of **1c**, 1.18 g (5 mmoles) of phenylamidine hydrogen chloride, 3 ml of triethylamine in 100 ml of ethanol was refluxed for 5 hours. After removal of the solvent and excess of triethylamine, the residue was washed with 10% hydrochloric acid and recrystallized from acetic acid to give 1.09 g (4.12 mmoles) of colorless needles of **7a**, in 89% yield. Compound **7f** was also prepared in 77% yield from acetoamidine hydrochloride (0.57 g, 2 mmoles) and **1c** (0.87 g, 5 mmoles) in a manner similar to that above described for **7a**.

Methyl 6-Mercapto-2-methyl-4-methylthiopyrimidine-5-carboxylate (**8**).

Sodium hydride (50% in paraffin, 0.48 g, 10 mmoles) was added portionwise to the solution of 1.02 g (5 mmoles) of **1a**, 0.75 g (10 mmoles) of thioacetamide in a solution of 50 ml of benzene and 50 ml of *N,N*-dimethylacetamide under stirring at 0°. The mixture was stirred at room temperature for 20 hours. The color of the reaction mixture was turned to reddish brown. After the reaction, the reaction mixture was poured into 100 ml of ice-water, acidified with 10% hydrogen chloride and extracted with 2 x 50 ml of benzene. The benzene layer was dried over anhydrous sodium sulfate. Removal of the solvent gave a brown solid which was recrystallized from benzene-petroleum ether to give 0.83 g (0.361 mmoles) of tan needles, mp 212°, in 36% yield; ir (potassium bromide): ν max cm^{-1} 1730 (CO); uv (ethanol): λ max nm (log ϵ) 252 (3.84), 279 (4.19), 305 (4.11), 350 (3.97); ^1H nmr (deuteriodimethylsulfoxide): δ 2.47 (3H, s,

2-Me), 2.50 (3H, s, SMe), 4.02 (3H, s, OMe).

Anal. Calcd. for $C_8H_{10}N_2O_2S_2$: C, 41.72; H, 4.38; N, 12.16; S, 27.84. Found: C, 41.75; H, 4.24; N, 12.01; S, 27.71.

Methyl 2-Methyl-4,6-bis(methylthio)pyrimidine-5-carboxylate (**9**).

To a solution of 0.23 g (1 mmole) of **8** and a sodium hydroxide solution (sodium hydroxide, 0.1 g + water 1 ml) in 20 ml of dimethylsulfoxide, methyl iodide (0.28 g, 2 mmoles) was added portionwise under stirring for 3 hours at room temperature. The reaction mixture was poured into 100 ml of ice-water and extracted with 3 x 20 ml of benzene. The benzene layer was dried over anhydrous sodium sulfate. Removal of the solvent gave a brown viscous product which was added 5 ml of methanol and stand over 48 hours to give 0.18 g (0.738 mmole) of yellow needles, mp 90°, in 74% yield. An analytical sample was recrystallized from benzene-petroleum ether to give yellow needles, mp 90°; ir (potassium bromide): ν max cm^{-1} 1700 (CO); uv (ethanol): λ max nm (log ϵ) 270 (4.44), 296 (2.69); ^1H nmr (deuteriochloroform): δ 2.50 (6H, s, SMe), 2.61 (3H, s, 2-Me), 3.95 (3H, s, OMe).

Anal. Calcd. for $C_9H_{12}N_2O_2S_2$: C, 44.24; H, 4.95; N, 11.46; S, 26.25. Found: C, 44.14; H, 5.19; N, 11.25; S, 26.21.

6-Methylthiouracil-5-carbonitrile (**10a**).

This compound (0.35 g, 1.90 mmoles) was synthesized in 19% yield from urea **2h** (0.6 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a manner similar to that described for **7a**. A part of the sample was recrystallized from acetic acid to give pure colorless needles, mp 293° [lit 22, mp 299°]: ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1710, 1660 (CO); uv (ethanol): λ max nm (log ϵ) 236 (4.20), 257 (3.77), 300 (4.16); ^1H nmr (deuteriodimethylsulfoxide): δ 2.68 (3H, s, SMe), 11.67 (2H, bs, NH or OH).

6-Methylthio-3-phenyluracil-5-carbonitrile (**10b**).

This compound (0.91 g, 3.51 mmoles) was synthesized in 35% yield from *N*-phenylurea **2i** (1.36 g, 10 mmoles) and **1a** (2.03 g, 10 mmoles) in a manner similar to that described for **7a**. An analytical sample was recrystallized from acetic acid to give colorless needles, mp 311°; ir (potassium bromide): ν max cm^{-1} 2201 (CN), 1735, 1658 (CO); uv (ethanol): λ max nm (log ϵ) 239 (4.37), 259 (4.01), 302 (4.16); ^1H nmr (deuteriodimethylsulfoxide): δ 2.77 (3H, s, SMe), 7.30 (5H, m, aromatic-H), 9.60 (1H, s, NH or OH).

Anal. Calcd. for $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.50; N, 16.21; S, 12.35. Found: C, 55.60; H, 3.41; N, 15.98; S, 11.99.

3,4-Dihydro-2-methyl-3-morpholino-4-oxopyrimidine-5-carbonitrile (**12**).

A mixture of 0.36 g (2 mmoles) of **7f** and 0.52 g (6 mmoles) of morpholine was heated at 200° for 4 hours. After cooling, 5 ml of ethanol was added to the reaction mixture and white solid was collected by filtration. An analytical sample was recrystallized from acetic acid to give 0.35 g (1.62 mmoles) colorless needles, mp 268°, in 78% yield; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1650 (CO); uv (ethanol): λ max nm (log ϵ) 239 (4.28), 278 (4.05), 296 (4.25); ^1H nmr (deuteriochloroform): δ 2.22 (3H, s, 2-Me), 3.42 (8H, m, morpholino-H), 12.18 (1H, s, OH or NH).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.64; H, 5.47; N, 25.13.

Methyl 2-Phenyl-4-methylsulfonyl-6-oxopyrimidine-5-carboxylate (**13a**).

A solution of 0.55 g (2 mmoles) of **4a**, 1 ml of hydrogen peroxide (30%) in 2 ml of acetic acid was heated at 60° for 6 hours. After cooling, the precipitate was collected by filtration and recrystallized from acetic acid to give 0.43 g (1.40 mmoles) of colorless needles, mp 262°, in 70% yield; (potassium bromide): ν max cm^{-1} 1740, 1650 (CO); uv (ethanol): λ max nm (log ϵ) 252 (4.17), 315 (4.05); ^1H nmr (deuteriodimethylsulfoxide): δ 3.34 (3H, s, SO_2Me), 3.80 (3H, s, OMe), 7.55-8.22 (5H, m, aromatic-H).

Anal. Calcd. for $C_{13}H_{12}N_2O_5S$: C, 50.65; H, 3.92; N, 9.09; S, 10.38. Found: C, 50.53; H, 3.85; N, 9.05; S, 10.33.

Methyl 4-Methylsulfonyl-2-*p*-nitrophenyl-6-oxopyrimidine-5-carboxylate (**13b**).

This compound (0.37 g, 1.05 mmoles) was synthesized in 52% yield from **4b** (0.64 g, 2 mmoles) in a manner similar to that described for **13a**. An analytical sample was recrystallized from acetic acid to give pale yellow needles, mp 219°; ir (potassium bromide): ν max cm^{-1} 1735, 1662 (CO); uv (ethanol): λ max nm (log ϵ) 272 (4.25), 300 (4.15); ^1H nmr (deuteriodimethylsulfoxide): δ 3.38 (3H, s, SO_2Me), 3.84 (3H, s, OMe), 8.40 (4H, m, aromatic-H).

Anal. Calcd. for $C_{13}H_{11}N_3O_7S$: C, 44.19; H, 3.14; N, 11.89; S, 9.08. Found: C, 44.01; H, 3.15; N, 11.52; S, 8.85.

Methyl 6-Benzylamino-3,4-dihydro-2-phenyl-4-oxopyrimidine-5-carboxylate (**11a**).

Method a.

A mixture of 0.31 g (1 mmole) of **13a** and 0.214 g (2 mmoles) of benzylamine was heated at 100° for 1 hour. After cooling, the white product was recrystallized from methanol to give 0.325 g (0.97 mmole) of colorless needles, mp 259°, in 97% yield.

Method b.

A mixture of 0.276 g (1 mmole) of **3a** and 0.214 g (2 mmoles) of benzylamine was heated at 100° for 1 hour. Methanol (50 ml) was added to the above reaction mixture and the this mixture was refluxed for 5 hours. After evaporation of the solvent, the residue was recrystallized from methanol to give 0.188 g (0.56 mmoles) of colorless needles, mp 259°, in 56% yield; ir (potassium bromide): ν max cm^{-1} 1640 (CO); uv (ethanol): λ max nm (log ϵ) 216 (4.50), 236 (4.56), 288 (4.11); ^1H nmr (deuteriodimethylsulfoxide): 3.72 (3H, s, OMe), 4.84 (2H, d, J = 6.0 Hz, $-CH_2-$), 7.30-8.18 (10H, m, aromatic-H), 8.09 (1H, bs, NH or OH), 9.58 (1H, bs, OH or NH).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.67; H, 5.12; N, 12.64.

Methyl 6-Cyclohexylamino-3,4-dihydro-2-phenyl-4-oxopyrimidine-5-carboxylate (**11b**).

This compound was synthesized in 87% (Method a) or 42% (Method b) from **13a** (0.308 g, 1 mmole) or **3a** (0.276 g, 1 mmole) and 0.198 g (2 mmoles) of cyclohexylamine in a manner similar to that described for **11a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 233°; ir (potassium bromide): ν max cm^{-1} 1650 (CO); uv (ethanol): λ max nm (log ϵ) 217 (4.31), 236 (4.42), 259 (4.28), 288 (3.98); ^1H nmr (deuteriochloroform): 1.40-2.14 (10H, m, cyclohexyl-H), 3.93 (3H, s, OMe), 4.29 (1H, bs, N-CH-), 7.05-8.36 (5H, m, aromatic-H), 8.40 (1H, d, J = 7.5 Hz, 6-NH).

Anal. Calcd. for $C_{17}H_{20}N_3O_3$: C, 66.60; H, 6.47; N, 12.83. Found: C, 66.47; H, 6.40; N, 12.74.

Methyl 3,4-Dihydro-6-morpholino-2-phenyl-4-oxopyrimidine-5-carboxylate (**11c**).

This compound (0.192 g, 0.610 mmole) was synthesized in 61% yield (Method a) from **13a** (0.308 g, 1 mmole) and morpholine (0.174 g, 2 mmoles) in a manner similar to that described for **11a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 296°; ir (potassium bromide): ν max cm^{-1} 1720 (CO); uv (methanol): λ max nm (log ϵ) 220 (4.19), 255 (4.51), 296 (4.03); ^1H nmr (deuteriodimethylsulfoxide): δ 3.60 (8H, m, morpholino-H), 3.72 (3H, s, OMe), 7.35-8.16 (5H, m, aromatic-H), 12.16 (1H, bs, OH or NH).

Anal. Calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 61.44; H, 5.44; N, 13.25.

Methyl 6-Anilino-3,4-dihydro-2-phenyl-4-oxopyrimidine-5-carboxylate (**11d**).

This compound (0.202 g, 0.629 mmole) was synthesized in 63% yield (Method b) from **3a** (0.276 g, 1 mmole) and 0.186 g (2 mmoles) of aniline in a manner similar to the described for **11a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 268°; ir (potassium bromide): ν max cm^{-1} 1650 (C=O); uv (ethanol): λ max nm 255, 263, 311; λ min nm 229, 288; ^1H nmr (trifluoroacetic acid): δ 4.08 (3H, s, OMe), 7.30-8.30 (10H, m, aromatic-H).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.95; H, 4.64; N, 13.19.

Methyl 3,4-Dihydro-2-methylphenylamino-4-oxo-pyrimidine-5-carboxylate (**11e**).

This compound (0.288 g, 0.860 mmole) was synthesized in 86% yield (Method b) from **3a** (0.276 g, 1 mmole) and *o*-toluidine (0.214 g, 2 mmoles) in a manner similar to that described for **11a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 280°; ir (potassium bromide): ν max cm^{-1} 1650 (C=O); uv (ethanol): λ max nm (log ϵ) 254 (4.46), 311 (4.20); ^1H nmr (deuteriodimethylsulfoxide): δ 2.28 (3H, s,PH-Me), 3.80 (3H, s, OMe), 7.10-8.08 (9H, m, aromatic-H), 10.94 (1H, bs, NH or OH), 12.24 (1H, bs, OH or NH).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.20; H, 5.09; N, 12.55.

Methyl 4-Chloro-6-methylthio-2-phenylpyrimidine-5-carboxylate (**19**).

A mixture of 2.76 g (10 mmoles) of **4a**, 20 ml of phosphorus oxychloride and 2 ml of *N,N*-dimethylamine was refluxed for 2 hours. After removal of the excess of phosphorus oxychloride, the residue was added to 200 ml of ice-water. The precipitates that appeared was collected by filtration and recrystallized from benzene to give 0.265 g (0.901 mmole) of colorless needles of **19**, mp 97°, in 9% yield. The insoluble products in benzene was **20** which was recrystallized from methanol to give 0.436 g of colorless needles, mp 240, in 20% yield; **19**: ir (potassium bromide): ν max cm^{-1} 1718 (C=O); uv (ethanol): λ max nm (log ϵ) 271 (4.18); ^1H nmr (deuteriochloroform): δ 2.67 (3H, s, SMe), 3.96 (3H, s, OMe), 7.00-8.54 (5H, m, aromatic-H).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2S$: C, 52.97; H, 3.76; N, 9.50; S, 10.22. Found: C, 53.25; H, 3.86; N, 9.35; S, 10.22.

Compound **20** had ir (potassium bromide): ν max cm^{-1} 1630 (C=O); uv (ethanol): λ max nm (log ϵ) 255 (4.52), 284 (4.10); ^1H nmr (trifluoroacetic acid): δ 2.60 (3H, s, SMe), 6.50 (1H, s, 6-H), 7.24-8.30 (5H, m, aromatic-H).

Anal. Calcd. for $C_{11}H_{11}N_2OS$: C, 60.54; H, 4.62; N, 12.84; S, 14.67. Found: C, 60.45; H, 4.59; N, 12.86; S, 14.60.

4-Chloro-6-methylthio-2-phenylpyrimidine-5-carbonitrile (**21a**).

A mixture of 2.43 g (10 mmoles) of **7a** and 20 ml of phosphorus oxychloride, and 2 ml of *N,N*-dimethylaniline was refuxed for 2 hours. After removal of the excess of phosphorus oxychloride, the residue was added to 200 ml of ice-water. The precipitate was collected by filtration and recrystallized from benzene to give 2.24 g (8.58 mmoles) colorless plates, mp 167°, in 86%; ir (potassium bromide): ν max cm^{-1} 2200 (CN); uv (ethanol): λ max nm (log ϵ) 246 (3.97), 282 (4.52), 298 (4.42), 334 (3.79); ^1H nmr (deuteriochloroform): δ 2.82 (3H, s, SMe), 7.16-8.53 (5H, m, aromatic-H).

Anal. Calcd. for $C_{12}H_8ClN_3S$: C, 55.06; H, 3.08; N, 16.06; S, 12.35. Found: C, 55.28; H, 3.13; N, 16.12; S, 12.37.

4-Chloro-2-methyl-6-methylthiopyrimidine-5-carbonitrile (**21b**).

This compound (1.32 g, 6.63 mmoles) was synthesized in 66% yield from **7f** (1.81 g, 10 mmoles) in a manner similar to that described for **21b**. An analytical sample was recrystallized from benzene to give yellow plate, mp 112°; ir (potassium bromide): ν max cm^{-1} 2204 (CN); uv (ethanol): λ max nm (log ϵ) 236 (4.46), 277 (4.30); ^1H nmr (trifluoroacetic acid): δ 2.60, 2.66, 2.73, 2.80 (6-H, s, 2-Me or 6-MeS).

Anal. Calcd. for $C_7H_6ClN_3S$: C, 42.11; H, 3.30; N, 21.00; S, 16.12. Found: C, 42.12; H, 3.12; N, 21.14; S, 16.12.

Methyl 6-Anilino-4-methylthio-2-phenylpyrimidine-5-carboxylate (**22a**).

A mixture of 0.294 g (1 mmole) of **19** and 0.186 g (2 mmoles) of aniline was heated at 100° for 3 hours. After cooling, the crude product was washed with methanol and recrystallized from benzene-methanol to give 0.293 g (0.918 mmole) of colorless needles, mp 148°, in 90% yield; ir (potassium bromide): ν max cm^{-1} 3120 (NH), 1670 (C=O); uv (ethanol): λ max nm (log ϵ) 218 (4.32), 228 (4.18), 278 (5.18); ^1H nmr (deuteriodimethylsulfoxide): δ 3.96 (3H, s, OMe), 7.00-8.60 (10H, m, aromatic-H), 10.19 (1H, bs, NH).

Anal. Calcd. for $C_{19}H_{17}N_3O_2S$: C, 64.94; H, 4.88; N, 11.96; S, 9.12. Found: C, 64.50; H, 4.80; N, 12.05; S, 9.16.

6-Anilino-4-methylthio-2-phenylpyrimidine-5-carbonitrile (**22b**).

A mixture of 0.261 g (1 mmole) of **22a** and 0.186 g of (2 mmoles) of aniline was heated at 100° for 2 hours. The crude product was recrystallized from methanol to give 0.223 g (0.701 mmoles) of colorless needles, mp 242°, in 70% yield; ir (potassium bromide): ν max cm^{-1} 3500 (NH), 2197 (CN); uv (ethanol): λ max nm (log ϵ) 215 (4.35), 228 (4.25), 275 (4.70), 343 (3.90); ^1H nmr (deuteriodimethylsulfoxide): δ 2.73 (3H, s, SMe), 6.90-8.48 (10H, m, aromatic-H), 9.65 (1H, bs, NH).

Anal. Calcd. for $C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60; S, 10.07. Found: C, 67.68; H, 4.44; N, 17.55, S, 9.84.

6-Methylthio-4-morpholino-2-phenylpyrimidine-5-carbonitrile (**22c**).

This compound (0.243 g, 0.757 mmole) was synthesized in 78% yield from **21a** (0.261 g, 1 mmole) and morpholine (0.174 g, 2 mmoles) in a manner similar to that described for **22a**. An analytical sample was recrystallized from methanol to give colorless needles, mp 137°; ir (potassium bromide): ν max cm^{-1} 2200 (CN); uv (ethanol): λ max nm 221, 270, 311, 343: λ min nm 248, 300 (insufficient solubility); ^1H nmr (deuteriochloroform): δ 2.72 (3H, s, SMe), 3.90 (8H, m, morpholino-H), 7.20-8.50 (5H, m, aromatic-H).

Anal. Calcd. for $C_{16}H_{16}N_4OS$: C, 61.52; H, 5.16; N, 17.93; S, 10.26. Found: C, 61.35; H, 5.10; N, 17.83; N, 10.28.

4-Anilino-2-methyl-6-methylthiopyrimidine-5-carbonitrile (**22d**).

This compound (0.205 g, 0.800 mmole) was synthesized in 80% yield from **21a** (0.261 g, 1 mmole) and aniline (0.186 g, 2 mmoles) in a manner similar to that described for **22a**. An analytical sample was recrystallized from methanol to give yellow needles, mp 185°; ir (potassium bromide): δ max cm^{-1} 3300 (NH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 218 (3.23), 276 (4.53); ^1H nmr (deuteriodimethylsulfoxide): δ 2.39 (3H, s, 2-Me), 2.54 (3H, s, SMe), 6.90-7.70 (5H, m, aromatic-H), 9.43 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.80; S, 12.51. Found: C, 60.73; H, 4.77; N, 21.76; S, 12.47.

6-*o*-Anisidino-2-methyl-4-methylthiopyrimidine-5-carbonitrile (**22e**).

This compound (0.205 g, 0.800 mmole) was synthesized in 80% yield from **21b** (0.197 g, 1 mmole) and anisidine (0.246 g, 2 mmoles) in a manner similar to that described for **22a**. An analytical sample was recrystallized from methanol to give yellow needles, mp 185°; ir (potassium bromide): ν max cm^{-1} 3360 (NH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 218 (3.23), 276 (4.53); ^1H nmr (deuteriodimethylsulfoxide): δ 2.39 (3H, s, 2-Me), 2.54 (3H, s, SMe), 6.90-7.70 (5H, m, aromatic-H), 9.43 (1H, bs, NH).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.80; S, 12.51. Found: C, 60.73; H, 4.77; N, 21.76; S, 12.47.

Methyl 1-Cyano-1-(5-cyano-4-methylthio-2-phenylpyrimidin-6-yl)acetate (**23a**).

A mixture of 0.20 g (2 mmoles) of methyl cyanoacetate, 0.261 g (1 mmole) of **21a**, 0.096 g (2 mmoles) of sodium hydride (50% in paraffin), and 30 ml of dimethylsulfoxide was stirring at room temperature for 5 hours. The reaction mixture was poured into 200 ml of ice-water and acidified with 10% hydrogen chloride. The precipitate that appeared was collected by filtration and recrystallized from acetic acid to give 0.136 g (0.42 mmole) of yellow needles, mp 245°, in 38% yield; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1585 (CO); uv (ethanol): λ max nm (log ϵ) 215 (4.24), 274 (4.39), 300 (4.37), 335 (4.40), 392 (3.60); ^1H nmr (trifluoroacetic acid + deuteriochloroform 1:1): δ 2.93 (3H, s, SMe), 4.03 (3H, s, OMe), 7.70-7.90 (3H, m, phenyl-H), 8.20-8.37 (2H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; S, 12.22. Found: C, 50.36; H, 3.86; N, 21.45; S, 12.08.

Ethyl 1-Cyano-1-(5-cyano-4-methylthio-2-phenylpyrimidine-6-yl)acetate (**23b**).

This compound (0.122 g, 0.36 mmole) was synthesized in 36% yield from **21a** (0.261 g, 1 mmole) and ethyl cyanacetate (0.226 g, 2 mmoles) in

a manner similar to that described for **23a**. An analytical sample was recrystallized from methanol to give yellow needles, mp 272°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1585 (CO); uv (ethanol): λ max nm (log ϵ) 217 (4.29), 265 (4.48), 302 (4.32), 335 (4.40), 396 (shoulder, 3.53); ^1H nmr (deuteriodimethylsulfoxide): δ 1.25 (3H, t, J = 7.0 Hz, $O-CH_2-CH_3$), 2.73 (3H, s, SMe), 4.23 (2H, q, J = 7.0 Hz, $O-CH_2-$), 7.60-7.76 (3H, m, phenyl-H), 8.12-8.28 (2H, m, phenyl-H).

Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.44; H, 4.16; N, 16.57; S, 9.36.

1-Cyano-1-(5-cyano-4-methyltho-2-phenylpyrimidin-6-yl)acetonitrile (**23c**).

This compound (0.12 g, 0.46 mmole) was synthesized in 46% yield from **21a** (0.261 g, 1 mmoles) and malononitrile (0.226 g, 2 mmoles) in a manner similar to that described for **23a**. An analytical sample was recrystallized from benzene-methanol to give yellow needles, mp 255°; ir (potassium bromide): ν max cm^{-1} 2205 (CN), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 272 (4.44), 300 (4.38), 327 (4.47), 395 (3.43); ^1H nmr (deuteriodimethylsulfoxide): δ 2.59 (3H, s, SMe), 7.40-7.56 (3H, m, Phenyl-H), 8.26-8.38 (2H, m, Phenyl-H).

Anal. Calcd. for $C_{15}H_9N_5$: C, 61.84; H, 3.11; N, 24.04; S, 11.01. Found: C, 61.71; H, 3.04; N, 23.95; S, 11.05.

Methyl 1-Cyano-1-(5-cyano-2-methyl-4-methylthiopyrimidin-6-yl)acetate (**23d**).

This compound (0.10 g, 0.38 mmole) was synthesized in 38% yield from **21b** (0.199 g, 1 mmole) and methyl cyanoacetate (0.20 g, 2 mmoles) in a manner similar to that described for **23a**. An analytical sample was recrystallized from acetic acid to give pale yellow needles, mp 268°; ir (potassium bromide): ν max cm^{-1} 2200 (CN), 1598 (CO); uv (ethanol): λ max nm (log ϵ) 217 (4.29), 260 (3.99), 283 (4.05), 331 (4.39); ^1H nmr (trifluroacetic acid + deuteriochloroform 1:1): δ 2.65 (6H, 2-Me, SMe), 3.80 (3H, s, OMe).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; S, 12.22. Found: C, 50.36; H, 3.86; N, 21.45; S, 12.08.

1,2-Dichloro-10-hydroxy-1-oxo-2-phenylpyrimido[4,5-*b*]quinoline (**24**).

A mixture of 0.642 g (2 mmoles) of **11d** and 15 ml of diphenyl ether was refluxed for 2 hours. After cooling, to the reaction mixture, 30 ml of petroleum ether was added. The resulting percipitate was collected by filtration and recrystallized from acetic acid to give 0.366 g (1.20 mmoles), colorless needles, mp >350°, in 60% yield; ir (potassium bromide): ν max cm^{-1} 1678 (C=O), 1605, 1550; uv (ethanol): λ max nm 211, 233, 262, 270, 290, 302; λ min nm 226, 240, 274 (insufficient solubility); ^1H nmr (trifluoroacetic acid): δ 7.30-8.34 (8H, m, aromatic-H), 8.56 (1H, d, J = 8.0 Hz, 6-H).

Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.52. Found: C, 70.38; H, 3.75; N, 14.57.

6-Anilino-4-methylthio-2-phenylpyrimidine-5-carboxyaldehyde (**25**).

Diisobutylaluminum hydride (25% solution in toluene, 3 mmoles) was added *via* a syringe to a solution of **22b** (0.636 g, 2.0 mmoles) in dry benzene (30 ml) under nitrogen atmosphere. The mixture was stirred at room temperature for 4 hours. Aqueous 10% hydrochloric acid (20 ml) was added and then the reaction mixture was stirred for 2 hours. The reaction mixture was neutralized with aqueous 10% sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted twice with 20 ml of chloroform. The organic layer and extracts were successively combined, washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford a crude tan product. The aldehyde **25** was used in the next reaction without further purification. An analytical sample was recrystallized from methanol to give 0.166 g (0.52 mmole) of pale yellow needles, mp 129°, in 26% yield; ir (potassium bromide): ν max cm^{-1} 1600 (C=O); uv (ethanol): λ max nm 232, 286, 236; λ min nm 244 (insufficient solubility); ^1H nmr (deuteriochloroform): δ 2.73 (3H, s, SMe), 7.00-8.68 (10H, m, aromatic-H), 10.33 λ (1H, s, CHO), 11.10 (1H, s, NH).

Anal. Calcd. for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07; S, 9.98. Found: C, 66.92; H, 4.68; N, 13.17; S, 9.92.

4-Hydroxy-2-phenylpyrimido[4,5-*b*]quinoline (**26**).

A mixture of the crude aldehyde **25** (0.10 g, 0.31 mmole) and 10 g of polyphosphoric acid was heated at 100-120° for 2 hours with stirring. After cooling, the reaction mixture was poured into 200 ml of ice-water, neutralized with aqueous 10% sodium bicarbonate, and extracted with twice 20 ml of chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from methanol to give 0.051 g (0.19 mmole) of **26**, mp 357°, in 60% yield, pale yellow plates; ir (potassium bromide): ν max cm^{-1} 3050 (OH), 1675 (CO); uv (ethanol): λ max nm (log ϵ) 230 (4.49), 260 (4.46), 290 (4.58), 366 (4.02); ^1H nmr (deuteriodimethylsulfoxide): δ 7.54-8.37 (10H, m, Ar-H, OH), 9.23 (1H, s, 5-H); ms: m/z 273 (M^+, 100), 170, 113.

Anal. Calcd. for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.72; H, 4.03; N, 15.28.

3,4-Dihydro-2-phenyl-4,5-dioxo-5*H*-pyrido[1,2-*a*]pyrimido[4,5-*d*]pyrimidine (**27**).

A mixture of 0.62 g (2 mmoles) of **13a** and 0.376 g (4 mmoles) of 2-aminopyridine was heated at 100° for 2 hours. After cooling, the crude product was recrystallized from benzene-methanol to give 0.394 g (1.34 mmoles) of colorless plates, mp >350°, in 67% yield; ir (potassium bromide): ν max cm^{-1} 1718 (C=O); uv (ethanol): λ max nm: 261, 293, 306, 354, 370; λ min nm 235, 270, 343 (insufficient solubility); ^1H nmr (trifluoroacetic acid): 7.22-8.28 (8H, m, aromatic-H), 8.94 (1H, d, J = 7.0 Hz, 7-H).

Anal. Calcd. for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30. Found: C, 65.99; H, 3.34; N, 19.00.

3-Amino-6-hydroxy-2-methylpyrazolo[3,4-*d*]pyrimidine (**28a**).

A mixture of 1.81 g (10 mmoles) of **7f** and 0.75 g (20 mmoles) of hydrazine hydrate was heated at 100° for 2 hours. The crude product was recrystallized from ethanol to give 1.42 g (8.67 mmoles) of colorless crystals, mp >350°, in 80% yield; ir (potassium bromide): ν max cm^{-1} 3160 (NH); uv (ethanol): λ max nm (log ϵ) 226 (4.06), 272 (4.56); ^1H nmr (deuteriodimethylsulfoxide): δ 2.24 (3H, s, 2-Me), 5.10 (2H, bs, NH), 11.43 (1H, bs, NH or OH), 11.93 (1H, bs, NH or OH).

Anal. Calcd. for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.29; H, 4.28; N, 42.04.

3-Amino-6-hydroxy-2-phenylpyrazolo[3,4-*d*]pyrimidine (**28b**).

This compound (1.86 g, 0.819 mmole) was synthesized in 82% yield from **7a** (2.43 g, 10 mmoles) and 1.08 g (10 mmoles) of phenyl hydrazine in a manner similar to that described for **28a**. An analytical sample was recrystallized from ethanol to give colorless crystals, mp >350°; ir (potassium bromide): ν max cm^{-1} 3400 (NH); uv (ethanol): λ max nm 239, 265, 330; λ min nm 222, 258 (insufficient solubility); ^1H nmr (deuteriodimethylsulfoxide): δ 5.37 (2H, bs, NH_2), 7.35-8.14 (5H, m, aromatic-H), 11.91 (1H, bs, NH or OH).

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found: C, 58.12; H, 3.96; N, 30.82.

3-Amino-4-hydroxy-6-methyl-2-phenylpyrazolo[3,4-*d*]pyrimidine (**28c**).

A mixture of 1.81 g (10 mmoles) of **7f** and 1.08 g (10 mmoles) of phenylhydrazine was heated at 120° for 2 hours. The crude product was recrystallized from methanol to give 1.83 g (7.59 mmoles) of colorless needles, mp 295°, in 76% yield; ir (potassium bromide): ν max cm^{-1} 3300, 3150 (NH), 1670 (C=O); uv (ethanol): λ max nm (log ϵ) 242 (4.23), 270 (3.71), 305 (3.32); ^1H nmr (deuteriodimethylsulfoxide): δ 2.23 (3H, s, 2-Me), 6.25 (2H, bs, NH_2), 7.37-7.63 (5H, m, aromatic-H), 11.12 (1H, bs, NH or OH).

Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 60.07; H, 4.59; N, 28.99.

3-Amino-4-methylthio-2,6-diphenylpyrazolo[3,4-*d*]pyrimidine (**29**).

A mixture of 0.261 g (1 mmole) of **21a** and 0.108 g (1 mmole) of phenylhydrazine was heated at 120° for 2 hours. The reaction mixture was

washed with 100 ml of water and recrystallized from methanol to give 0.196 g (0.651 mmoles) of pale yellow needles, mp 180°, in 65% yield; ir (potassium bromide): ν max cm^{-1} 3270, 3160 (NH); uv (ethanol): λ max nm (log ϵ) 226 (4.53), 305 (4.20); ^1H nmr (deuteriodimethylsulfoxide): δ 2.69 (3H, s, SMe), 6.68-8.58 (10H, m, aromatic-H), 9.95 (2H, bs, NH_2).

Anal. Calcd. for $C_{18}H_{15}N_5$: C, 64.84; H, 4.53; N, 21.00; S, 9.62. Found: C, 65.08; H, 4.62; N, 20.50; S, 9.43.

5-Cyano-4-hydrazino-6-morpholino-2-phenylpyrimidine (**30**).

This compound (2.22 g, 7.5 mmoles) was synthesized in 75% yield from **22c** (3.12 g, 10 mmoles) and 0.75 g (19 mmoles) of hydrazine hydrate in a manner similar to that described for **29**. An analytical sample was recrystallized from methanol to give colorless needles, mp 220°; ir (potassium bromide): ν max cm^{-1} 3300 (NH), 2190 (CN); uv (ethanol): λ max nm (log ϵ) 216 (4.34), 256 (4.63), 315 (3.89); ^1H nmr (deuteriodimethylsulfoxide): δ 3.78 (8H, m, morpholino-H), 4.70 (2H, bs, NH_2), 7.40-8.42 (5H, m, aromatic-H), 8.63 (1H, bs, NH).

Anal. Calcd. for $C_{15}H_{16}N_6O$: C, 60.80; H, 5.44; N, 28.36. Found: C, 60.89; H, 5.41; N, 28.33.

5-Amino-4-hydrazino-2-phenyl-7*H*-pyrazolo[3,4-*d*]pyrimidine (**31**).

A mixture of 0.31 g (1 mmole) of **22c** and 1.0 g (31 mmoles) of hydrazine hydrate was heated at 180° for 2 hours. After cooling, the reaction mixture was washed with methanol, the crude product was recrystallized from methanol to give 0.22 g (0.91 mmole) of colorless crystals, mp 260°; ir (potassium bromide): ν max cm^{-1} 3400-2800 (broad, NH); uv (ethanol): λ max nm (log ϵ) 255 (4.49), 325 (3.57); ms: m/z 241 (M^+, 100), 210 (10), 104 (28), 78 (26), 66 (15).

Anal. Calcd. for $C_{11}H_{11}N_7$: C, 54.76; H, 4.60; N, 40.64. Found: C, 54.71; H, 4.61; N, 40.60.

Methyl 3,4-Dihydroxy-6-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (**32**).

A solution of 0.62 g (2 mmoles) of **13a**, 0.212 g (2 mmoles) of methyl thioglycolate and 0.5 ml of triethylamine in 100 ml of methanol was refluxed for 6 hours. After evaporation of the solvent, the residue was recrystallized from benzene-methanol to give 0.314 g (1.04 mmoles) of pale yellow needles, mp >300°, in 52% yield; ir (potassium bromide): ν max cm^{-1} 1680 (C=O); uv (ethanol): λ max nm; 222, 257, 300, 350: λ min nm 235, 286, 310 (insufficient solubility); ^1H nmr (deuteriochloroform): δ 3.84 (3H, s, OMe), 7.46-8.20 (5H, m, aromatic-H), 12.73 (2H, bs, OH).

Anal. Calcd. for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27; S, 10.61. Found: C, 55.36; H, 3.27; N, 9.06; S, 10.60.

Methyl 5-Amino-4-methylthio-2-methylthieno[2,3-*d*]pyrimidine-6-carboxylate (**33**).

A solution of 1.99 g (10 mmoles) of **22b**, 1.06 g (10 mmoles) methyl thioglycolate, and 0.5 ml of triethylamine in 50 ml of methanol was refluxed for 4 hours. After evaporation of solvent and excess of triethylamine, the residue was washed with 50 ml of water and recrystallized from methanol to give 1.69 g (6.28 mmole) of yellow needles, mp 188°, in 63% yield; ir (potassium bromide): ν max cm^{-1} 3300, 3400 (NH), 1677 (C=O); uv (ethanol): λ max nm (log ϵ) 239 (4.18), 253 (4.10), 275 (4.25), 310 (4.25); ^1H nmr (deuteriochloroform): δ 2.70 (3H, s, Me or SMe), 2.73 (3H, s, Me or SMe), 3.85 (3H, s, OMe), 6.50 (2H, s, NH_2).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S_2$: C, 44.59; H, 4.12; N, 15.60; S, 23.81. Found: C, 44.67; H, 4.28; N, 15.51; S, 23.56.

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