Synthesis of Pyrazolo[3,4-*d*]pyrimidine Derivatives Using Ketene Dithioacetals

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Received August 28, 1989

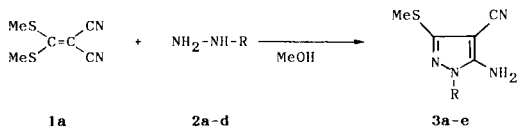
The cyclization of 5-amino-3-methylthiopyrazole-4-carbonitriles or 4-carboxamides **3a-j**, which were prepared by the reaction of ketene dithioacetals **1a,b** [**1a**: bis(methylthiomethylenemalononitrile; **1b**: bis(methylthio)methylenecyanoacetamide] with hydrazines (hydrazine hydrate, phenylhydrazine, *p*-chlorophenylhydrazine, *p*-nitrophenylhydrazine), with formamide or carbon disulfide proceeded to give the corresponding 4-amino- or 4-hydroxy-3-methylthiopyrazolo[3,4-*d*]pyrimidines **6a-h** in good yields. 3-Aminopyrazolo[3,4-*d*]pyrimidine derivatives **6i-l** were also obtained by the application of the cyclization reaction of 3,5-diaminopyrazoles with formamide.

J. Heterocyclic Chem., **27**, 775 (1990).

Pyrazolo[3,4-*d*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs [1,2]. Various related compounds of these also have anti-tumor and anti-leukemic activities. Several 3-substituted pyrazolo[3,4-*d*]pyrimidine derivatives have also shown pharmacological activity like allopurinol which namely is the inhibitor of xanthine oxidase [2]. As a part of an extension of our studies on ketene dithioacetals, we now wish to report the synthesis of various types of 3-substituted pyrazolo[3,4-*d*]pyrimidine derivatives by using ketene dithioacetals. Ketene dithioacetals are important and versatile reagents, especially, which have been used for the synthesis of polyfunctionalized heterocycles [3-8]. These ketene dithioacetals are extensively used for the synthesis of pyrazole and pyrimidine derivatives by the displacement of the methylthio group with bifunctionalized amine such as hydrazines or amidines [8]. Pyrazolo[3,4-*d*]pyrimidines are mainly synthesized by two routes; A) pyrazole derivatives; B) pyrimidine derivatives as the starting materials. We now tried the synthesis of pyrazolo[3,4-*d*]pyrimidines by the method A.

The reaction of ketene dithioacetals **1a,b** (**1a**: bis(methylthio)methylenemalononitrile; **1b**: bis(methylthio)methylenecyanoacetamide) with hydrazine derivatives **2a-d** (**2a**: hydrazine hydrate, **2b**: phenylhydrazine, **2c**: *p*-chlorophenylhydrazine, **2d**: *p*-nitrophenylhydrazine, **2e**: phenylhydrazone) at 100° for 3-4 hours gave the corresponding 5-aminopyrazole derivatives **3a-j** in good yields. 4-Carbamoylpyrazoles **3f-i** were alternatively prepared by the hydrolysis of 3-cyanopyrazoles **3a-d** with concentrated sulfuric acid. Next, we tried the synthesis of 3-aminopyrazoles which are key intermediates for the synthesis of

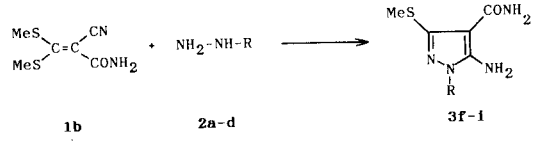
Scheme 1



1a 2a-d 3a-e

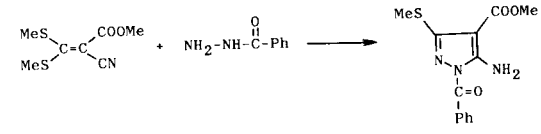
	R
2a:	H
b:	C_6H_5
c:	C_6H_4-Cl(p)
d:	C_6H_4-NO_2
e:	CO-C_6H_5

	R
3a:	H
b:	C_6H_5
c:	C_6H_4-Cl(p)
d:	C_6H_4-NO_2(p)
e:	CO-C_6H_5

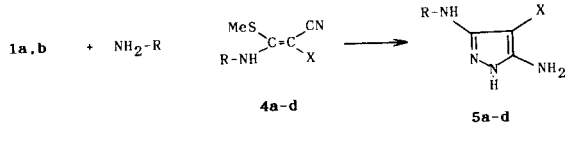


1b 2a-d 3f-i

	R
3f:	H
g:	C_6H_5
h:	C_6H_4-Cl(p)
i:	C_6H_4-NO_2(p)



1c 2e 3j



4a-d 5a-d

	X	R
4a:	CN	C_6H_5
b:	CN	C_6H_4-Cl(p)
c:	CN	C_6H_4-OMe(p)
d:	$CONH_2$	C_6H_5

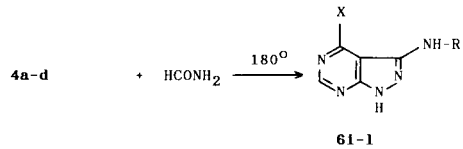
	X	R
5a:	CN	C_6H_5
b:	CN	C_6H_4-Cl(p)
c:	CN	C_6H_4-OMe(p)
d:	$CONH_2$	C_6H_5

3-aminopyrazolo[3,4-*d*]pyrimidine derivatives. 3-Arylamino-5-aminopyrazole-4-carbonitriles **5a-d** were synthesized by the reaction of hydrazine hydrate and 3-*N*-substituted aminoacrylonitriles **4a-c** which were prepared by the displacement reaction of **1a** with aromatic amines (aniline, *p*-chloroaniline, *p*-anisidine) at 100° [9] (Scheme 1).

Gompper has first reported the preparation of 4-amino-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**6a**) by the condensation of **3a** with orthoformate followed by the cyclization with ammonia [10]. We tried directly the synthesis of pyrazolo[3,4-*d*]pyrimidines by treatment of **3** with formamide. The reaction of **3a-d** with formamide at 180° for 2 hours gave the corresponding desired 4-amino-3-methylthiopyrazolo[3,4-*d*]pyrimidines **6a-d** in good yields. 4-Hydroxy-3-methylthiopyrazolo[3,4-*d*]pyrimidines **6e-h** and 4-arylamino-3-methylthiopyrazolo[3,4-*d*]pyrimidines **6i-k** were also prepared from **3f-i** and **4a-d** in a manner similar to that the preparation of **6a-d**. Desulfurization of **6i** with Raney-nickel in ethanol at reflux gave an allopurinol, 1*H*-pyrazolo[3,4-*d*]pyrimidine (**7**) in 42% yield. In general, the methylthio group on heterocycles undergoes the displacement reaction with amines to give the corresponding amino heterocyclic compounds. However, the methylthio group of compounds **6** could not react with amines under various conditions. In the case of pyrazole ring, the methylsulfonyl group of **8a,b** also did not react with amines to give 3-aminopyrazolo[3,4-*d*]pyrimidines (Scheme 2).

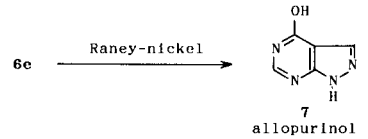
The reaction of **3b** with guanidine carboxylate at 200° for 4 hours afforded 4,6-diamino-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**9a**) in 95% yield. Compound **3b** was allowed to react with urea to give 4-amino-6-hydroxy-3-methylthio-1-phenylpyrazolo[3,4-**d**]pyrimidine (**9b**). Similarly, the reaction of **3g** with urea gave the corresponding cyclized product, 4,6-dihydroxy-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**10**) in 92% yield.

Since it is well known that the reaction of *o*-aminobenznitrile with carbon disulfide in the presence of the corresponding base gives cyclized product, quinolizine derivatives [11], we tried the application of the above reaction to

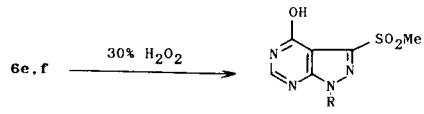


6i-l

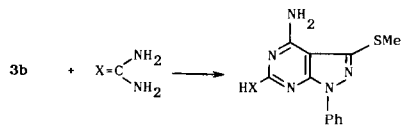
	X	R
6i:	NH_2	C_6H_5
j:	NH_2	C_6H_4-Cl(p)
k:	NH_2	C_6H_4-OMe(p)
l:	OH	C_6H_5



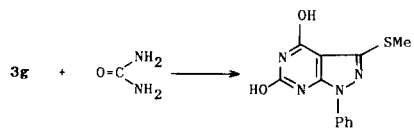
7
allopurinol



8a,b
a: R = H
b: R = Ph



9a,b



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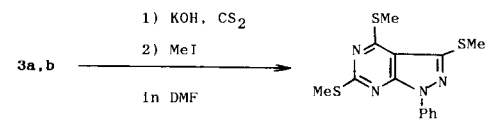
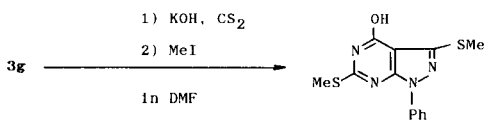


11a,b



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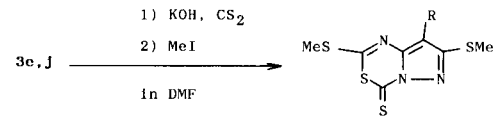
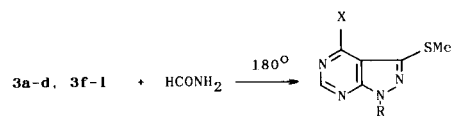


13a,b
11a: R = CN
11b: R = COOMe

Scheme 2

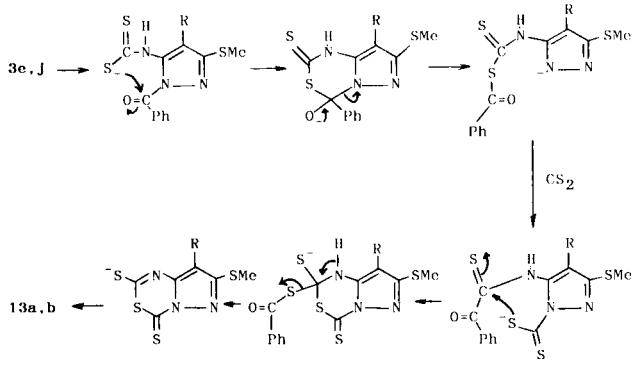


6a-h

	X	R
6a:	NH_2	H
b:	NH_2	C_6H_5
c:	NH_2	C_6H_4-Cl(p)
d:	NH_2	C_6H_4-NO_2(p)
e:	OH	H
f:	OH	C_6H_5
g:	OH	C_6H_4-Cl(p)
h:	OH	C_6H_4-NO_2(p)

the synthesis of pyrazolo[3,4-*d*]pyrimidines. Compounds **3a,b,g** were allowed to react with carbon disulfide in the presence of potassium hydroxide in dimethyl formamide (DMF), followed by treatment with methyl iodide to give the desired products, 3,4,6-trimethylthiopyrazolo[3,4-*d*]-pyrimidine (**11a,b** and **12**), in good yields. When **3e,j** was allowed to react with carbon disulfide under the same reaction condition, pyrazolo[5,1-*d*]-s-thiadiazoline derivatives (**13a,b**) were obtained in 53 and 64% yields, respectively. The outline of the reaction mechanism is shown in Scheme 3.

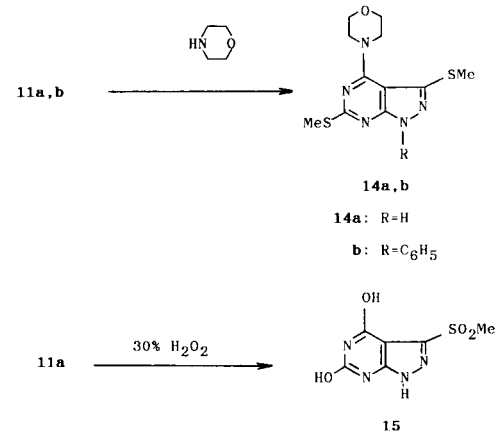
Reaction Mechanism.

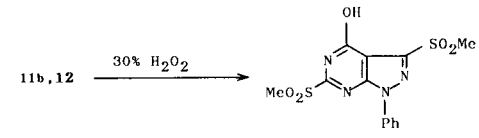


The reaction of **11a,b** with morpholine gave only 4-morpholino derivatives **14a,b** in 62 and 46% yields, respectively.

The treatment of **11a** with 30% hydrogen peroxide afforded hydrolysis compound, 3-methylsulfonyl-4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine (**15**). Though, in the case of 1-phenyl derivative **12**, this reaction gave 3,6-bimethylthiosulfonyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (**16**) which was also prepared from **11b** in a similar manner. These results suggested that the methylthio group on the 4-position is more active than that of on the 6-position.

Scheme 3





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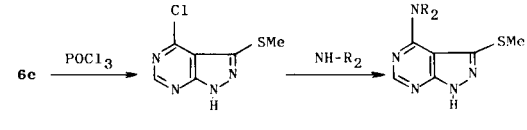
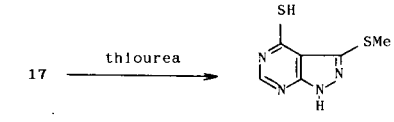


17 18a-c

18a: benzylamino
b: morpholino
c: piperidino



19

4-Chloropyrazolo[3,4-*d*]pyrimidines are key intermediates for the preparation of pharmacological active compounds. So we attempted the chlorination of **6e** with phosphoryl chloride to give **17** in good yield, respectively. The aminolysis of **17** with alkyl amines (benzylamine, morpholine, piperidine) gave the corresponding 4-aminopyrazolo-[3,4-*d*]pyrimidines **18a-c** in good yields. Treatment of **17** with thiourea afforded thiopurinol analogue, 3-methylthio-4-mercaptopyrazolo[3,4-*d*]pyrimidine (**19**) which is expected pharmacological activity like 6-mercaptopurine.

In conclusion, ketene dithioacetals shown in this paper are found to be useful reagents for the synthesis of various types of pyrazolo[3,4-*d*]pyrimidine derivatives.

EXPERIMENTAL

All melting points were determined in a capillary tube and uncorrected. Infrared (ir) spectra were recorded in potassium bromide pellets on a 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 MHz) and JNM-FX-90Q(90 MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (ms) were recorded on a JEOL JMS-01SG mass spectrometer.

5-Amino-3-methylthiopyrazole-4-carbonitrile (**3a**).

A solution of 17.0 g (0.1 mole) of **1a** and 6.0 g (0.12 mole) of hydrazine hydrate in 200 ml of methanol was refluxed for 3 hours. After evaporation of the solvent, the residue was recrystallized from methanol to give 15.0 g (0.097 mole) of colorless needles, mp 152° [lit 10, mp 152°], in 97% yield; ^{1}H-nmr (deuteriochloroform): δ 2.45 (3H, s, SMe), 6.25 (2H, bs, NH_2).

5-Amino-3-methylthio-1-phenylpyrazole-4-carbonitrile (**3b**).

This compound (22.5 g, 0.098 mole) was synthesized in 98% yield from **1a** (17.0 g, 0.1 mole) and phenylhydrazine (10.8 g, 0.1 mole) in a manner similar to that described for the preparation of **3a**. This compound was recrystallized from methanol to give tan needles, mp 136°; ir (potassium bromide): ν max cm^{-1} 3300, 3400 (NH), 2190 (CN); uv (ethanol): λ max nm (log ϵ) 234 (4.10), 290 (3.67), 330 (2.82); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.48 (3H, s, SMe), 6.70 (2H, bs, NH_2), 7.48 (5H, s, phenyl-H).

Anal. Calcd. for $C_{11}H_{10}N_4S$: C, 57.38; H, 4.37; N, 24.33. Found: C, 57.31; H, 4.39; N, 24.28; S, 13.72.

5-Amino-1-(4-chlorophenyl)-3-methylthiopyrazole-4-carbonitrile (**3c**).

This compound (20.67 g, 0.078 mole) was synthesized in 78% yield from **1a** (17.0 g, 0.1 mole) and 4-chlorophenylhydrazine (14.3 g, 0.1 mole) in a manner similar to that described for **3a**. This compound was recrystallized from methanol to give tan needles, mp 159°; ir (potassium bromide): ν max cm^{-1} 3280, 3380 (NH), 2210 (CN); uv (ethanol): λ max nm (log ϵ) 234 (4.41), 282 (3.96); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.63 (3H, s, SMe), 7.27-7.70 (4H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_9ClNS$: C, 49.91; H, 3.43; N, 21.21; S, 12.11. Found: C, 49.82; H, 3.45; N, 21.24; S, 12.24.

5-Amino-3-methylthio-1-(4-nitrophenyl)pyrazole-4-carbonitrile (**3d**).

This compound (21.2 g, 0.077 mole) was synthesized in 77% yield from **1a** (17.0 g, 0.1 mole) and phenylhydrazine (10.8 g, 0.1 mole) in a manner similar to that described for the preparation of **3a**. This compound was recrystallized from methanol to give tan needles, mp 231°; ir (potassium bromide): ν max cm^{-1} 3300, 3360 (NH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 224 (4.21), 260 (3.77), 320 (3.73); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.54 (3H, s, SMe), 7.15 (2H, bs, NH_2), 7.73-8.43 (4H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44; S, 11.65. Found: C, 47.94; H, 3.26; N, 25.62; S, 11.73.

5-Amino-1-benzoyl-3-methylthiopyrazole-4-carboxamide (**3e**).

A mixture of 1.70 g (10 mmoles) of **1a** and 1.36 g (10 mmoles) of benzoylhydrazine was heated at 150° for 1 hour. This mixture was immediately melted with heat and then become solid. The reaction product was recrystallized from a mixture of methanol and benzene to give 2.40 g (9.3 mmoles) of **3e** as colorless needles, mp 290°, in 93% yield; ir (potassium bromide): ϵ max cm^{-1} 2200 (CN), 1670 (CO); uv (ethanol): λ max nm (log ϵ) 227 (4.35), 264 (4.14); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.48 (3H, s, SMe), 7.55-8.23 (5H, m, phenyl-H).

Anal. Calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28; S, 11.60. Found: C, 52.23; H, 4.37; N, 20.26; S, 11.61.

5-Amino-3-methylthiopyrazole-4-carboxamide (**3f**).

This compound (1.39 g, 8.1 moles) was synthesized in 81% yield from **1b** (1.88 g, 10 mmoles) and hydrazine hydrate (0.6 g, 12 mmoles) in a manner similar to that described for the preparation of **3a**. This compound was recrystallized from methanol to give colorless needles, mp 176°; ir (potassium bromide): ν max cm^{-1} 3240, 3300, 3400 (NH), 1655 (CO); uv (ethanol): λ max nm (log ϵ) 230 (4.01), 260 (3.88); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.40 (3H, s, SMe), 6.00 (2H, bs, NH_2), 6.75 (2H, bs, NH_2), 11.80 (1H, bs, NH).

Anal. Calcd. for $C_5H_6N_4OS$: C, 34.87; H, 4.68; N, 32.53; S, 18.62. Found: C, 34.74; H, 4.66; N, 32.69; S, 18.22.

5-Amino-3-methylthio-1-phenylpyrazole-4-carboxamide (**3g**).

This compound (1.59 g, 6.40 mmoles) was synthesized in 64% yield from **1b** (1.88 g, 10 mmoles) and phenylhydrazine (1.08 g, 10 mmoles) in a manner similar to that described for the preparation of **3a**. This compound was recrystallized from methanol to give tan needles, mp 151°; ir (potassium bromide): ν max cm^{-1} 3430, 3380, 3300, 3240 (NH), 1660 (CO); uv (ethanol): λ max nm (log ϵ) 241 (4.39); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.50 (3H, s, SMe), 6.50 (2H, bs, NH_2), 6.81 (2H, bs, NH_2), 7.46 (5H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.56; S, 12.91. Found: C, 53.31; H, 4.82; N, 22.64; S, 12.87.

5-Amino-1-(4-chlorophenyl)-3-methylthiopyrazole-4-carboxamide (**3h**).

This compound (2.19 g, 7.7 mmoles) was synthesized in 77% yield from **1b** (1.88 g, 10 mmoles) and 4-chlorophenylhydrazine (1.42 g, 10 mmoles) in a manner similar to that described for the preparation of **3a**. This compound was recrystallized from methanol to give tan needles, mp 135°; ir (potassium bromide): ν max cm^{-1} 3380, 3320, 3280, 3240 (NH); uv (ethanol): λ max nm (log ϵ) 247 (4.45); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.50 (3H, s, SMe), 6.58 (2H, bs, NH_2), 7.49 (4H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_{11}ClN_4OS$: C, 46.73; H, 3.92; N, 19.87; S, 11.34. Found: C, 46.57; H, 4.07; N, 19.51; S, 11.01.

5-Amino-3-methylthio-1-(*p*-nitrophenyl)pyrazole-4-carboxamide (**3i**).

This compound (2.40 g, 8.2 mmoles) was synthesized in 82% yield from **1a** (1.88 g, 10 mmoles) and 4-nitrophenylhydrazine (1.53 g, 10 mmoles) in a manner similar to that described for **3a**. This compound was recrystallized from methanol to give tan needles, mp 180°; ir (potassium bromide): ν max cm^{-1} 3330, 3260 (NH), 1640 (CO); uv (ethanol): λ max nm (log ϵ) 227 (4.34), 2.64 (4.08), 344 (3.98); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.55 (3H, s, SMe), 6.85 (2H, bs, NH_2), 7.35 (2H, bs, $CONH_2$), 7.80-8.45 (4H, m, phenyl-H).

Anal. Calcd. for $C_{11}H_{11}N_5O_3S$: C, 45.05; H, 3.78; N, 23.88; S, 10.93. Found: C, 44.93; H, 3.67; N, 24.02; S, 11.08.

Methyl 5-Amino-1-benzoyl-3-methylthiopyrazole-4-carboxylate (**3j**).

This compound (22.5 g, 0.098 mole) was synthesized in 98% yield from **1a** (17.0 g, 0.1 mole) and phenylhydrazine (10.8 g, 0.1 mole) in a manner similar to that described for the preparation of **3e**. This compound was recrystallized from methanol to give tan needles, mp 149°; ir (potassium bromide): ν max cm^{-1} 3300, 3400 (NH), 1685, 1660 (CO); uv (ethanol): λ max nm (log ϵ) 247 (4.35), 282 (4.08); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.32 (3H, s, SMe), 3.75 (3H, s, OMe), 7.50-8.14 (5H, m, phenyl-H).

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42; S, 11.01. Found: C, 53.31; H, 4.47; N, 14.15; S, 11.01.

3-Anilino-2-cyano-3-methylthioacrylonitrile (**4a**).

A solution of 1.86 g (20 mmoles) of aniline and 3.40 g (20 mmoles) of **1a** in 50 ml of ethanol was refluxed for 1 hour. After evaporation of the solvent, the residue was recrystallized from

solvent, the residue was recrystallized from methanol to give 3.55 g (17.5 mmoles) of colorless needles, mp 177° [lit 9, mp 176°], in 88% yield; ir (potassium bromide): ν max cm^{-1} 3295 (NH), 2195 (CN); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.45 (3H, s, SMe), 7.55 (5H, m, phenyl-H), 10.36 (1H, bs, NH).

3-(4-Chloroaniline)-2-cyano-3-methylthioacrylonitrile (**4b**).

This compound (3.39 g, 14.3 mmoles) was synthesized in 72% yield from **1a** (3.40 g, 20 mmoles) and 4-chloroaniline (2.54 g, 20 mmoles) in a manner similar to that described for the preparation of **4a**. This compound was recrystallized from methanol to give tan needles, mp 157°; ir (potassium bromide): ν max cm^{-1} 3240 (NH), 2210 (CN); uv (ethanol): λ max nm (log ϵ) 322 (4.19); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.54 (3H, s, SMe), 7.30 (2H, d, J = 9.0 Hz, phenyl-H), 7.48 (2H, d, J = 9.0 Hz, phenyl-H), 10.49 (1H, bs, NH).

Anal. Calcd. for $C_{11}H_8ClN_3S$: C, 52.91; H, 3.23; N, 16.83; S, 12.84. Found: C, 52.89; H, 3.25; N, 16.85; S, 12.69.

2-Cyano-3-(4-methoxyphenylamino)-3-methylthioacrylonitrile (**4c**).

This compound (3.53 g, 14.4 mmoles) was synthesized in 72% yield from **1a** (3.40 g, 20 mmoles) and *p*-anisidine (2.46 g, 20 mmoles) in a manner similar to that described for the preparation of **4a**. This compound was recrystallized from methanol to give tan needles, mp 154° [lit 9, mp 151°]; ir (potassium bromide): ν max cm^{-1} 3360 (NH), 2195 (CN); ^{1}H-nmr (deuteriochloroform): δ 2.30 (3H, s, SMe), 3.83 (3H, s, OMe), 6.91 (2H, d, J = 9.23 Hz, phenyl-H), 7.18 (2H, J = 9.23 Hz, phenyl-H), 7.96 (1H, bs, NH).

3-Anilino-2-cyano-3-methylthioacrylamide (**4d**).

This compound (1.91 g, 8.20 mmoles) was synthesized in 82% yield from **1b** (1.88 g, 10 mmoles) and aniline (1.40 g, 15 mmoles) in a manner similar to that described for **3a**. This compound was recrystallized from methanol to give tan needles, mp 155°; ir (potassium bromide): ν max cm^{-1} 3475-3195 (NH), 2190 (CN), 1651 (CO).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.57; H, 4.77; N, 17.99; S, 13.68.

5-Amino-3-phenylaminopyrazole-4-carbonitrile (**5a**).

A mixture of 2.03 g (10 mmoles) of **3a** and 0.6 g (12 mmoles) of hydrazine hydrate was heated at 100° for 1 hour. The reaction product was recrystallized from methanol to give 1.67 g (8.4 mmoles) of **5a** as colorless needles, mp 205°, in 84% yield; ir (potassium bromide): ν max cm^{-1} 2200 (CN); uv (ethanol): λ max nm (log ϵ) 229 (4.26), 274 (4.33).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.36; H, 4.45; N, 35.16.

5-Amino-3-(4-chlorophenylamino)pyrazole-4-carbonitrile (**5b**).

This compound (2.0 g, 8.6 mmoles) was synthesized in 86% yield from **4a** (2.37 g, 10 mmoles) and hydrazine hydrate (0.6 g, 12 mmoles) in a manner similar to that described for **5a**. This compound was recrystallized from methanol to give tan needles, mp 249°; ir (potassium bromide): ν max cm^{-1} 3420 (NH), 2200 (CN); uv (ethanol): λ max nm (log ϵ) 229 (4.26), 274 (4.33); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 6.18 (2H, bs, NH_2), 7.11 (2H, d, J = 6.0 Hz, phenyl-H), 7.45 (2H, d, J = 6.0 Hz, phenyl-H).

Anal. Calcd. for $C_{10}H_8ClN_5$: C, 51.40; H, 3.45; N, 35.16. Found: C, 51.47; H, 3.39; N, 35.16.

5-Amino-3-(*p*-methoxyphenylamino)pyrazole-4-carbonitrile (**5c**).

This compound (2.24 g, 9.8 mmoles) was synthesized in 98% yield from **4c** (2.45 g, 10 mmoles) and hydrazine hydrate (0.6 g, 12 mmoles) in a manner similar to that described for **5a**. This compound was recrystallized from a mixture of benzene and methanol to give tan needles, mp 189°; ir (potassium bromide): ν max cm^{-1} 3440 (NH), 2190 (CN); uv (ethanol): λ max nm (log ϵ) 230 (4.16), 268 (4.14); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 3.77 (3H, s, OMe), 6.12 (2H, bs, NH_2), 6.75 (2H, J = 6.0 Hz, phenyl-H), 7.38 (2H, d, J = 6.0 Hz, phenyl-H).

Anal. Calcd. for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.31; H, 4.88; N, 30.21.

3-Anilino-5-aminopyrazole-4-carboxamide (**5d**).

This compound (0.97 g, 4.5 mmoles) was synthesized in 90% yield from **4d** (1.17 g, 5 mmoles) and hydrazine hydrate (0.6 g, 12 mmoles) in a manner similar to that described for **5a**. This compound was recrystallized from methanol to give colorless needles, mp 136°; ir (potassium bromide): ν max cm^{-1} 3475-3200 (NH), 1652 (CO).

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.29; H, 5.14; N, 32.23.

4-Amino-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**6a**).

A mixture of 1.0 g (6.49 mmoles) of **3a** and 1 ml of formamide was heated at 200° for 1 hour. After cooling, the solid was washed with 10 ml of water and recrystallized from a mixture of methanol and benzene to give 0.85 g (4.7 mmoles) of colorless needles, mp 248°, in 72% yield; ir (potassium bromide): ν max cm^{-1} 3450-3300 (NH); uv (ethanol): λ max nm (log ϵ) 229 (4.04), 259 (3.91), 282 (3.42), 289 (3.71); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.78 (3H, s, SMe), 8.60 (1H, s, 6-H).

Anal. Calcd. for $C_6H_7N_5S$: C, 39.77; H, 3.89; N, 38.65; S, 17.69. Found: C, 39.64; H, 3.73; N, 38.47; S, 17.55.

4-Amino-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**6b**).

This compound (0.99 g, 3.83 mmoles) was synthesized in 88% yield from **3b** (1.0 g, 4.35 mmoles) and formamide (1 ml) in a manner similar to that described for **6a**. This compound was recrystallized from methanol to give colorless needles, mp 182°; ir (potassium bromide): ν max cm^{-1} 3420-3280 (NH); uv (ethanol): λ max nm (log ϵ) 244 (4.47), 258 (4.17), 307 (4.02); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.72 (3H, s, SMe), 7.00-8.30 (6H, m, 6-H, phenyl-H).

Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.22. Found: C, 56.09; H, 4.40; N, 27.01.

4-Amino-3-methylthio-1-(*p*-chlorophenylpyrazolo[3,4-*d*]pyrimidine (**6c**).

This compound (0.82 g, 3.1 mmoles) was synthesized in 81% yield from **3c** (1.0 g, 3.8 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless crystals, mp 248°; ir (potassium bromide): ν max cm^{-1} 3460-3300 (NH); uv (ethanol): λ max nm (log ϵ) 247 (4.55), 260 (4.22), 310 (4.13); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.77 (3H, s, SMe), 7.50 (2H, d, J = 8.0 Hz, phenyl-H), 8.05 (2H, d, J = 8.0 Hz, phenyl-H), 8.45 (1H, s, 6-H).

Anal. Calcd. for $C_{12}H_{10}ClN_5$: C, 49.40; H, 3.45; N, 24.00. Found: C, 49.35; H, 3.47; N, 23.89.

4-Amino-3-methylthio-1-(*p*-nitrophenyl)pyrazolo[3,4-*d*]pyrimidine (**6d**).

This compound (0.98 g, 3.24 mmoles) was synthesized in 89% yield from **3d** (1.0 g, 3.64 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give pale yellow crystals, mp 310°; ir (potassium bromide): ν max cm^{-1} 3360-3300 (NH); uv (ethanol): λ max nm (insufficient solubility) 217, 263, 348; λ min 280; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.51 (3H, s, SMe), 7.73-8.62 (5H, m, 6-H, phenyl-H).

Anal. Calcd. for $C_{12}H_{10}N_6O_2S$: C, 47.68; H, 3.33; N, 27.80; S, 10.61. Found: C, 47.71; H, 3.20; N, 27.50; S, 10.73.

3-Methylthio-4-hydroxypyrazlo[3,4-*d*]pyrimidine (**6e**).

This compound (0.59 g, 3.25 mmoles) was synthesized in 61% yield from **3f** (0.59 g, 5.32 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless needles, mp 288°; ir (potassium bromide): ν max cm^{-1} 3150-2800 (NH), 1680 (CO); uv (ethanol): λ max nm (log ϵ) 230 (4.55), 249 (4.22); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.50 (3H, s, SMe), 8.00 (1H, s, 6-H).

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.32; N, 30.75. Found: C, 39.73; H, 3.37; N, 30.34; S, 17.33.

4-Hydroxy-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**6f**).

This compound (0.98 g, 3.79 mmoles) was synthesized in 94% yield from **3g** (1.0 g, 4.03 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless crystals, mp 269°; ir (potassium bromide): ν max cm^{-1} 2820 (NH or OH broad), 1675 (CO); uv (ethanol): λ max nm (log ϵ) 248 (4.52), 302 (3.98); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.48 (3H, s, SMe), 7.30-8.24 (6H, m, 6-H, phenyl-H).

Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.92; N, 21.69; S, 12.41. Found: C, 55.80; H, 3.85; N, 21.68; S, 12.41.

1-(*p*-Chlorophenyl)-4-hydroxy-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**6g**).

This compound (0.71 g, 2.84 mmoles) was synthesized in 80% yield from **3h** (1.0 g, 3.55 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless needles, mp 278°; ir (potassium bromide): ν max cm^{-1} 2800 (NH or OH broad), 1675 (CO); uv (ethanol): λ max nm (log ϵ) 241 (4.54), 305 (4.11); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.64 (3H, s, SMe), 7.51-8.31 (6H, m, 6-H, phenyl-H).

Anal. Calcd. for $C_{12}H_9ClNOS$: C, 49.23; H, 3.10; N, 19.14; S, 10.95. Found: C, 49.26; H, 3.10; N, 19.05; S, 10.89.

4-Hydroxy-1-(*p*-nitrophenyl)-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**6g**).

This compound (0.806 g, 2.66 mmoles) was synthesized in 78% yield from **3i** (1.0 g, 3.41 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless crystals, mp 345°; ir (potassium bromide): ν max cm^{-1} 2820-3070 (NH or OH broad), 1700 (CO); uv (ethanol): λ max nm (insufficient solubility) 229, 263; λ min nm; 250, 297; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.65 (3H, s, SMe), 8.27 (1H, s, 6-H), 8.41 (4H, m, phenyl-H).

Anal. Calcd. for $C_{12}H_9N_5O_3S$: C, 47.52; H, 2.99; N, 23.09; S, 10.57. Found: C, 47.56; H, 2.96; N, 22.80; S, 10.64.

4-Amino-3-anilinopyrazolo[3,4-*d*]pyrimidine (**6h**).

This compound (0.51 g, 2.27 mmoles) was synthesized in 46% yield from **5a** (1.0 g, 4.93 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give tan crystals, mp 246°; ir (potassium bromide): ν max cm^{-1} 3400-3000 (NH broad); uv (ethanol): λ max nm (log ϵ) 238 (4.06), 263 (4.12).

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 62.25; H, 4.75; N, 33.00. Found: C, 62.01; H, 4.88; N, 33.39.

4-Amino-3-(*p*-chlorophenylamino)pyrazolo[3,4-*d*]pyrimidine (**6i**).

This compound (0.51 g, 1.98 mmoles) was synthesized in 46% yield from **5b** (1.0 g, 4.30 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give tan crystals, mp 285°; ir (potassium bromide): ν max cm^{-1} 3300-2980 (NH broad); uv (ethanol): λ max nm (log ϵ) 239 (4.21), 263 (4.24), 310 (3.78).

Anal. Calcd. for $C_{11}H_9ClN_6$: C, 51.47; H, 3.53; N, 31.18. Found: C, 51.60; H, 3.38; N, 31.03.

4-Amino-3-(*p*-methoxyphenylamino)pyrazolo[3,4-*d*]pyrimidine (**6j**).

This compound (0.55 g, 2.14 mmoles) was synthesized in 49% yield from **5c** (1.0 g, 4.37 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give tan crystals, mp 232°; ir (potassium bromide): ν max cm^{-1} 3200-2980 (NH broad); uv (ethanol): λ max nm (log ϵ) 239 (4.21), 263 (4.24), 310 (3.78).

Anal. Calcd. for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.79. Found: C, 56.22; H, 4.69; N, 32.65.

3-Anilino-4-hydroxypyrazolo[3,4-*d*]pyrimidine (**6l**).

This compound (0.92 g, 4.06 mmoles) was synthesized in 88% yield from **5d** (1.0 g, 4.61 mmoles) and 1 ml of formamide in a manner similar to that described for the preparation of **6a**. This compound was recrystallized from methanol to give colorless crystals, mp 344°; ir (potassium bromide): ν max cm^{-1} 3405 (NH), 1676 (CO); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 7.25-7.45 (5H, m, phenyl-H), 8.38 (1H, s, 6-H).

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found: C, 58.01; H, 4.12; N, 30.65.

4-Hydroxypyrazolo[3,4-*d*]pyrimidine (Allopurinol) (**7**).

A mixture of 1.0 g (5.5 mmoles) of **6e**, *ca.* 3 g of Raney-nickel (preparation by W-2 method from 7 g of a mixture of nickel and zinc) and 50 ml of ethanol was refluxed for 40 hours. After removal of the Raney-nickel and the solvent, the residue was recrystallized from methanol to give colorless crystals (0.42 g, 3.09 mmoles), mp >380° [lit 14, 384] in 66% yield. This compound was in accord with commercially available sample (Aldrich) comparing with its ir spectrum.

4-Hydroxy-3-sulfonylpyrazolo[3,4-*d*]pyrimidine (**8a**).

A mixture of 1.0 g (5.49 mmoles) of **6e**, 1 ml of 30% hydrogen peroxide, and 30 ml of acetic acid was stirred at room temperature for 1 hour and stirring was continued 2 more hours at 70°. After removal of the acetic acid and water, the residue was washed twice with 10 ml of water and then 10 ml of methanol. This product was recrystallized from a mixture of methanol and benzene to give 1.09 g (5.11 mmoles) colorless needles, mp 295°,

in 93% yield; ir (potassium bromide): ν max cm^{-1} 3200-2800 (NH or OH, broad), 1685 (CO); uv (ethanol): λ max nm (log ϵ) 213 (4.17), 220 (4.15), 256 (3.96).

Anal. Calcd. for $C_6H_6N_4O_3S$: C, 33.64; H, 2.82; N, 26.16; S, 14.97. Found: C, 33.81; H, 2.91; N, 26.21; S, 15.07.

4-Hydroxy-3-methylsulfonyl-1-phenylpyrazolo[3,4-*d*]pyrimidine (**8b**).

This compound (1.00 g, 3.45 mmoles) was synthesized in 89% yield from **6f** (1.0 g, 3.88 mmoles) in a manner similar to that described for **8a**. This compound was recrystallized from a mixture of methanol and benzene to give colorless crystals, mp 304°; ir (potassium bromide): ν max cm^{-1} 3140-2840 (NH or OH broad), 1680 (CO); uv (ethanol): λ max nm (ethanol) 233 (4.37), 247 (4.06).

Anal. Calcd. for $C_{12}H_{10}N_4O_3S$: C, 49.65; H, 3.47; N, 19.30; S, 11.05. Found: C, 49.61; H, 3.53; N, 19.21; S, 11.01.

4,6-Diamino-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**9a**).

A mixture of 1.15 g (5 mmoles) of **3b** and 0.90 g (5 mmoles) of guanidine carbonate was heated at 200° for 2 hours. After cooling, this crude product was washed twice with 10 ml of hot-water, dried in air, and recrystallized from a mixture of methanol and benzene to give 1.19 g (4.37 mmoles) as colorless crystals, mp 192°, in 95% yield; ir (potassium bromide): ν max^{-1} 3300-3100 (NH_2); uv (ethanol): λ max nm (log ϵ) 218 (4.50), 258 (4.48), 304 (4.30); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.68 (3H, s, SMe), 6.45 (2H, bs, NH_2), 6.74 (2H, bs, NH_2), 7.25-8.30 (5H, m, phenyl-H).

Anal. Calcd. for $C_{12}H_{12}N_6S$: C, 52.93; H, 4.44; N, 30.86; S, 11.77. Found: C, 52.83; H, 4.53; N, 30.58; S, 11.63.

4-Amino-6-hydroxy-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**9b**).

A mixture of **3b** (1.15 g, 5 mmoles) and 0.30 g (5 mmoles) of urea was heated at 200° for 2 hours. After cooling, the crude product was washed two times with 10 ml of hot water, dried in air, and recrystallized from methanol to give 1.19 g (4.35 mmoles) as yellow needles, mp 246°, in 87% yield; ir (potassium bromide): ν max cm^{-1} 3020 (NH or OH), 1675 (CO); uv (ethanol): λ max nm (insufficient solubility) 264, 295; λ min nm 220.

Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06; N, 25.62; S, 11.73. Found: C, 52.64; H, 3.96; N, 25.82; N, 11.75.

4,6-Dihydroxy-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**10**).

A mixture of 1.24 g (5 mmoles) of **3f** and 1.20 g (10 mmoles) of urea was heated at 160° for 20 minutes. The clear solution became mushy and heating was continued for another 1 hour at 190° until the mushy mixture become solid. The resulting solid was dissolved in a hot dilute sodium hydroxide solution and the boiling basic solution was then carefully acidified with acetic acid. The solution was allowed to stand approximately ten minutes and was then filtered. The crude yield of **10** was 1.27 g (4.62 mmoles, 92%), mp 341°. Further purification was accomplished by the reprecipitation from a hot basic solution with acetic acid. A small amount was recrystallized from a large volume of water and dried at 150° for analysis; ir (potassium bromide): ν max cm^{-1} 3160-3040 (NH or OH, broad), 1680 (CO); uv (ethanol): λ max nm (insufficient solubility): max nm 250, 288.

Anal. Calcd. for $C_{12}H_{11}N_4O_2S$: C, 52.55; H, 3.66; N, 20.43; S, 11.69. Found: C, 52.45; H, 3.68; N, 20.33; S, 11.59.

3,4,6-Tris(methylthio)pyrazolo[3,4-*d*]pyrimidine (**11a**).

To a solution of 1.54 g (10 mmoles) of **3a** and about 20% potassium hydroxide solution (potassium hydroxide, 1.68 g, 30 mmoles, water 7 ml) in 20 ml of dimethyl sulfoxide, stirred at 0°, 1.14 g (15 mmoles) of carbon disulfide was added in several portions during 30 minutes. After another 1 hour at room temperature, 4.26 g (30 mmoles) of methyl iodide was slowly added to the stirring solution over a period of 30 minutes and stirring was continued for 1 hour at room temperature. The reaction mixture was poured into 100 ml of ice-water and then acidified with 10% hydrochloric acid. The precipitate was collected by filtration and washed several times with water. This crude product was recrystallized from methanol to give 1.88 g (7.3 mmoles) or orange needles, mp 288°, in 73% yield; ir (potassium bromide): ν max cm^{-1} 3160 (NH); uv (ethanol): λ max nm (insufficient solubility) 258, 295, 306, 325; λ min nm 228, 280; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.55 (3H, s, SMe), 2.60 (3H, s, SMe), 2.62 (3H, s, SMe).

Anal. Calcd. for $C_8H_{10}N_4S_3$: C, 37.19; H, 3.90; N, 21.68; S, 37.23. Found: C, 37.16; H, 3.96; N, 21.82; S, 37.06.

3,4,6-Tris(methylthio)-1-phenylpyrazolo[3,4-*d*]pyrimidine (**11b**).

This compound (2.94 g, 8.8 mmoles) was synthesized in 88% yield from **3b** (2.30 g, 10 mmoles) in a manner similar to that described for the preparation of **11a**. This compound was recrystallized from methanol to give yellow needles, mp 160°; ir (potassium bromide): ν max cm^{-1} 2905, 1590, 1530, 1500, 1200, 1005, 745; uv (ethanol): λ max nm (ethanol) 261 (4.50), 274 (4.51); ^{1}H-nmr (deuteriodimethyl sulfoxide and trifluoroacetic acid, 5:1): δ 2.62 (3H, s, SMe), 2.67 (3H, s, SMe), 2.73 (3H, s, SMe), 7.45-8.28 (5H, m, phenyl-H).

Anal. Calcd. for $C_{14}H_{14}N_4S_3$: C, 50.30; H, 4.22; N, 16.75; S, 28.76. Found: C, 50.30; H, 4.24; N, 16.76; S, 28.70.

4-Hydroxy-3,6-bis(methylthio)-1-phenylpyrazolo[3,4-*d*]pyrimidine (**12**).

This compound (1.88 g, 6.2 mmoles) was synthesized in 62% yield from **3f** (2.48 g, 10 mmoles) in a manner similar to that described for the preparation of **11a**. This compound was recrystallized from methanol to give colorless crystals, mp 304°; ir (potassium bromide): ν max cm^{-1} 2800 (OH broad), 1670 (CO); uv (ethanol): λ max nm (log ϵ) 228 (4.37), 249 (4.54), 268 (4.35), 304 (4.07); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.62 (6H, s, SMe), 7.45-8.17 (5H, m, phenyl-H).

Anal. Calcd. for $C_{13}H_{12}N_4S_2O$: C, 51.30; H, 3.97; N, 18.41; S, 21.07. Found: C, 51.08; H, 3.91; N, 18.39; S, 21.62.

1-Cyano-2,7-bis(methylthio)pyrazolo[1,5-*c*][1,3,5]thiadiazine-5(5*H*)-thione (**13a**).

To a solution of 2.58 g (10 mmoles) of **3e** and *ca.* 20% potassium hydroxide (potassium hydroxide, 1.68 g, 30 mmoles), water (7 ml) in 20 ml of dimethyl sulfoxide, stirred 0°, 2.28 g (30 mmoles) of carbon disulfide was added in several portions during 30 minutes. After another 1 hour at room temperature, 2.86 g (20 mmoles) of methyl iodide was slowly added to the stirring solution over a period of 30 minutes and stirring was continued for 1 hour at room temperature. The reaction mixture was poured into 100 ml of ice-water and then acidified with 10% hydrochloric acid. The precipitate was collected by filtration and washed several times with water. This crude product was recrystallized from methanol to give 1.52 g (5.31 mmoles) as yellow needles, mp 214°, in 53% yield; ir (potassium bromide): ν max cm^{-1} 2210 (CN); uv (ethanol): λ max nm (log ϵ) 221 (4.23), 286 (3.40), 315

(3.39); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.69 (3H, s, SMe), 2.79 (3H, s, SMe).

Anal. Calcd. for $C_8H_6N_4S_4$: C, 33.55; H, 2.11; N, 19.56; S, 44.78. Found: C, 33.59; H, 2.08; N, 19.73; S, 44.57.

1-Methoxycarbonyl-2,7-bis(methylthio)pyrazolo[1,5-*c*][1,3,5]-thiadiazine-5(5*H*)-thione (**14b**).

This compound (1.30 g, 6.40 mmoles) was synthesized in 64% yield from **3j** (2.91 g, 10 mmoles) in a manner similar to that described for **13a**. This compound was recrystallized from methanol to give yellow needles, mp 217°; ir (potassium bromide): ν max cm^{-1} 1690 (CO); uv (ethanol): λ max nm (ethanol) 221 (4.22), 284 (4.38), 317 (4.45); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.59 (3H, s, SMe), 2.81 (3H, s, SMe), 3.87 (3H, s, OMe).

Anal. Calcd. for $C_9H_9N_3S_4O_2$: C, 33.86; H, 2.84; N, 13.17; S, 40.15. Found: C, 33.59; H, 2.84; N, 13.59; S, 40.07.

3,6-Bis(methylthio)-4-morpholinopyrazolo[3,4-*d*]pyrimidine (**14a**).

A mixture of 1.29 g (5 mmoles) of **11a** and 0.87 g (10 mmoles) of morpholine was refluxed at 180° for 2 hours. The product was crystallized by treating of the reaction mixture with a small amount of methanol. This product was recrystallized from methanol to give 0.92 g (3.10 mmoles) of colorless needles, mp 216°, in 62% yield; ir (potassium bromide): ν max cm^{-1} 3200 (NH), 1580, 1540, 1442; uv (ethanol): λ max nm (log ε) 213 (4.25), 256 (4.58), 290 (4.01); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.47 (3H, s, SMe), 2.57 (3H, s, SMe), 3.72 (8H, bs, C-CH_2-CH_2-N).

Anal. Calcd. for $C_{11}H_{15}N_5OS_2$: C, 44.43; H, 5.08; N, 23.55; S, 21.56. Found: C, 44.23; H, 5.18; N, 23.42; S, 21.09.

3,6-Bis(methylthio)-4-morpholino-1-phenylpyrazolo[3,4-*d*]pyrimidine (**14b**).

This compound (0.858 g, 2.36 mmoles) was synthesized in 46% yield from **11b** (1.17 g, 5 mmoles) in a manner similar to that described for **14a**. This compound was recrystallized from methanol to give colorless crystals, mp 158°; ir (potassium bromide): ν max cm^{-1} 2840, 1560, 1256; uv (ethanol): λ max nm (log ε) 246 (4.59), 268 (4.53), 318 (4.01); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.69 (3H, s, SMe), 3.75 (8H, bs, O-CH_2-CH_2-N), 7.50-8.18 (5H, m, phenyl-H).

Anal. Calcd. for $C_{17}H_{19}N_5OS_2$: C, 54.67; H, 5.13; N, 18.75; S, 17.71. Found: C, 54.55; H, 5.19; N, 18.73; S, 17.92.

4,6-Dihydroxy-3-methylsulfonylpyrazolo[3,4-*d*]pyrimidine (**15**).

A solution of 2.58 g (10 mmoles) of **11a**, 10 ml of 30% hydrogen peroxide in 50 ml of acetic acid was heated at 70° for 2 hours. After evaporation of the solvent, the residue was washed with 10 ml of water. The product was dried in air and recrystallized from methanol to give 2.12 g (9.22 mmoles) of colorless crystals, mp > 300° in 92% yield; ir (potassium bromide): ν max cm^{-1} 3210-2820 (NH or OH, broad), 1670 (CO); uv (ethanol): λ max nm (insufficient solubility) 251, 284: λ min 267; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 3.47 (3H, s, S_2O Me).

Anal. Calcd. for $C_6H_6N_4O_4S$: C, 31.31; H, 2.63; N, 24.35; S, 13.90. Found: C, 31.36; H, 2.64; N, 24.20; S, 13.77.

4-Hydroxy-3,6-bis(methylsulfonyl)-1-phenylpyrazolo[3,4-*d*]pyrimidine (**16**).

This compound (3.35 g, 9.1 mmoles; 3.64 g, 9.9 mmoles) was synthesized in 91 and 99% yields, respectively, from **11a** (3.34 g, 10 mmoles) or **12** (3.04 g, 10 mmoles) in a manner similar to that described for the preparation of **15**. This compound was recrystallized from methanol to give colorless crystals, mp 283°; ir (potassium bromide): ν max cm^{-1} 1720 (CO); uv (ethanol): λ max nm (insufficient solubility) 225, 256, 300; λ min nm; 250, 297; ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 3.49 (3H, s, SMe), 3.58 (3H, s, SO_2Me), 7.68-8.10 (5H, m, phenyl-H).

Anal. Calcd. for $C_{13}H_{12}N_4O_5S_2$: C, 42.39; H, 3.28; N, 15.16; S, 17.28. Found: C, 42.27; H, 3.31; N, 15.16; S, 17.28.

4-Chloro-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**17**).

A mixture of 8 ml of phosphorus oxychloride and 1.82 g (10 mmoles) of 4-hydroxy-3-methylthiopyrazolo[3,4-*d*]pyrimidine (**6e**) was refluxed for 3 hours. Excess phosphorus oxychloride was distilled under reduced pressure, and the residual syrup was poured, with stirring, onto crushed ice. The mixture was allowed to stand for 30 minutes. The precipitate was collected by filtration and washed well with ice-water until free from acid. The crude compound was dried in air and recrystallized from benzene to give 1.46 g (7.3 ml) of colorless needles, mp 183°, in 73% yield; ir (potassium bromide): ν max cm^{-1} 3100 (NH); uv (ethanol): λ max nm (log ε) 237 (4.31), 266 (3.41), 330 (3.49); ^{1}H-nmr (deuteriochloroform and trifluoroacetic acid, 3:1): δ 2.70 (3H, s, SMe), 8.90 (1H, s, 6-H).

Anal. Calcd. for $C_6H_5ClN_4S$: C, 35.92; H, 2.51; N, 27.92; S, 15.98. Found: C, 35.91; H, 2.53; N, 27.78; S, 15.95.

4-Benzylamino-3-methylthio-1-phenylpyrazolo[3,4-*d*]pyrimidine (**18a**).

A solution of 2.0 g (10 mmoles) of **17** and 2.67 g (25 mmoles) of benzylamine dissolved in 100 ml of absolute ethanol was refluxed for 5 hours. On cooling, colorless needles crystallized slowly from the reaction solution. The product was recrystallized from ethanol to yield 2.03 g (7.5 mmoles), mp 183° in 75% yield; ir (potassium bromide): ν 3400 (NH); uv (ethanol): λ max nm (log ε) 267 (4.08), 275 (4.09), 234 (3.95); ^{1}H-nmr (deuteriochloroform): δ 2.60 (3H, s, SMe), 4.86 (2H, d, J = 3.0 Hz, N-CH_2-), 6.48 (1H, t, J = 3.0 Hz, NH), 7.22-7.50 (5H, m, phenyl-H).

Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.76; H, 4.47; N, 25.91; S, 11.86. Found: C, 57.82; H, 4.45; N, 25.99; S, 11.81.

3-Methylthio-4-morpholinopyrazolo[3,4-*d*]pyrimidine (**18b**).

This compound (0.90 g, 3.59 mmoles) was synthesized in 36% yield from **17** (2.0 g, 10 mmoles) in a manner similar to that described for the preparation of **18a**. This compound was recrystallized from methanol to give colorless needles, mp 205°; ir (potassium bromide): ν max cm^{-1} 3180 (NH), 3100, 1685, 1650, 1250, 1110; uv (ethanol): λ max nm (log ε) 221 (4.27), 282 (4.11), 307 (3.97).

Anal. Calcd. for $C_{10}H_{13}N_5OS$: C, 47.79; H, 5.21; N, 27.87; S, 12.79. Found: C, 47.76; H, 5.18; N, 27.81; S, 12.90.

3-Methylthio-4-piperidinopyrazolo[3,4-*d*]pyrimidine (**18c**).

This compound (1.49 g, 6.0 mmoles) was synthesized in 60% yield from **17** (2.0 g, 10 mmoles) in a manner similar to that described for the preparation of **18a**. This compound was recrystallized from methanol to give colorless needles, mp 160°; ir (potassium bromide): ν max cm^{-1} 3190, 3080 (NH), 1590, 1550, 1500, 1264; uv (ethanol): λ max nm (log ε) 221 (4.26), 285 (4.12), 305 (4.05).

Anal. Calcd. for $C_{11}H_{15}N_5S$: C, 52.99; H, 6.06; N, 28.06; S, 12.86. Found: C, 53.02; H, 6.06; N, 28.06; S, 13.06.

3-Methylthio-4-mercaptopyrazolo[3,4-*d*]pyrimidine (**19**).

A solution of 2.0 g (10 mmoles) of **17** and 1.52 g (20 mmoles) of thiourea in 100 ml of absolute ethanol was refluxed for 3 hours. The solution was cooled and filtered. The product was collected by the filtration and recrystallized from a mixture of methanol and benzene to give 1.10 g (5.56 mmoles) of white crystals, mp 270°, in 56% yield; ir (potassium bromide): ν max cm^{-1} 1585, 1560, 1180, 845; uv (ethanol): λ max nm (log ϵ) 321 (4.30); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 2.55 (3H, s, SMe), 8.10 (1H, s, 6-H), 13.35 (1H, bs, NH); ms: m/z 198 (M^+, 100), 183 (50), 165 (20), 152 (90).

Anal. Calcd. for $C_6H_6N_4S_2$: C, 36.35; H, 3.05; N, 28.26; S, 32.34. Found: C, 36.10; H, 2.98; N, 28.22; S, 32.11.

Acknowledgements.

The work was supported to A. H. in part by Grant-in-Aids for Scientific Research of the Ministy of Education, Science, and Culture (No. 01470091 and on Priority Areas: No.01649516), and the Mitsubishi Foundation, CIBA-GEIGY Foundation for the Promotion of Science, the Naito Foundation.

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