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Pyrimidine Derivatives. II.[1] New Synthesis and Reactions of 4-Amino-2-methylthiopyrimidine Derivatives[2]

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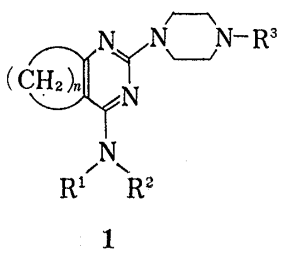
4-Amino-2-methylthiopyrimidine derivatives (**4**) were synthesized by the cyclization of 3-cyano-2-methylisothiourea (**2**) with ketones (**3**). Oxidation of **4** produced 4-amino-2-methylsulfinyl or 2-methylsulfonylpyrimidine derivatives (**7** or **8**). Amination of **7** or **8** gave hypoglycemic 2-(1-piperazinyl)pyrimidines (**1**). Compounds **4** were converted to 4(3H)-pyrimidinone derivatives (**12**). Derivatives **1** were also synthesized *via* **12**.

Keywords——hypoglycemic drug; base-catalyzed cyclization; 3-cyano-2-methylisothiourea; 4-amino-2-methylthiopyrimidines; 4-amino-2-methylthio-5,6,7,8-tetrahydroquinazoline; 2-methylthio-4(3H)-pyrimidinones; 2-methylsulfinylpyrimidines amination; 2-methylsulfonylpyrimidines amination

In a previous paper[1] of this series, we reported the synthesis of 4-amino-2-(1-piperazinyl))-5,6-polymethylenepyrimidine derivatives (**1**) and their hypoglycemic activity with inhibition of platelet aggregation.

As part of our studies on pyrimidine derivatives, a simple method for the synthesis of 4-amino-2-methylthiopyrimidines was sought and the reactions of these compounds were studied.

Many methods of pyrimidine synthesis are known,[3] but there are only a few reports that describe a reaction of the type(–C–C– plus –N–C–N–C–). Modest *et al.* reported the synthesis of 2,4-diamino-5,6-polymethylenepyrimidines by the cyclization of cycloalkanones with cyanoguanidine.[4] Although this procedure was attractive for the synthesis of 2-(1-piperazinyl)pyrimidines (**1**), it did not give satisfactory yields in the reaction of cycloalkanones with 1,1-dimethyl-2-cyanoguanidine. Thus, we required a simple and direct method for synthesizing key intermediates that could produce biologically active pyrimidines (**1**).



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$n=3$ and 4. $NR^1R^2=NH_2$, mono-alkylamino, and di-alkylamino. $R^3=H$, CH_2Ph, Alkyl.

Chart 1

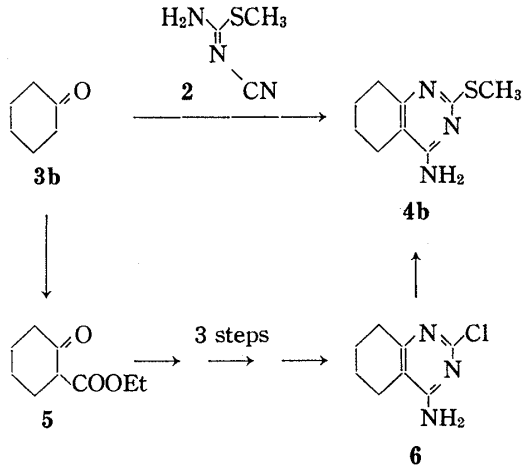
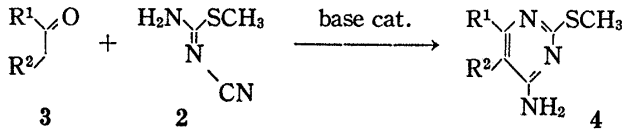
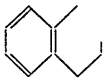


Chart 2

TABLE I. Cyclization of Ketones (3) with 3-Cyano-2-methylisothiourea (2)



3 2 4

Compd. No.	R^1	R^2	Cat.	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
4a	$-(CH_2)_3-$		Pyrrolidine	56	163—164	$C_8H_{11}N_3S$	53.01 (53.11	6.21 6.43	23.18 23.16)
			DBU	67[b]					
4b	$-(CH_2)_4-$		Pyrrolidine	67	134—135	$C_9H_{13}N_3S$	55.35 (55.32	6.71 6.63	21.52 21.72)
			DBU	56					
			Non cat.	50					
4c	$-(CH_2)_5-$		DBU	54	143—144	$C_{10}H_{15}N_3S$	57.38 (57.37	7.22 7.42	20.08 20.17)
4d	CH_3	H	DBU	0					
4e	CH_3	CH_3	DBU	4	157—159	$C_7H_{11}N_3S$	49.68 (49.41	6.55 6.65	24.83 25.04)
4f	CH_2CH_3	CH_3	DBU	21	122—123	$C_8H_{13}N_3S$	52.43 (52.41	7.15 7.15	22.93 23.02)
4g	Ph	H	DBU	13	177—178	$C_{11}H_{11}N_3S$	60.80 (60.58	5.10 5.21	19.34 19.46)
4h			DBU	10	169—170	$C_{13}H_{13}N_3S$	64.17 (64.21	5.38 5 64	17.27 17.38)

a) Recrystallized from EtOAc.
b) Reaction temperature was 170°.

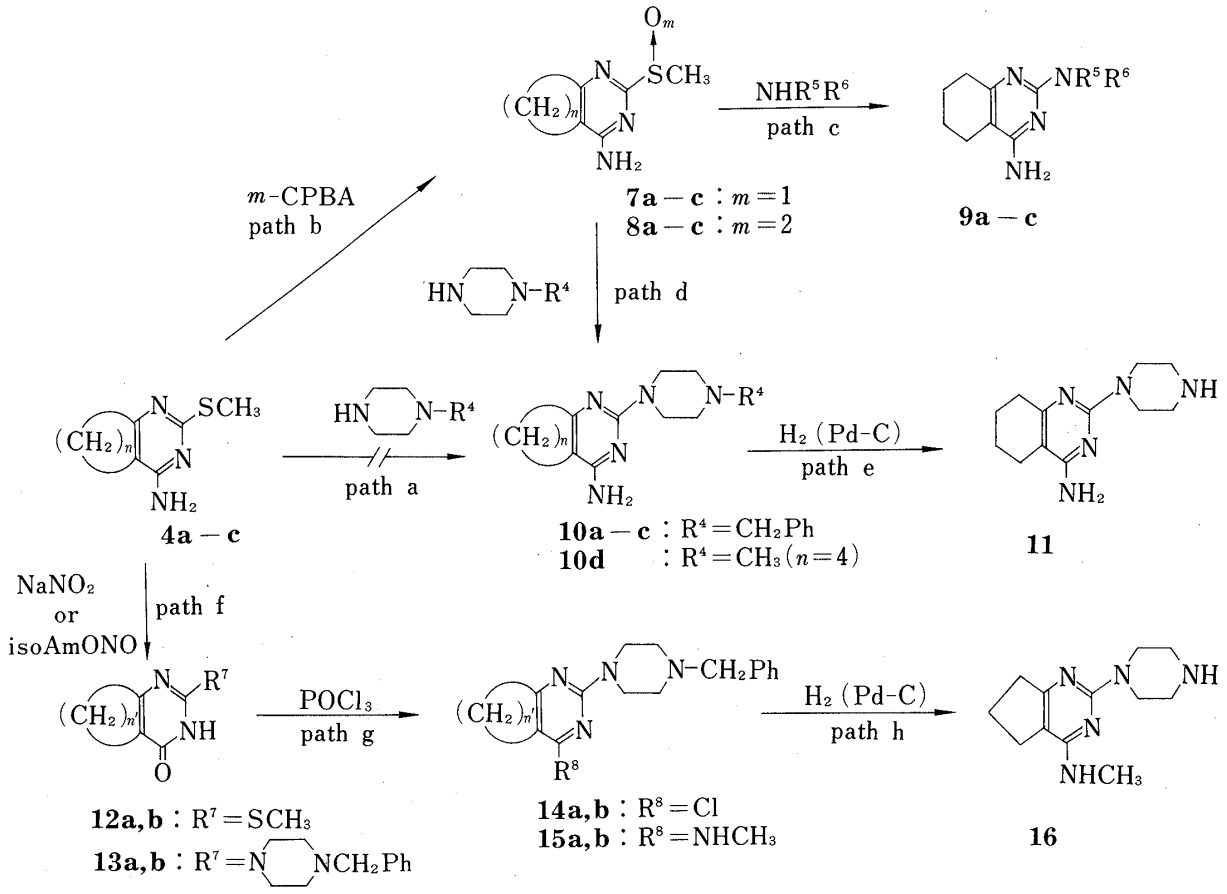
This paper describes the synthesis of 4-amino-2-methylthio-5,6-polymethylenepyrimidines (**4**) by the cyclization of cycloalkanones with 3-cyano-2-methylisothiourea (**2**) (Chart 2 and Table I), and new methods for the synthesis of 4-amino-2-(1-piperazinyl)-5,6-polymethylenepyrimidines (**1**) (compounds **10**, **11**, **15**, and **16**) *via* **4** (Chart 3).

3-Cyano-2-methylisothiourea (**2**), a useful intermediate for heterocyclic compounds such as triazoles[5] and oxazoles,[6] was prepared by the method of Turner.[7] Treatment of the isothiourea (**2**) with an excess of cyclohexanone (**3b**) in the presence of a catalytic amount of pyrrolidine gave 4-amino-2-methylthio-5,6,7,8-tetrahydroquinazoline (**4b**) in 67% yield. The elemental analysis, mass spectrum (MS) *m/e*: 195 (M^+), infrared (IR) spectrum ν_{max}^{KBr} cm^{-1}: 3500, 3280, 3140 ($-NH_2$), and nuclear magnetic resonance (NMR) spectrum δ: 2.47 (3H, s, $-SCH_3$) were consistent with this structure. This same compound was obtained independently by the substitution of the chloro group in 4-amino-2-chloro-5,6,7,8-tetrahydroquinazoline (**6**) with a methylthio group. Compound **6** was prepared from **3b** *via* 2-ethoxycarbonylcyclohexanone (**5**) as described by Budesinsky,[8] and was heated with sodium methylmercaptide in aqueous ethanol in a sealed tube. The spectra (IR, NMR) and the melting point of the resulting product were in good agreement with those of compound **4b**.

The results of the cyclization of some ketones with the isothiourea (**2**) are given in Table I. The methylthiopyrimidines (**4a—c**) were produced in fairly good yields from cyclic ketones, but the pyrimidines (**4d—g**) were recovered in much lower yields from acyclic ketones.

Several 4-amino-2-(1-piperazinyl)-5,6-polymethylenepyrimidines (**9**, **10**, **11**, **15**, and **16**) were synthesized through the pathways illustrated in Chart 3.

The reaction of 2-methylthiopyrimidine (**4b**) with 1-benzylpiperazine in isoamyl alcohol at 180° for 8 hr in a sealed tube did not yield any substituted products (path a). As described



n=3,4, and 5. n'=3 and 4. NR^5R^6=NH_2, $NHCH_3$, and pyrrolidino. Path c; from **7b**. Path e; from **10b**. Path h; from **15a**.

Chart 3

later, 2-methylthio-5,6,7,8-tetrahydro-4(3H)quinazolinone (**12b**) gave the corresponding 2-(4-benzyl-1-piperazinyl)quinazolinone (**13b**) upon refluxing it with benzylpiperazine in isoamyl alcohol. The difference between these findings is explained by the different electronic effects on the reactivity of the 2-methylthio group of the 4-amino group and 4-oxo group.[9] To activate the 2-methylthio group in substitution,[10] derivative **4b** was oxidized with 1 eq. or 2 eq. of *m*-chloroperbenzoic acid to produce the 2-methylsulfinyl or 2-methylsulfonylpyrimidine derivative (**7b** or **8b**) in 60% or 40% yield, respectively (path b). In the NMR spectrum of **7b**, a singlet was observed at 2.85 ppm (3H, s, $-SOCH_3$), and in that of **8b** there was a singlet at 3.17 ppm (3H, s, $-SO_2CH_3$). The IR spectrum of **7b** showed an absorption at 1065 cm^{-1} ($-SOCH_3$), and that of **8b** showed an absorption at 1300 and 1135 cm^{-1} ($-SO_2CH_3$). Other 2-methylthiopyrimidine derivatives (**4**) were also oxidized, as shown in Table II.

Amination of 2-methylsulfinylpyrimidine **7b** with ammonia, methylamine, pyrrolidine, or benzylpiperazine in aq. ethanol or isoamyl alcohol at 200° in a sealed tube gave the corresponding 2-amino-pyrimidine (**9a**, **9b**, **9c**, or **10b**) in 36, 58, 87, or 37% yield, respectively (path c or d). These findings suggest that the methylsulfinyl group is more active than the methylthio group. However, this procedure did not provide a good yield of **10b**, so it was modified as follows. A suspension of **7b** in 3 eq. of benzylpiperazine was heated at 180° for 1 hr to produce the 2-(4-benzyl-1-piperazinyl)pyrimidine derivative (**10b**) in 75% yield. The spectra (IR and mass) and the melting point of the product agreed with those of the compound prepared from 4-amino-2-chloro-5,6,7,8-tetrahydroquinazoline (**6**).[1] Similarly, the 2-methylsulfonylpyrimidine **8b** gave **10b** in 93% yield. Some 2-(4-substituted-1-piperazinyl)pyri-

TABLE II. 2-Methylsulfinyl or 2-Methylsulfonyl-4-amino-5,6-polymethylenepyrimidines (**7**) or (**8**)

Compd. No.	*m*	*n*	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd (Found) C	H	N
7a	1	3	60	175—176.5[b]	$C_8H_{11}N_3OS$	47.74 (47.57	5.51 5.58	20.88 20.86)
7b	1	4	60	192—194[b]	$C_9H_{13}N_3OS$	51.16 (51.10	6.20 6.35	19.89 19.81)
7c	1	5	62.5	169—170	$C_{10}H_{15}N_3OS$	53.31 (53.04	6.71 6.75	18.65 18.61)
8a	2	3	41	184—185	$C_8H_{11}N_3O_2S$	45.06 (45.17	5.20 5.14	19.70 19.69)
8b	2	4	40	195—196	$C_9H_{13}N_3O_2S$	47.56 (47.68	5.76 5.90	18.49 18.36)
8c	2	5	52	161—162	$C_{10}H_{15}N_3O_2S$	49.77 (49.84	6.27 6.32	17.41 17.37)

a) Recrystallized from isopropyl alcohol.
b) Recrystallized from EtOAc.

TABLE III. 4-Amino-2-(4-substituted piperazinyl)-5,6-polymethylenepyrimidine (**10**)[a]

Compd. No.	*n*	R^4	Start. Compd. No.	*n*	*m*	Yield (%)	mp (°C)
10a	3	CH_2Ph	**8a**	3	2	85	195—198 (HCl salt)[c]
10b	4	CH_2Ph	**7b**	4	1	75	283—285 (HCl salt)[c]
			8b	4	2	93	
10c	5	CH_2Ph	**8c**	5	2	95	200—202 (malate)[d]
10d	4	CH_3	**7b**	4	1	94[b]	265—267 (HCl salt)[c]

a) See "Experimental" (method A).
b) Reaction at 180° in a sealed tube.
c) Analytical data were identical with those for an authentic sample.[1]
d) Analytical data are given in "Experimental."

midines were synthesized under the same conditions, and the results are shown in Table III.

The 2-(1-piperazinyl)pyrimidine derivative (**11**) could be prepared from 2-(4-benzyl-1-piperazinyl)pyrimidine (**10b**) by hydrogenation in the presence of 5% palladium on carbon (path e).

To synthesize piperazinylpyrimidines such as compound **10**, we found that methods involving cyclization (Chart 2), oxidation (path b), and amination (path d) are superior to the conventional procedure *via* 2-chloropyrimidines both in the number of reaction steps and in the overall yields. Namely, compound **10b** was synthesized in 30% yield from cyclohexanone (**3b**) in three steps, but the procedure reported previously[1,8,11] requires five steps from **3b** to obtain **10b**, and the overall yield was only 11%.

To synthesize many kinds of 4-substituted aminopyrimidines, conversion of the 4-amino group of the pyrimidines (**4**) was performed. Treatment of 4-amino-2-methylthio-5,6-trimethylenepyrimidine (**4a**) with sodium nitrite in 25% aq. acetic acid gave 2-methylthio-5,6-trimethylene-4(3H)-pyrimidinone (**12a**), mp 274—276°, MS *m/e*: 182 (M^+), IR ν_{max}^{KBr} cm^{-1}: 1650 (–CONH–). The melting point and the spectra of **12a** were consistent with those of the product prepared by the reaction of 2-ethoxycarbonylcyclohexanone and 2-methylisothiourea.[12] Under the same conditions, 4-amino-2-methylthio-5,6,7,8-tetrahydroquinazoline (**4b**) did not give the corresponding 4(3H)-quinazolinone (**12b**). Compound **12b** could be obtained in 66% yield in the reaction of **4b** with isoamyl nitrite in the presence of trifluoroacetic acid; mp 225—227°, MS *m/e*: 196 (M^+), IR ν_{max}^{KBr} cm^{-1}: 1650 (–CONH–). Derivative **12b** was

identical with an authentic sample prepared by Curd's method[13] (path f).

These 4(3H)-pyrimidinones (**12**) were converted to 2-(4-benzyl-1-piperazinyl)-4(3H)-pyrimidinones (**13**) by refluxing them with benzypilperazine in isoamyl alcohol. Treatment of compounds **13** with phosphoryl chloride gave the chloropyrimidine derivatives (**14**) (path g), important intermediates in the synthesis of 4-substituted pyrimidines. 4-Chloropyrimidines (**14**) reacted with methylamine to yield 4-methylaminopyrimidines (**15**), 4-Methylamino-2-(1-piperazinyl)-5,6,7,8-tetrahydroquinazoline (**16**) was obtained on hydrogenation catalyzed by 5% palladium on carbon (path h).

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were run on a JASCO IRA-1 grating infrared spectrophotometer. NMR spectra were measured with a Hitachi R-24B high resolution NMR spectrometer; chemical shifts are expressed in ppm downfield from TMS as an internal standard. Mass spectra were taken with a Shimadzu LKB-900 GC/MS machine; mass numbers are given in *m/e*, and relative intensity in % in parentheses.

General Procedure for the Reaction of Ketones (3) with 3-Cyano-2-methylisothiourea (2)——A suspension of 3-cyano-2-methylisothiourea (0.01 mol), a base (0.5 mmol) and a ketone (3) (0.1 mol) was heated in a sealed tube at 150° for 7 hr. After the removal of excess ketone *in vacuo*, the residue was chromatographed on silica gel, and eluted with chloroform to give **4**. The products and yields are listed in Table I.

4-Amino-2-methylthio-5,6,7,8-tetrahydroquinazoline (4b)——A suspension of 4-amino-2-chloro-5,6,7,8-tetrahydroquinazoline (**6**)[8] (3.31 g, 20 mmol), 20% aq. solution of sodium methylmercaptide (14 g, 40 mmol), and EtOH (20 ml) in a sealed tube was heated at 180° for 6 hr. After addition of water (20 ml), the reaction mixture was extracted with $CHCl_3$ (50 ml × 2). The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated to yield 3.45 g of a crude product (**4b**), which was recrystallized from isopropanol to give colorless prisms of **4b** (2.19 g, 56%). The data are given in Table I. IR ν_{max}^{KBr} cm^{-1}: 3500, 3280, 3150, 2920, 1630, 1550, 1455. NMR δ: 1.80 (4H, m), 2.30 (2H, m), 2.47 (3H, s, $-SCH_3$), 2.63 (2H, m), 5.07 (2H, s, $-NH_2$). MS *m/e*: 195 (M^+, 100), 149 (85).

General Procedure for the Oxidation of 2-Methylthiopyrimidine (4) to 2-Methylsulfinylpyrimidine (7)——A solution of 70% *m*-chloroperbenzoic acid (5 mmol) in $CHCl_3$ (30 ml) was added to a solution of 2-methylthiopyrimidine (**4**) (5 mmol) in $CHCl_3$ (20 ml) at −10°. The reaction mixture was kept at −10° for 1 hr, and allowed to stand at room temperature overnight. After the mixture had been washed with 10% aq. K_2CO_3 solution, the $CHCl_3$ solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, and eluted with 2% EtOH–$CHCl_3$ to yield 2-methylsulfinylpyrimidine **7**. The products and yields are listed in Table II.

General Procedure for the Oxidation of 2-Methylthiopyrimidines (4) to 2-Methylsulfonylpyrimidines (8)——2-Methylthiopyrimidines (**4**) were oxidized to 2-methylsulfonylpyrimidines (**8**) in a manner similar to that used for the oxidation of **4** to **7** except that the amount of *m*-chloroperbenzoic acid was 10 mmol (2 eq.) and that the eluting solvent in chromatography was $CHCl_3$. The products and yields are listed in Table II.

2,4-Diamino-5,6,7,8-tetrahydroquinazoline (9a)——A suspension of 4-amino-2-methylsulfinyl-5,6,7,8-tetrahydroquinazoline (**7b**) (211 mg, 1 mmol) and 28% aq. ammonia (2 ml) in EtOH (3 ml) was heated in a sealed tube at 180° for 7 hr. After concentration of the reaction mixture, 10% aq. K_2CO_3 solution was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated to give a crude product, which was recrystallized from isopropanol to yield **9a** (60 mg, 36%), mp 241—243°, (lit. mp 243—245°).[4]

4-Amino-2-methylamino-5,6,7,8-tetrahydroquinazoline (9b)——A suspension of **7b** (316 mg, 1.5 mmol) and 40% aq. CH_3NH_2 solution (3 ml) in EtOH (4.5 ml) was heated in a sealed tube at 180° for 7 hr. The reaction mixture was concentrated, then 10% aq. K_2CO_3 solution was added to the residue, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, and eluted with $CHCl_3$ to yield **9b** (155 mg, 58%), mp 205—206°, (lit. mp 204—205°).[5]

4-Amino-2-pyrrolidino-5,6,7,8-tetrahydroquinazoline (9c)——A suspension of **7b** (211 mg, 1 mmol) and pyrrolidine (142 mg, 2 mmol) in isoamyl alcohol (10 ml) was heated in a sealed tube at 200° for 7 hr. The reaction mixture was concentrated, then 10% aq. K_2CO_3 solution was added to the residue, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, and eluted with 0—50% EtOH–$CHCl_3$ to yield **9c** (190 mg, 87%), mp 210—212°. The analytical data (mp, IR spectrum, and MS) of **9c** were identical with those of an authentic sample.[1]

4-Amino-2-(4-benzyl-1-piperazinyl)-5,6,7,8-tetrahydroquinazoline (10b)——Compound **10b** was prepared from **7b** in a manner similar to that described for **9c** in 37% yield, mp 283—285° (HCl salt). The analytical data (mp, IR spectrum, and MS) were identical with those of an authentic sample.[1]

General Procedure for the Reaction of 4-Amino-2-methylsulfinyl or 2-Methylsulfonylpyrimidine (8 or 9)

with Monosubstituted Piperazine (Method A)——A suspension of **7** or **8** (1 mmol) and mono-substituted piperazine (3 mmol) was heated at 180° for 1 hr. The reaction mixture was chromatographed on silica gel, and eluted with 2% EtOH–$CHCl_3$ to yield **10**. The products and yields are listed in Table III.

4-Amino-2-(4-benzyl-1-piperazinyl)-5,6-pentamethylenepyrimidine (10d)——Compound **10d** was prepared by Method A. The yield and melting point are given in Table III. *Anal.* Calcd for $C_{20}H_{27}N_5 \cdot 2(C_4H_4O_4)$: C, 59.04; H, 6.19; N, 12.30. Found: C, 58.90; H, 6.08; N, 12.19. IR ν_{max}^{KBr} cm^{-1}: 3460, 2940, 2580, 1600, 1490. NMR (free **10d** in $CDCl_3$) δ: 1.70 (6H, br s), 2.30—3.00 (8H, m), 3.50 (2H, s, $-CH_2Ph$), 3.75 (4H, t, $J=5$ Hz), 4.56 (2H, s, 4-NH_2), 7.27 (5H, s, ArH). MS *m/e*: 337 (M^+, 9), 191 (100).

4-Amino-2-(1-piperazinyl)-5,6,7,8-tetrahydroquinazoline (11)——A suspension of **10b** (1.61 g, 5 mmol) and 5% Pd-carbon (0.5 g) in methanol was stirred under hydrogen at 60° for 7 hr, then filtered. The filtrate was concentrated, and the residue was treated with conc. HCl (1 ml) to yield **11** as hydrochloride (1.05 g, 59%), colorless plates, mp 200—210°. The analytical data (IR spectrum and MS) of **11** were identical with those of an authentic sample.[1)]

2-Methylthio-5,6-trimethylene-4(3H)-pyrimidinone (12a)——A solution of sodium nitrite (83 mg, 1.2 mmol) in water (1 ml) was added to a solution of **4a** (181 mg, 1 mmol) in 25% aq. AcOH (4 ml), and the reaction mixture was kept at room temperature for 1 hr. After the mixture had been refluxed for 2 hr, it was cooled to room temperature, and allowed to stand overnight. The precipitated crystals were collected to give **12a** (70 mg, 39%), mp 274—276° (dec.). The analytical data (IR spectrum and MS) of **12a** were identical with those of an authentic sample.[12)]

2-Methylthio-5,6,7,8-tetrahydro-4(3H)-quinazolinone (12b)——A solution of **4b** (195 mg, 1 mmol), trifluoroacetic acid (1 ml), and isoamyl nitrite (0.5 ml) in $CHCl_3$ (10 ml) was refluxed for 3 hr, then concentrated. A 10% aq. K_2CO_3 solution was added to the residue, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, and eluted with 5% EtOH–$CHCl_3$ to yield **12b** (125 mg, 64%), which was recrystallized from EtOH to give colorless needles, mp 225—227°, (lit. mp 220—222°).[13)]

2-(4-Benzyl-1-piperazinyl)-5,6-trimethylene-4(3H)-pyrimidinone (13a)——A suspension of 2-methylthio-5,6-trimethylene-4(3H)-pyrimidinone (**12a**) (910 mg, 5 mmol) and benzylpiperazine (880 mg, 5 mmol) in isoamyl alcohol (10 ml) was refluxed for 3 hr. After the mixture had been cooled, it was filtered to give **13a** (1.09 g, 70%), which was recrystallized from EtOH to give colorless needles, mp 198—201°. *Anal.* Calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.68; H, 7.20; N, 18.13. IR ν_{max}^{KBr} cm^{-1}: 2900, 2800, 1640, 1590, 1565. MS *m/e*: 310 (M^+, 20), 164 (100), 91 (82).

2-(4-Benzyl-1-piperazinyl)-5,6,7,8-tetrahydro-4(3H)-quinazolinone (13b)——Compound **13b** was prepared in a manner similar to that described for **13a** in 63% yield. The product **13b** was recrystallized from EtOH to give colorless needles, mp 195—198°. *Anal.* Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.28; H, 7.57; N, 17.27. IR ν_{max}^{KBr} cm^{-1}: 2940, 1635, 1580. MS *m/e*: 324 (M^+, 14), 178 (100), 91 (62).

2-(4-Benzyl-1-piperazinyl)-4-chloro-5,6-trimethylenepyrimidine (14a)——A suspension of **13a** (1.07 g, 3.5 mmol) in $POCl_3$ (5 ml) was refluxed for 1 hr. After removal of excess $POCl_3$ by evaporation, 10% aq. K_2CO_3 solution was added to the residue and the suspension was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated to give **14a** (0.92 g, 80%), which was recrystallized as the oxalate from EtOH to give needles, mp 234—236°. *Anal.* Calcd for $C_{18}H_{21}N_4Cl \cdot (COOH)_2$: C, 57.34; H, 5.49; N, 13.38. Found: C, 57.40; H, 5.43; N, 13.46. IR ν_{max}^{KBr} cm^{-1}: 3020, 2865, 1710, 1600, 1535, 1450. MS *m/e*: 328 (M^+, 32), 172 (100), 91 (92).

2-(4-Benzyl-1-piperazinyl)-4-chloro-5,6,7,8-tetrahydroquinazoline (14b)——Compound **14b** was prepared in a manner similar to that described for **14a** in 74% yield. The product was recrystallized from Et_2O–hexane to give pale yellow plates, mp 103—104°. IR ν_{max}^{KBr} cm^{-1}: 2950, 1585, 1515. MS *m/e*: 342 (M^+, 20), 196 (100), 91 (99).

2-(4-Benzyl-1-piperazinyl)-4-methylamino-5,6-trimethylenepyrimidine (15a)——A suspension of **14a** (0.45 g, 1.4 mmol) and 40% aq. methylamine solution (7 ml) in EtOH (10 ml) was heated in a sealed tube at 100° for 8 hr, then concentrated. A 10% aq. K_2CO_3 solution was added to the residue, and the whole was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel, and eluted with 5% EtOH–$CHCl_3$ to yield **15a** (0.41 g, 93%), which was recrystallized from isopropyl alcohol as the hydrochloride, mp 195—204° (dec.). *Anal.* Calcd for $C_{19}H_{25}N_5 \cdot 2HCl \cdot 0.75H_2O$: C, 55.69; H, 7.01; N, 17.09. Found: C, 55.58; H, 6.64; N, 17.03. IR ν_{max}^{KBr} cm^{-1}: 3420, 2960, 1650, 1610, 1575. MS *m/e*: 323 (M^+, 9), 177 (100).

2-(4-Benzyl-1-piperazinyl)-4-methylamino-5,6,7,8-tetrahydroquinazoline (15b)——Compound **15b** was prepared in a manner similar to that described for **15a** in 74% yield. The product was recrystallized from isopropyl alcohol as the hydrochloride to give colorless needles, mp 235—245° (dec.). *Anal.* Calcd for $C_{20}H_{27}N_5 \cdot 2HCl \cdot 0.75H_2O$: C, 56.66; H, 7.25; N, 16.52. Found: C, 56.62; H, 6.98; N, 16.40. IR ν_{max}^{KBr} cm^{-1}: 3470, 2930, 1650, 1575. MS *m/e*: 327 (M^+, 17), 191 (100).

4-Methylamino-2-(1-piperazinyl)-5,6-trimethylenepyrimidine (16)——Compound **16** was prepared from **15a** in a manner similar to that described for **11** in 75% yield. The analytical data (mp, IR spectrum, and MS) of the product were identical with those of an authentic sample.[1)]

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References and Notes

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