Synthesis and Sedative-Hypnotic Effects of N^3-Allyl- and N^1-Allyl-5,6-substituted 2-Thiouracil Derivatives in Mice

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Twenty four thiouracil derivatives, including N^3-allyl- (19) and N^1-allyl-2-thiouracil (20) were synthesized and their pharmacological effects [sedative-hypnotic activity (loss of righting reflex and spontaneous activity), convulsant activity, effect on pentobarbital (PB)-induced sleep and mortality] were evaluated in mice at doses of 320 mg/kg, i.p. and 2 μmol/mouse by intracerebroventricular (i.c.v.) injections, respectively. N^3-Allyl-6-propyl-2-thiouracil (3), N^3-allyl-5,6-dimethyl-2-thiouracil (10), N^3-allyl-1,2,3,4,5,6,7,8,9-nonahydro-4-oxo-2-thiocyclohepta[d]pyrimidine (16) and N^3-allyl-5-methyl-2-thiouracil (18) exhibited sedative-hypnotic activity, whereas N^3-allyl-6-ethyl-5-methyl-2-thiouracil (11), N^1-allyl-5-methyl-2-thiouracil (21), N^1-allyl-1,2,3,4,5,6,7,8,9-nonahydro-4-oxo-2-thiocyclohepta[d]pyrimidine (23) and N^1-allyl-5,6-dimethyl-2-thiouracil (24) conversely displayed clonic- and/or tonic-convulsant seizures. N^3-Allyl-6-propyl-2-thiouracil (3) and N^3-allyl-5-methyl-2-thiouracil (18) decreased spontaneous activity. Other compounds examined were inactive, or only slightly active in the sedative-hypnotic assay even at high doses. Fifteen compounds (1—4, 7, 10, 11, 14—16, 18—21, and 23) significantly prolonged the PB-induced sleeping time. Interestingly, only N^1-allyl-5,6-dimethyl-2-thiouracil (24) shortened the PB-induced sleeping time. These results showed that these thiouracils possessed many different effects such as sedative-hypnotic, anticonvulsant and/or convulsant, and that N^3-allyl-5-methyl-2-thiouracil (18) and N^1-allyl-5,6-dimethyl-2-thiouracil (24) had the most potent hypnotic activity and antagonistic effect against PB, respectively.

Key words N^3-allyl-2-thiouracil; N^1-allyl-2-thiouracil; N^3-allyl-5-methyl-2-thiouracil; N^1-allyl-5,6-dimethyl-2-thiouracil; sedative-hypnotic activity; convulsant activity

In our previous studies,[2)] we reported that *N*-allyl-substituted derivatives of uracil (U), thymine (T) and 6-methyluracil (6-MU) exhibited central nervous system (CNS)-depressant effects, and that N^1,N^3-diallyluracil showed some hypnotic activity.[2)] Furthermore, N^1-allyl-N^3-benzyluracil had potent CNS-depressant activity and its hypnotic ED_{50} value in mice was 155 mg/kg, i.p.[2)] Since *N*-substituted uracils have some effects on the CNS, it may be possible for these compounds to lead to new sedative-hypnotics. On the other hand, 2-thiouracils are well known to possess antithyroid activity.[3)] For example, 6-propyl-2-thiouracil, which has low toxicity, is useful as an antihyperthyroid. However, there are few reported studies on the pharmacological activity of thiouracil derivatives in the CNS.

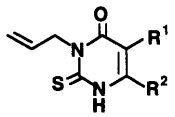
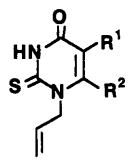
In the present study, 5- and/or 6-substituted *N*-allyl-2-thiouracil derivatives (Table 1) were synthesized and their pharmacological activities evaluated and compared with our previous results.[2)]

Synthesis Structures of N^3-allyl- and N^1-allyl-2-thiouracil derivatives synthesized in the present study are listed in Table 1. N^1-Allyl and N^3-allyl-2-thiouracils were synthesized by condensation of *N*-allylthiourea with a β-ketoacetal in the presence of sodium ethoxide as a condensation agent or H_2SO_4 as catalyst (Chart 1). *N*-Allyl-2-thiouracils **6**, **15** and **17** were synthesized by the methods described previously, as shown in Chart 2.[4,5)] Isomers **17** and **22** were separated by silica gel column chromatography using chloroform as eluent. The synthesis of new compounds was performed according to the known method[6)] *via* condensation of *N*-allylthiourea with the requisite β-ketoesters in the presence of sodium ethoxide as a condensation agent.

Results

The pharmacological effects of the *N*-allyl-2-thiouracil derivatives are summarized in Table 2. Compounds **3**, **7**, **9**, **10**,

Table 1. Structures of N^3-Allyl- and N^1-Allyl-2-thiouracil Derivatives

Structure	Compd. No.	R^1	R^2
 1—19	1	H	$-CH_3$
	2	H	$-CH_2CH_3$
	3	H	$-CH_2CH_2CH_3$
	4	H	-cyclo-C_6H_{11}
	5	H	$-CH_2$-cyclo-C_6H_{11}
	6	H	-1-adamantyl
	7	H	$-C_6H_5$
	8	H	$-CH_2C_6H_5$
	9	H	$-CH_2CH_2C_6H_5$
	10	$-CH_3$	$-CH_3$
	11	$-CH_3$	$-CH_2CH_3$
	12	$-CH_2CH_3$	$-CH_3$
	13	$-(CH_2)_3-$	
	14	$-(CH_2)_4-$	
	15	$-CH_2CH(CH_3)CH_2CH_2-$	
	16	$-(CH_2)_5-$	
	17	$-(CH_2)_{10}-$	
	18	$-CH_3$	H
	19	H	H
 20—24	20	H	H
	21	$-CH_3$	H
	22	$-(CH_2)_{10}-$	
	23	$-(CH_2)_5-$	
	24	$-CH_3$	$-CH_3$

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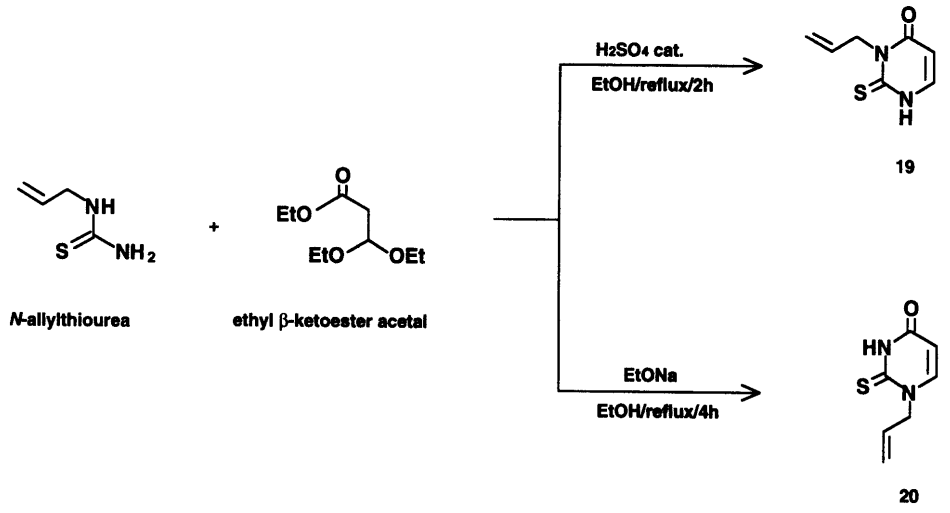

Chart 1. Synthetic Route for Compounds **19** and **20**

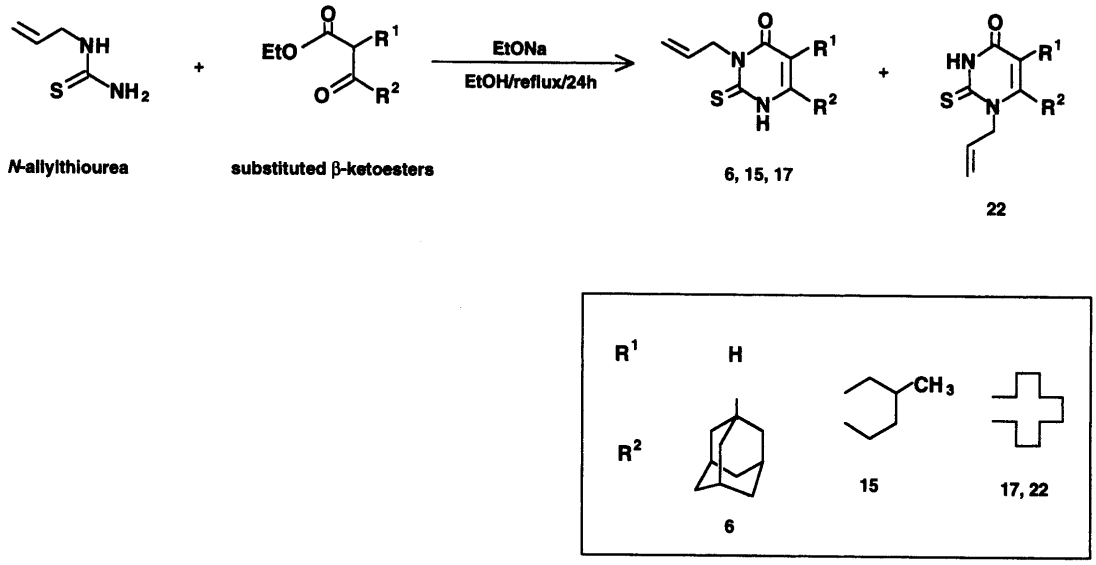

Chart 2. Synthetic Route for Compounds **6**, **15**, **17**, and **22**

16, **17** and **18** showed some hypnotic activity upon i.p. or i.c.v. administration in mice. Sleeping time of mice treated with **7**, **9** and **17** by i.c.v. injection was from 2 to 6 min. By i.p. injection at a dose of 320 mg/kg, **3**, **16** and **18** resulted in 68, 140 and 152 min of the sleeping time, respectively. The hypnotic ED_{50} value for **18** was 220 (200—242) mg/kg, i.p. In contrast, **11**, **13**, **14**, **21**, **23** and **24** showed some stimulant activity, and in particular, compound **24** induced tonic seizure.

The effects of *N*-allyl-2-thiouracil derivatives on PB-induced sleeping time are shown in Table 3. Compounds **1**—**4**, **7**, **10**, **11**, **14**—**16**, **18**—**21** and **23** significantly prolonged PB-induced sleeping time, while others did not cause any significant prolongation. It was noted that **24** showed a tendency to shorten the PB-induced sleeping time. Therefore, the effects of **24** on the CNS were compared with a well-known stimulant, pentyleneterazol (PTZ). The effects of **24** and PTZ on pentobarbital (PB)-induced sleeping time are shown in Table 4. Compound **24** significantly shortened the sleeping time induced by PB, while PTZ did not show any significant effect.

Figure 1 shows the effects of **1**—**3**, **16**, **18** and **19** on the spontaneous activity of mice at a dose of 160 mg/kg, i.p. Compounds **3** and **18** significantly decreased the total distance, and the values were about 40% of control.

Mortality after i.p. injection of **11**, **21**, **23** and **24** at 320 mg/kg was 83, 100, 85 and 83%, respectively, while that for **3**, **14**, **15** and **19** was low. The other compounds did not show any acute toxicity, at the high dose of 320 mg/kg, i.p. (Table 2).

Discussion

The present study demonstrated that N^3-allyl-2-thiouracil (**19**) had some central depressant activity. The introduction of alkyl groups onto positions 5 and/or 6 of the 2-thiouracil ring influenced the CNS depressant effect, and N^3-allyl-6-propyl-2-thiouracil (**3**) showed some sedative-hypnotic activity. Furthermore, N^3-allyl-5,6-dimethyl-2-thiouracil (**10**), N^3-allyl-1,2,3,4,5,6,7,8,9-nonahydro-4-oxo-2-thiocyclohepta-[d]pyrimidine (**16**) and N^3-allyl-5-methyl-2-thiouracil (**18**) also showed some sedative-hypnotic activity. The central depressant activity of **18** seems to be more potent than that of N^3-allylthymine, previously reported.[2] Compound **18** significantly prolonged PB-induced sleep to 1594% of control

Table 2. Pharmacological Effects of N^3-Allyl- and N^1-Allyl-2-thiouracil Derivatives

Compd. No.	Activity[a] 320 mg/kg, i.p.	Mortality	Activity 2 μmol/mouse, i.c.v.	Mortality
1	None	0/6	None	0/6
2	None	0/6	None	0/6
3	Depressant 68±26 (3/8)[b]	1/8	None	0/6
4	None	0/6	None	0/7
5	None	0/6	None	0/6
6	None	0/6	None	3/6
7	None	0/6	Depressant 2 (1/6)	3/6
8	None	0/6	None	0/6
9	None	0/6	Depressant 3±1 (4/8)	3/8
10	Depressant 29 (2/8)	0/8	None	0/6
11	Stimulant Clonic seizure (6/6)	5/6	None	0/6
12	None	0/6	None	0/6
13	Stimulant Clonic seizure (6/7)	0/7	Stimulant Clonic seizure (2/6)	0/6
14	Stimulant Clonic seizure (5/7)	3/7	None	1/6
15	None	3/7	None	3/7
16	Depressant 140±29 (4/6)	0/6	None	0/6
17	None	0/7	Depressant 6±1 (3/6)	0/6
18	Depressant 152±34 (6/6)	0/6	None	0/6
19	None	1/6	None	0/6
20	None	0/6	None	0/6
21	Stimulant Clonic seizure (6/7)	7/7	None	2/6
22	None	0/7	None	2/7
23	Stimulant Clonic seizure (6/7)	6/7	None	0/7
24	Stimulant Tonic seizure (6/6)	5/6	None	0/6

a) Results of depressant activity are expressed as mean sleeping time (min)±S.E.M. "None" indicates both no hypnotic activity and no convulsant activity. *b*) Numbers in parentheses represent numbers of responding animals/numbers of animals used.

Table 3. Effects of N^3-Allyl- and N^1-Allyl-5,6-substituted 2-Thiouracil Derivatives on Pentobarbital-Induced Sleep

Compd. No.	Sleeping time[a,b] (% of control)[c]	Compd. No.	Sleeping time (% of control)
Control	100±17		
1	813±80[e]	**13**	527±90
2	1107±93[e]	**14**	793±187[e]
3	1773±173[e]	**15**	813±120[e]
4	920±93[e]	**16**	1214±94[e]
5	173±40	**17**	267±114
6	360±33	**18**	1594±106[e]
7	467±67[e]	**19**	1319±131[e]
8	287±26	**20**	692±117[e]
9	313±53	**21**	575±17[e]
10	1393±107[e]	**22**	192±25
11	1830±140[e]	**23**	346±50[d]
12	460±103	**24**	62±7

a) Compounds tested were administered by i.p. injection at a dose of 160 mg/kg prior to pentobarbital injection (40 mg/kg, i.p.). *b*) Compound **21** was administered at a dose of 80 mg/kg, i.p. *c*) Results are expressed as mean % of control (1% Tween 80–saline: 24±4 min) sleeping time±S.E.M. *d*) Significantly different from control ($p<0.05$). *e*) Significantly different from control ($p<0.01$).

Table 4. Effects of Compound **24** and PTZ on Pentobarbital-Induced Sleep

Compd. No.	Dose (mg/kg, i.p.)	Sleeping time (min)
Control		27±5
24	160	5±1[a]
PTZ	120	23±6

Compound **24** and PTZ were administered 15 min after 50 mg/kg, i.p. injection of PB. Data are expressed as the mean±S.E.M. $n=8$. *a*) Significantly different from control ($p<0.01$).

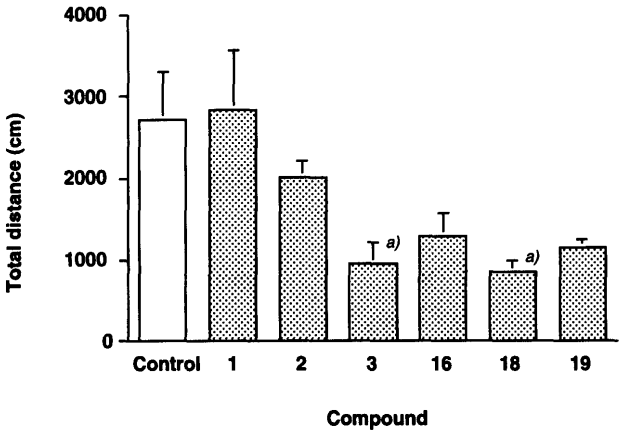

Fig. 1. Effects of N^3-Allyl- and N^1-Allyl-5,6-substituted 2-Thiouracil Derivatives on Spontaneous Activities of Mice

Each compound tested was injected i.p. at a dose of 160 mg/kg. The mean total distance of control was 2727±587 cm. $n=6$. *a*) Significantly different from control ($p<0.05$).

sleeping at 160 mg/kg, i.p., while N^3-allylthymine exhibited 324% prolongation at the same dose. Although **19** significantly potentiated PB-induced sleep (1319% of control sleeping time), N^3-allyluracil showed no synergistic effect (138%). From these findings, it appeared that a sulfur atom was more effective than an oxygen atom on the 2 position of the pyrimidine base for CNS depressant activity. Unexpectedly, compounds substituted with cyclic groups at the 5 and 6 positions did not show any pharmacological activity. Imaizumi *et al.*[7] reported that 1-amino-5-halogeno-4-thiouracils exhibited some anesthetic activity. On the other hand, derivatives of N^1-allyl-2-thiouracil (**20**) showed some central stimulant activity. Especially, N^1-allyl-5-methyl-2-thiouracil (**21**), N^1-allyl-1,2,3,4,5,6,7,8,9-nonahydro-4-oxo-2-thiocyclohepta[d]pyrimidine (**23**) and N^1-allyl-5,6-dimethyl-2-thiouracil (**24**) had potent stimulant effects. Interestingly, mice treated with compound **24** underwent a tonic-extensor convulsant seizure.

Interaction study with PB indicated that the compounds tested in the present study, except for **24**, prolonged PB-induced sleeping time. Compound **24**, which exhibited stimulant activity as already described above, shortened the PB-induced sleeping time. This might be due to binding of **24** to the receptor of a stimulant amino acid, such as glutamic acid. Recently, we reported that the pharmacological activity of N^3-phenacyluridine, having the structure of uracil, may be partially mediated through the benzodiazepine receptor.[8] In connection with the mechanism of action of uracil and related compounds, the role of uridine receptors in the CNS has been studied in our laboratory. *N*-Allyl-2-thiouracil de-

rivatives showing hypnotic activity may act on these receptors.

The present results indicate that *N*-allyl-2-thiouracil derivatives have more potent CNS depressant effects than *N*-allyluracil derivatives, except for **24**, which shortens PB-induced sleep due to its stimulant effect on the CNS.

Experimental

Chemistry The starting compounds, 1-adamantyl-β-ketoester and ethyl β-ketoester acetal were obtained from Aldrich Chemical Co., Inc. (U.S.A.). Other β-ketoesters were prepared according to the method of Rhoads *et al.*[6] Melting points (uncorrected) were measured on a Boetius hotstage apparatus. DC-Plastikfolien Kieselgel 60 F_{254} (Merck Art. 5735) and Kieselgel 60 (Merck Art. 7734) were used for column chromatography using the solvent system; $CHCl_3$–EtOH 92 : 8 v/v. ^{1}H-NMR spectra were measured at 300 MHz with a Bruker MSL 300 spectrometer in $CDCl_3$ solution. UV spectra were recorded on a Lambda 17 Perkin Elmer spectrophotometer in EtOH : 0.02 M HCl=1 : 1 v/v (pH=2) and EtOH : 0.02 M NaOH=1 : 1 v/v (pH=12). MS spectra were recorded on a JEOL JMS-SX-102A spectrometer.

Synthesis of N^3-Allyl-2-thiouracil (19) To a mixture of ethyl β-ketoester acetal (5.7 g, 30 mmol) and *N*-allylthiourea (7.0 g, 60 mmol) in dry ethanol (25 ml), conc. H_2SO_4 (0.34 ml, 6 mmol) was added and the mixture refluxed for 2 h. The solvent was then evaporated under reduced pressure. To the obtained oil, 40 ml of 1.6 M NaOH was added, and the mixture maintained at 60 °C for 0.5 h, then cooled in a freezer and acidified with 3.5 M HCl. The crude product was filtered off and dissolved in a small amount of chloroform. The crude product **19** was purified by silica gel column chromatography with chloroform as solvent. Yield 20%, mp 119.5—121 °C (lit.,[9] 119.2 °C). UV $\lambda_{max}^{(pH=2)}$ nm (ε): 278.0 (12810), 216.2 (13260), 190.8 (8940). $\lambda_{max}^{(pH=12)}$ nm (ε): 318.7 (13190), 261.8 (7230), 210.8 (14470). ^{1}H-NMR ($CDCl_3$) δ: 1.89 (0.5H, s, SH-enol), 5.02 (2H, ddd, J=5.7 Hz, N^3-CH_2–), 5.25 (1H, ddt, J=10.3 Hz, =CH_2), 5.32 (1H, ddt, J=17.2 Hz, =CH_2), 5.93 (1H, ddt, J_{trans}=17.2 Hz, J_{cis}=10.3 Hz, J=5.7 Hz –CH=), 6.07 (1H, dd, J=7.6 Hz, ^4J=1.2 Hz, C5-H), 7.16 (1H, dd, J=7.6, 5.8 Hz, C6-H), 10.80 (0.5H, br s, N^1-H). MS *m/z* (rel. int. %): 168 (M^+, 36.7), 153 (M^+-15, 100). *Anal.* Calcd for $C_7H_8N_2OS$: C, 49.99; H, 4.79; N, 16.65; S, 19.06. Found: C, 50.15; H, 4.97; N,16.76; S,18.99.

Synthesis of N^1-Allyl-2-thiouracil (20) *N*-Allylthiourea (5.6 g, 48 mmol) and ethyl β-ketoester acetal (7.6 g, 40 mmol) were added to a solution of sodium ethoxide (0.92 g, 40 mmol Na and 30 ml of anhydrous EtOH). The reaction mixture was then refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue dissolved in cold water and acidified with 80% acetic acid. The crude product **20** was filtered off and recrystallized from ethanol. Yield 59%, mp 189—191 °C (lit.,[9] 189.8 °C). UV $\lambda_{max}^{(pH=2)}$ nm (ε): 268.9 (12160), 215.5 (14850). $\lambda_{max}^{(pH=12)}$ nm (ε): 269.8 (14230) 236.9 (17640). ^{1}H-NMR ($CDCl_3$) δ: 1.68 (0.5H, s, SH-enol), 4.85 (2H, ddd, J=5.9 Hz, N^1-CH_2–), 5.31 (1H, ddt, J=17.1 Hz, =CH_2), 5.37 (1H, ddt, J=10.3 Hz, =CH_2), 5.94 (1H, ddt, J_{trans}=17.1 Hz, J_{cis}=10.3 Hz, J=5.9 Hz, –CH=), 6.02 (1H, dd, J=8.0 Hz, ^4J=2.1 Hz, C5-H), 7.28 (1H, d, J=8.0 Hz, C6-H), 10.52 (1H, s, N^3-H). MS *m/z* (rel. int. %): 168 (M^+, 46.5), 153 (M^+-15, 100). *Anal.* Calcd for $C_7H_8N_2OS$: C, 49.99; H, 4.79; N, 16.65; S, 19.06. Found: C, 49.77; H, 4.91; N, 16.52; S, 19.10.

6-(1-Adamantyl)-N^3-allyl-2-thiouracil (**6**): Yield 36%, mp 182—185 °C. UV $\lambda_{max}^{(pH=2)}$ nm (ε): 272.9 (16510), 202.4 (14660). $\lambda_{max}^{(pH=12)}$ nm (ε): 334.7 (26120), 257.6 (18540), 209.6 (13970). ^{1}H-NMR ($CDCl_3$) δ: 1.72—2.14 (15H, m, adamantyl), 4.99 (2H, ddd, J=5.8 Hz, N^3-CH_2–), 5.25 (1H, ddt, J=10.2 Hz, =CH_2), 5.33 (1H, ddt, J=17.2 Hz, =CH_2), 5.80 (1H, d, ^4J=2.3 Hz, C5-H), 5.94 (1H, ddt, J_{trans}=17.2 Hz, J_{cis}=10.2 Hz, J=5.8 Hz, –CH=), 8.93 (1H, s, N^1-H). MS *m/z* (rel. int. %): 302 (M^+, 19.5), 287 (M^+-15, 100). *Anal.* Calcd for $C_{17}H_{22}N_2OS$: C, 67.51; H, 7.33; N, 9.27; S, 10.60. Found: C, 67.93; H, 7.71; N, 9.16; S, 10.69.

N^3-Allyl-1,2,3,4,5,6,7,8-octahydro-6-methyl-4-oxo-2-thioquinazoline (**15**): Yield 77%, mp 204.5—206 °C. UV $\lambda_{max}^{(pH=2)}$ nm (ε): 282.7 (13820), 220.7 (10370), 196.5 (13070). $\lambda_{max}^{(pH=12)}$ nm (ε): 312.3 (10210), 265.0 (10280), 199.6 (14220). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, J=6.5 Hz, –CH_3), 1.30—1.43 (1H, m, –CH_2–), 1.65 (0.5H, s, SH-enol), 1.68—1.79 (1H, m, –CH_2–),1.82—1.95 (2H, m, C5-CH_2–), 2.47—2.53 (2H, m, C6-CH_2–), 2.56—2.64 (1H, m, CH), 5.02 (2H, ddd, J=5.8 Hz, N^3-CH_2–), 5.24 (1H, ddt, J=10.2 Hz, =CH_2), 5.32 (1H, ddt, J=17.2 Hz, =CH_2), 5.94 (1H, ddt, J_{trans}=17.2 Hz, J_{cis}=10.2 Hz, J=5.8 Hz, –CH=), 10.40 (0.5H, s, N^1-H). MS *m/z* (rel. int. %): 236 (M^+, 25.8), 221 (M^+-15, 100). *Anal.* Calcd for $C_{12}H_{16}N_2OS$: C, 60.99; H, 6.83; N, 11.85; S, 13.57. Found: C, 59.59; H, 6.68; N, 11.82; S, 13.66.

N^3-Allyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-4-oxo-2-thiocyclododeca[d]pyrimidine (**17**): Yield 21%, mp 156.5—157.5 °C. UV $\lambda_{max}^{(pH=2)}$ nm (ε): 281.7 (16610), 220.5 (10180), 194.2 (13750). $\lambda_{max}^{(pH=12)}$ nm (ε): 313.8 (12100), 262.4 (9380), 208.0 (11460). ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.80 (16H, m, (–CH_2–)$_8$), 2.42 (2H, t, J=7.0 Hz, C5-CH_2–), 2.49 (2H, m, C6-CH_2–), 5.01 (2H, ddd, J=5.9 Hz, N^3-CH_2–), 5.24 (1H, ddt, J=10.2 Hz, =CH_2), 5.33 (1H, ddt, J=17.2 Hz, =CH_2), 5.95 (1H, ddt, J_{trans}=17.2 Hz, J_{cis}=10.2 Hz, J=5.9 Hz, –CH=), 9.51 (1H, s, N^1-H). MS *m/z* (rel. int. %): 306 (M^+, 18.6), 291 (M^+-15, 100). *Anal.* Calcd for $C_{17}H_{26}N_2OS$: C, 66.63; H, 8.55; N, 9.14; S, 10.46. Found: C, 66.80; H, 8.49; N, 9.37; S, 10.47.

N^1-Allyl-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-4-oxo-2-thiocyclododeca[d]pyrimidine (**22**): Yield 5%, mp 184.5—186 °C. UV $\lambda_{max}^{(pH=2)}$ nm (ε): 275.7 (14130), 222.3 (10200), 193.9 (8980). $\lambda_{max}^{(pH=12)}$ nm (ε): 270.0 (12750), 243.1 (16430). ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.72 (16H, m, (–CH_2–)$_8$), 2.47 (2H, dd, J=7.5 Hz, C5-CH_2–), 2.66 (2H, dd, J=7.5 Hz, C6-CH_2–), 5.09 (1H, ddt, J=17.3 Hz, =CH_2), 5.16 (2H, br s, N^1-CH_2), 5.27 (1H, ddt, J=10.5 Hz, =CH_2), 5.94 (1H, ddt, J_{trans}=17.3 Hz, J_{cis}=10.5 Hz, J=4.6 Hz, –CH=), 10.03 (1H, s, N^3-H). MS *m/z* (rel. int. %): 306 (M^+, 44.6), 291 (M^+-15, 29.3), 41 (100). *Anal.* Calcd for $C_{17}H_{26}N_2OS$: C, 66.63; H, 8.55; N, 9.14; S, 10.46. Found: C, 66.43; H, 8.72; N, 8.99; S, 10.22.

Animals and Drugs Male ddY strain mice weighing 22—28 g were used in groups consisting of 6—8 animals. All 2-thiouracil derivatives were suspended in physiological saline containing 1% Tween 80 and administered intraperitoneally (i.p.) and/or intracerebroventricularlly (i.c.v.). The i.c.v. administration was performed by the method of Haley and McCormick.[10] PB and PTZ were purchased from Tokyo Kasei Kogyo Co., Ltd. and Mallinckrodt Chem. Works, respectively, and dissolved in saline. All animal experiments were carried out at an ambient temperature of 22—24 °C.

Hypnotic and Convulsant Activity *N*-Allyl-2-thiouracil derivatives were administered to each group of 6—8 mice at the above dose and the behavior observed for 3 h after administration. Sleeping time was measured as the interval between loss and recovery of an effective righting reflex (considered to be recovery from a side position within 1 min).[11] Clonic and tonic extenser convulsions were considered to be evidence of CNS-stimulant activity.

Effect on PB-Induced Sleeping Time All compounds [160 or 80 mg/kg, i.p. (**21**)] were injected 15 min prior to the administration of PB (40 mg/kg, i.p.). PB-induced sleeping time was measured, in a similar way to hypnotic activity. Compounds **24** (160 mg/kg, i.p.) and PTZ (120 mg/kg, i.p.) were administered to groups of 8 mice, 15 min after the 50 mg/kg, i.p. injection of PB. PB-induced sleeping time was also measured from the time of injection of **24** and PTZ. Control mice were injected with the 1% Tween 80–saline solution instead of test compounds.

Spontaneous Activity *N*-Allyl-2-thiouracil derivatives were administered i.p. at a dose of 160 mg/kg. Control group was treated with 1% Tween 80–saline as the vehicle. Spontaneous activity of mice treated with *N*-allyl-2-thiouracil derivatives was measured by a Behavior Orbital Analyzer BTA-1 (Muromachi Kikai Co., Ltd.) with a personal computer (NEC, PC98). Total distance (cm) was measured for 30 min after injection.

Acute Toxicity *N*-Allyl-2-thiouracil derivatives were also administered at above dose. Mortality was observed for 3 d.

Statistical Analyses The statistical significance of differences was determined by means of the Bonferroni test.

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