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Pyrimidine Derivatives. VI.[1] Synthesis of 2-(1-Piperazinyl)-5,6-polymethylenepyrimidine Derivatives and Determination of Their Hypoglycemic Activity

TETSUO SEKIYA,*,[a] HIDETOSHI HIRANUMA,[a] TOSHIJI KANAYAMA,[a] SHUNSUKE HATA,[a] and SHUN-ICHI YAMADA[b]

Research Laboratory, Mitsubishi Yuka Pharmaceutical Co., Ltd.,[a] 500 Furuki, Wakaguri, Inashiki, Ibaraki 300–03, Japan, and Faculty of Pharmaceutical Sciences, Josai University,[b] 1–1 Keyakidai, Sakado, Saitama 350–02, Japan

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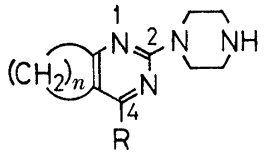
As part of our studies on pyrimidine derivatives, 27 4-alkyl-2-(1-piperazinyl)-5,6-polymethylenepyrimidines and structurally related derivatives were synthesized, and their hypoglycemic activities were examined in mice treated with 2-deoxy-D-glucose. Most of the derivatives showed higher activity at a dose of 30 mg/kg *p.o.* than tolbutamide at a dose of 100 mg/kg *p.o.* The structure-activity relationships are discussed.

Keywords——2-(1-piperazinyl)pyrimidine; 2-(1-piperazinyl)-5,6,7,8-tetrahydroquinazoline; hypoglycemic; 2-deoxy-D-glucose; structure-activity relationship; cross-coupling reaction; Grignard reagent

In previous papers in this series, we reported the synthesis of 4-amino- and 4-alkoxy-2-(1-piperazinyl)-5,6-polymethylenepyrimidine derivatives (I and II) and their hypoglycemic activity.[2,3] From a consideration of the structure-activity relationships of the derivatives, it was suggested that the presence of the 2-(1-piperazinyl) group is essential for the appearance of the activity, that a substituent in the piperazinyl group does not greatly affect the activity, and that a substituent at position 4 seems to have no significance, because no clear difference in activity between 4-aminopyrimidines and 4-alkoxypyrimidines could be seen. These results prompted us to clarify the contribution of the 4-substituent of pyrimidines. This paper describes the synthesis of 4-alkyl (or unsubstituted)-2-(1-piperazinyl)-5,6-polymethylenepyrimidine derivatives and the determination of their hypoglycemic activity.



I: $n=3$—5, R = amino group
II: $n=3$—4, R = alkoxy group

Chemistry

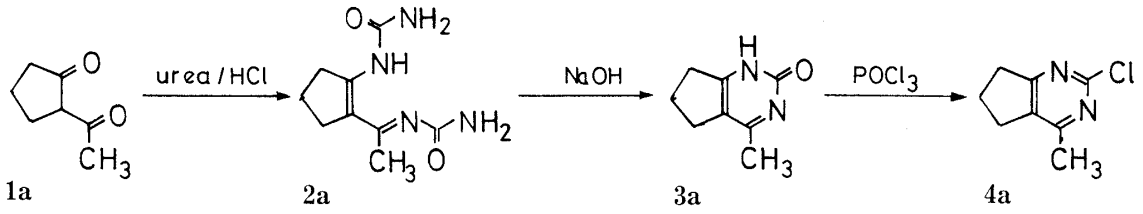
The reaction of 2-acetylcyclopentanone **1a**, urea, and hydrochloric acid in ethanol gave the bis-ureido-adduct **2a**, which was treated with sodium hydroxide to yield 4-methyl-2(1*H*)-5,6-trimethylenepyrimidinone **3a**. The 2(1*H*)-pyrimidinone derivatives **3b**—**d** were prepared in a similar manner. The 4-phenyl derivative **3e** was obtained from 2-benzoylcyclohexanone **1e** and urea directly under acidic conditions. The synthesis of 4,5-pentamethylenepyrimidinone **3h** was carried out using the same method as that reported for 4,5-tetramethylenepyrimidinone **3g** from 2-formylcyclohexanone and urea;[4] however, 4,5-trimethylenepyrimi-

dinone **3f** could not be obtained by this procedure. Synthesis of 2-(1-piperazinyl)-4,5-trimethylenepyrimidine derivatives was performed by a method described later. Table I shows the yields, mp, and analytical data of the 2(1*H*)-pyrimidinone derivatives **3a**—**e**, and **3h**. The 2(1*H*)-pyrimidinone derivatives **3a**—**e**, **3g**, **h** were converted to 2-chloropyrimidines **4a**—**e**, and **4g**, **h** by treatment with phosphoryl chloride. The results are shown in Table II.

The 2-(1-piperazinyl)-5,6-polymethylenepyrimidine derivatives **5**, **6**, and **7** (Table III) and the 2-(1-piperazinyl)pyrimidines **10** and **11** (Table IV) were obtained by the following procedures. Condensation of the 2-chloropyrimidines **4** and **9** with *N*-mono-substituted piperazine gave 2-(4-substituted 1-piperazinyl)pyrimidine derivatives **5a**—**e**, **5g**, **h**, **6a**, **c**, **g**, **h**, **8i**, **j**, and **10j**, **k**. Catalytic hydrogenation of the 2-(4-benzyl-1-piperazinyl)pyrimidines **5a**—**e**, **5g**, **h**, and **10k** produced 2-(1-piperazinyl)pyrimidines **7a**—**e**, **7g**, **h**, and **11k**, respectively. The *N*-alkylated piperazinylpyrimidines **6f** and **8k** were obtained by the alkylation of 2-(1-piperazinyl)pyrimidines **7f** and **7g**, respectively. The 2-(1-piperazinyl)-4,5-trimethylenepyrimidine **7f** was prepared by the catalytic hydrogenation of 2-(4-benzyl-1-piperazinyl)-4-chloro-5,6-trimethylenepyrimidine **16a**. The acid hydrolysis of 2-(4-formyl-1-piperazinyl)pyrimidine **10j** gave 2-(1-piperazinyl)pyrimidine **11j**.

On the other hand, the preparation of 4-amino- or 4-alkoxy-2-chloropyrimidines was carried out by selective substitutions of 2,4-dichloropyrimidines,[2,3] and 2-(1-piperazinyl)-pyrimidine derivatives could thence be obtained easily.

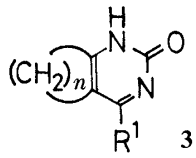
In a similar fashion, if 4-alkylpyrimidine derivatives can be obtained by the substitution



1a 2a 3a 4a

Chart 1

TABLE I. 2(1*H*)-Pyrimidinone Derivatives **3a**—**e**, and **3h**

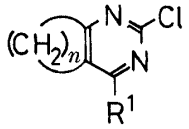


3

No.	R^1	*n*	Yield[a] (%)	mp (°C)[b]	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
3a	Me	3	46	235—237	iso-PrOH	$C_8H_{10}N_2O$	63.98 (63.95	6.71 6.71	18.65 18.59)
3b	Et	3	12	182—184	EtOAc	$C_9H_{12}N_2O$	65.83 (65.86	7.37 7.39	17.06 17.04)
3c	Me	4	46	210—215	iso-PrOH	$C_9H_{12}N_2O$	65.83 (65.78	7.37 7.41	17.06 17.06)
3d	Et	4	16	213—217	iso-PrOH–Et_2O	$C_{10}H_{14}N_2O$	67.39 (67.13	7.92 7.74	15.72 15.57)
3e	Ph	4	73	210—215	iso-PrOH	$C_{14}H_{14}N_2O$	74.31 (74.19	6.24 6.28	12.38 12.47)
3h	H	5	20[c]	172—179	EtOH	$C_9H_{12}N_2O \cdot HCl$	53.87 (53.91	6.53 6.47	13.96 13.97)

a) Yields from corresponding 2-acylcycloalkanones. *b*) With decomposition.
c) Yield from 2-formylcycloheptanone.

TABLE II. 2-Chloropyrimidine Derivatives **4a**—**e**, and **4g**, **h**



4

No.	R^1	n	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
4a	Me	3	64	71—72	iso-PrOH	$C_8H_9ClN_2$	56.98	5.38	16.61
							(56.97	5.38	16.74)
4b	Et	3	65	44—45[a]		$C_9H_{11}ClN_2$	59.18	6.07	15.34
							(59.09	6.07	15.38)
4c	Me	4	52	77—78	iso-PrOH	$C_9H_{11}ClN_2$	59.18	6.07	15.34
							(59.04	6.01	15.31)
4d	Et	4	67	48—49[a]		$C_{10}H_{13}ClN_2$	61.07	6.66	14.24
							(61.21	6.61	14.06)
4e	Ph	4	23	80—81	iso-PrOH	$C_{14}H_{13}ClN_2$	68.71	5.35	11.45
							(68.47	5.36	11.51)
4g	H	4	82	34—36[a]		$C_8H_9ClN_2$	56.98	5.38	16.61
							(56.91	5.38	16.57)
4h	H	5	75	67—68	iso-PrOH–H_2O	$C_9H_{11}ClN_2$	59.18	6.07	15.34
							(58.81	6.10	15.28)

a) Crystallized from oil.

of 4-chloropyrimidine with Grignard reagent, the synthesis of various kinds of 4-alkylpyrimidines should become easier. Kumada *et al.* recently reported that the cross-coupling reaction of aromatic halides and *n*-alkyl Grignard reagent in the presence of nickel phosphine complex gave *n*-alkyl derivatives.[5] Yamanaka *et al.* proved that there was no selectivity in the reaction of 2,4-dichloropyrimidine in this reaction.[6] Moreover, Takei *et al.* reported that the cross-coupling reaction of 2-methylthiopyrimidine gave 2-alkylpyrimidines.[7]

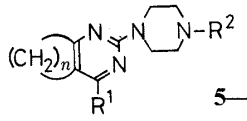
We examined the synthesis of 4-alkyl-2-methylthio-5,6-polymethylenepyrimidines **14** from 4-chloro-2-methylthio-5,6-polymethylenepyrimidines **13** and Grignard reagent as key intermediates for the synthesis of 2-(1-piperazinyl)pyrimidines. The derivatives **13** were prepared by the chlorination of 2-methylthio-5,6-polymethylene-4(3*H*)-pyrimidinones **12**. The alkylation of **13** with methylmagnesium iodide in the presence of dichloro-1,3-bis(diphenylphosphino)propane nickel ($Ni(dppp)Cl_2$) did not give the 4-methyl-2-methylthiopyrimidines **14**, but 2,4-dimethylpyrimidines **15**. Decrease of the amount of methylmagnesium iodide or lowering of the reaction temperature did not give the desired results. Next, we tried another procedure for the 2-(1-piperazinyl)pyrimidines, namely the substitution reaction of 2-(4-benzyl-1-piperazinyl)-4-chloropyrimidine **16b** with Grignard reagent. Derivative **16b** was synthesized by the method previously reported.[8] The cross-coupling reaction of **16b** with methylmagnesium iodide in the presence of $Ni(dppp)Cl_2$ gave the 4-methylpyrimidine derivative **5c**.

Biological Results and Discussion

The 2-(1-piperazinyl)pyrimidine derivatives **5**, **6**, **7**, **8**, **10**, and **11** were examined for hypoglycemic activity after oral administration in mice treated with 2-deoxy-D-glucose.[9] The results are given in Table V.

Most of the derivatives **5**, **6**, **7**, **8**, and **11** shown in Table V were considerably more active

TABLE III. 2-(1-Piperazinyl)-5,6-polymethylenepyrimidine Derivatives **5**, **6**, **7**, and **8**

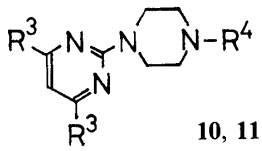


5—8

No.	R^1	R^2	n	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
5a	Me	CH_2Ph	3	47	220—225 (dec.)	iso-PrOH	$C_{19}H_{24}N_4 \cdot HCl$	66.17 (65.98)	7.31 7.26	16.25 16.26)
5b	Et	CH_2Ph	3	57	163—164	EtOH	$C_{20}H_{26}N_4 \cdot C_4H_4O_4$[b]	65.73 (65.74)	6.90 6.88	12.78 12.75)
5c	Me	CH_2Ph	4	51 23[c]	215—220 (dec.)	iso-PrOH	$C_{20}H_{26}N_4 \cdot HCl \cdot 1/2H_2O$	65.29 (65.13)	7.67 7.63	15.23 15.02)
5d	Et	CH_2Ph	4	51	170—172	EtOH	$C_{21}H_{28}N_4 \cdot C_4H_4O_4$[b]	66.35 (66.40)	7.13 7.07	12.38 12.34)
5e	Ph	CH_2Ph	4	77	98—100	EtOH	$C_{25}H_{28}N_4$	78.09 (77.98)	7.34 7.31	14.57 14.59)
5g	H	CH_2Ph	4	68	108—113 (dec.)	iso-PrOH	$C_{19}H_{24}N_4 \cdot HCl$	66.17 (65.86)	7.31 7.38	16.25 16.00)
5h	H	CH_2Ph	5	64	91—93	*n*-Hexane	$C_{20}H_{26}N_4$	74.50 (74.27)	8.13 8.10	17.38 17.33)
6a	Me	Me	3	78	235—240 (dec.)	iso-PrOH	$C_{13}H_{20}N_4 \cdot HCl$	58.09 (58.00)	7.88 7.92	20.85 20.78)
6c	Me	Me	4	69	221—225 (dec.)	iso-PrOH	$C_{14}H_{22}N_4 \cdot HCl$	59.46 (59.30)	8.20 8.07	19.81 19.45)
6f	H	Me	3	46[d]	173—175	EtOH	$C_{12}H_{18}N_4 \cdot C_4H_4O_4$[b]	57.47 (57.45)	6.63 6.62	16.76 16.65)
6g	H	Me	4	59	230—240 (dec.)	iso-PrOH	$C_{13}H_{20}N_4 \cdot HCl$	58.09 (58.39)	7.88 7.82	20.85 20.94)
6h	H	Me	5	41	208—209	EtOH	$C_{14}H_{22}N_4 \cdot C_4H_4O_4$[b]	59.65 (59.66)	7.23 7.23	15.46 15.46)
7a	Me	H	3	89	178—180	EtOH	$C_{12}H_{18}N_4 \cdot C_4H_4O_4$[b]	57.47 (57.06)	6.63 6.62	16.76 16.63)
7b	Et	H	3	91	169—171	EtOH	$C_{13}H_{20}N_4 \cdot C_4H_4O_4 \cdot 1/2H_2O$[b]	57.12 (57.30)	7.05 6.66	15.68 15.86)
7c	Me	H	4	83	254—260 (dec.)	EtOAc	$C_{13}H_{20}N_4 \cdot HCl$	58.09 (58.12)	7.88 7.77	20.85 20.52)
7d	Et	H	4	62	166—168	EtOH–EtOAc	$C_{14}H_{22}N_4 \cdot C_4H_4O_4$[b]	59.65 (59.25)	7.23 7.19	15.46 15.57)
7e	Ph	H	4	75	260—270 (dec.)	iso-PrOH	$C_{18}H_{22}N_4 \cdot HCl$	65.34 (65.11)	7.01 7.07	16.93 16.78)
7f	H	H	3	43[e]	227—231 (dec.)	EtOH	$C_{11}H_{18}N_4 \cdot HCl \cdot 1/2H_2O$	52.90 (53.03)	7.26 6.93	22.44 22.55)
7g	H	H	4	90	179—180	EtOH	$C_{12}H_{18}N_4 \cdot C_4H_4O_4$[b]	57.47 (57.50)	6.63 6.58	16.76 16.61)
7h	H	H	5	87	192—194	EtOH	$C_{13}H_{20}N_4 \cdot C_4H_4O_4$[b]	58.61 (58.34)	6.94 6.89	16.08 16.00)
8i	Me	CHO	5	30	123—125	iso-PrOH	$C_{13}H_{18}N_4O$	63.40 (63.33)	7.36 7.34	22.74 22.77)
8j	Me	Ph	5	77	60—61	EtOH	$C_{18}H_{22}N_4$	73.44 (73.25)	7.53 7.58	19.03 18.85)
8k	H	Et	4	45[f]	175—177	EtOH	$C_{14}H_{22}N_4 \cdot C_4H_4O_4$[b]	59.65 (59.31)	7.23 7.12	15.46 15.38)

a) In the case of derivatives **5** and **6**, yields are from the corresponding 2-chloropyrimidines **4**. In the case of derivatives **7**, yields are from the corresponding derivatives **5**. *b*) Maleate. *c*) From 4-chloropyrimidine derivative **16b**. *d*) From **7f**. *e*) From 4-chloropyrimidine derivative **16a**. *f*) From **7g**.

TABLE IV. 2-(1-Piperazinyl)pyrimidine Derivatives **10** and **11**



10, 11

No.	R^3	R^4	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)		
							C	H	N
10j	H	CHO	43[a]	60—63	iso-PrOH–H_2O	$C_9H_{12}N_4O$	56.23	6.29	29.15
							(56.16	6.31	29.25)
10k	Me	CH_2Ph	59[a]	233—236	EtOH	$C_{17}H_{22}N_4 \cdot HCl \cdot 1/2H_2O$	62.28	7.38	17.09
							(62.77	7.19	17.20)
11j	H	H	36[b]	156—158	EtOH	$C_8H_{12}N_4 \cdot C_4H_4O_4$[c]	51.42	5.75	19.99
							(51.21	5.80	19.92)
11k	Me	H	67[d]	300 <[e]	iso-PrOH	$C_{10}H_{16}N_4 \cdot HCl$	52.51	7.49	24.50
							(52.40	7.45	24.59)

a) From the corresponding 2-chloropyrimidines. *b*) From **10j**. *c*) Maleate. *d*) From **10k**.
e) Sublimed from 235 °C.

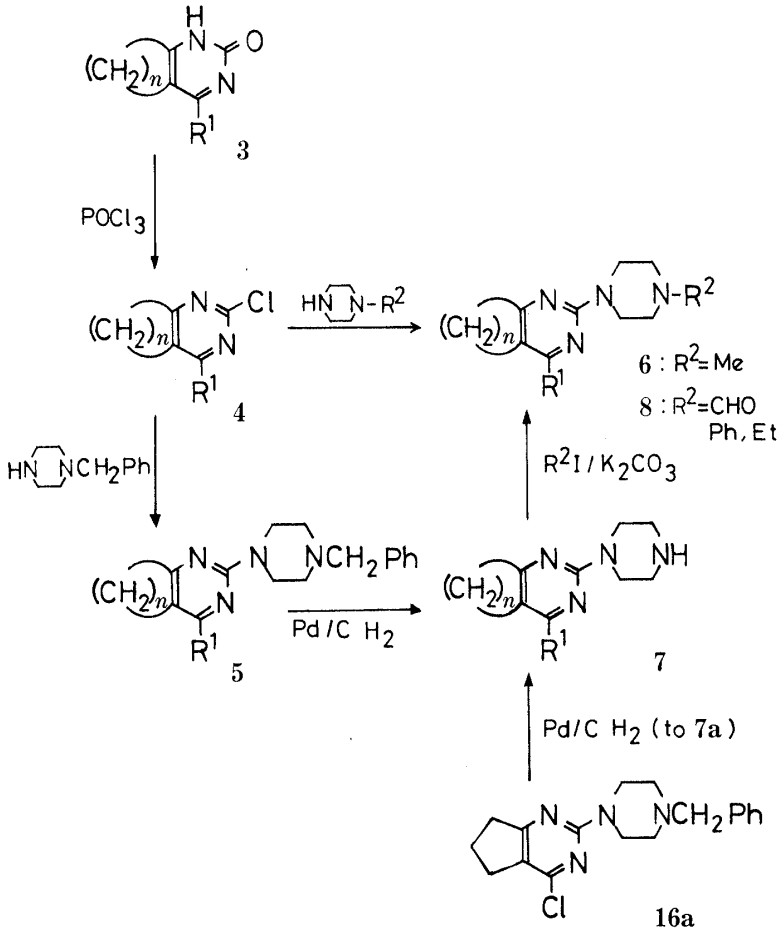
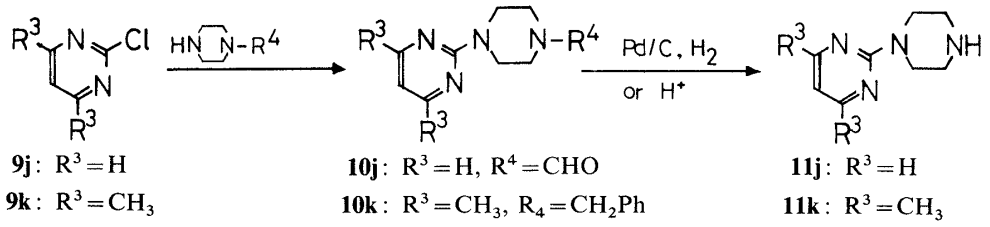


Chart 2

at a dose of 30 mg/kg than tolbutamide at 100 mg/kg (employed as the standard drug in the assay). In particular, the derivatives having the 2-(4-unsubstituted 1-piperazinyl) group, **7** and **11**, except **7e** (R^1 = Ph) showed significant activity. The 2-(4-substituted 1-piperazinyl)-pyrimidine derivatives **5**, **6**, **8**, and **10** had moderate activity; however, **5e** (R^1 = Ph, R^2 =

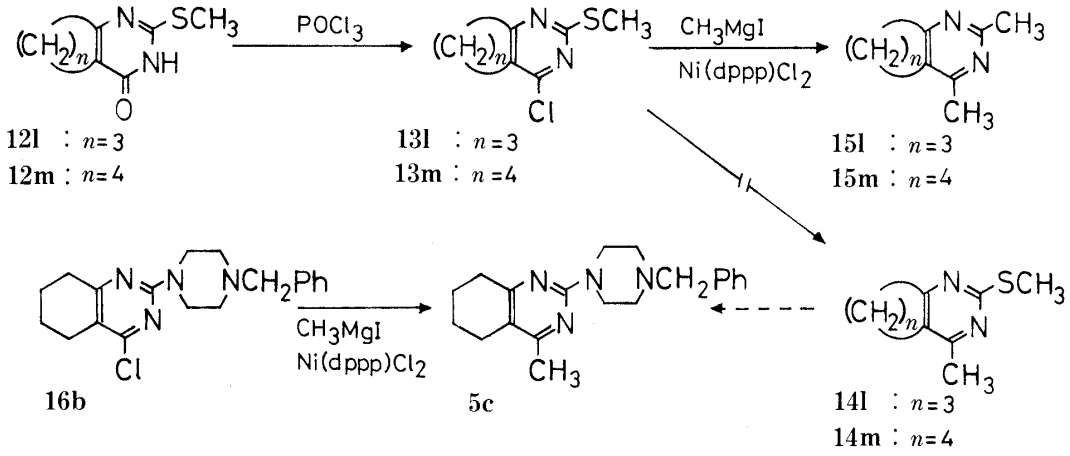


9j: $R^3=H$
9k: $R^3=CH_3$

10j: $R^3=H$, $R^4=CHO$
10k: $R^3=CH_3$, $R_4=CH_2Ph$

11j: $R^3=H$
11k: $R^3=CH_3$

Chart 3



12l : $n=3$
12m : $n=4$

13l : $n=3$
13m : $n=4$

15l : $n=3$
15m : $n=4$

16b

5c

14l : $n=3$
14m : $n=4$

Chart 4

TABLE V. Hypoglycemic Activity of 2-(1-Piperazinyl)pyrimidine Derivatives **5**, **6**, **7**, **8**, **10**, and **11**

Compd. No.	Activity[a] (%)	Compd. No.	Activity[a] (%)	Compd. No.	Activity[a] (%)	Compd. No.	Activity[a] (%)
5a	24	**6a**	23	**7d**	90	**10j**	52
5b	36	**6c**	54	**7e**	38	**10k**	NS
5c	25	**6f**	39	**7f**	74	**11j**	78
5d	34	**6g**	68	**7g**	81	**11k**	97
5e	NS	**6h**	64	**7h**	74		
5g	36	**7a**	99	**8i**	40		
5h	44	**7b**	80	**8j**	NS	Tolbutamide	30[b]
		7c	83	**8k**	33		

a) Hypoglycemic activity at 30 mg/kg *p.o.* NS indicates not significant ($p>0.05$).
b) Hypoglycemic activity at 100 mg/kg *p.o.*

CH_2Ph) and **8j** ($R^1=Me$, $R^2=Ph$) had no activity at a dose of 30 mg/kg *p.o.* These results suggest that the presence of the phenyl group as a substituent tends to decrease the activity, and that variation of the 4-substituent does not affect the efficacy except in the case of the phenyl group. These findings are similar to the results on 4-amino- and 4-alkoxy-2-(1-piperazinyl)pyrimidines reported in previous papers.[2,3] From these results it may be concluded that the 2-(1-piperazinyl)pyrimidine structure is essential for the hypoglycemic activity, and the 4-substituent of the pyrimidine does not contribute as much to the effect as a 2-substituent.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected.

Analyses were performed on a Perkin Elmer model 240 elemental analyzer. Infrared (IR) spectra were obtained for all compounds with a JASCO IRA-1 grating infrared spectrophotometer and were consistent with the assigned structures. Nuclear magnetic resonance (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 (MS) were taken with a Shimadzu LKB-9000 GC/MS machine; mass numbers are given in *m/e*, with relative intensity in % in parentheses.

Preparation of 2(1*H*)-Pyrimidinone Derivatives 3b, 3c, and 3d; Typical Example: 4-Methyl-5,6-trimethylene-2(1*H*)-pyrimidinone (3a)——A mixture of 2-acetylcyclopentanone **1a** (5.04 g, 40 mmol), urea (3.60 g, 60 mmol), and conc. HCl (3.4 ml) in EtOH (20 ml) was refluxed for 4 h, then allowed to stand overnight to give the bis-ureido derivative **2a** (12.9 g) as a precipitate; *Anal.* Calcd for $C_9H_{14}N_4O_2 \cdot HCl$: C, 43.81; H, 6.13; N, 22.71. Found: C, 43.73; H, 6.04; N, 22.44. The product was refluxed in 10% NaOH aq. solution (150 ml) for 8 h, and then neutralized with AcOH (16 ml). The precipitate was removed by filtration and the filtrate was extracted with $CHCl_3$. The organic solution was dried over anhydrous $MgSO_4$, and concentrated to give 5.12 g (46%) of **3a**, mp 225—235 °C. An analytical sample was obtained by recrystallization from iso-PrOH. MS *m/e*: 150 (M^+, 100). Other data are given in Table I.

4-Phenyl-5,6-tetramethylene-2(1*H*)-pyrimidinone (3e)——A mixture of 2-benzoylcyclohexanone **1e** (2.02 g, 10 mmol), urea (1.20 g, 20 mmol), and conc. HCl (1 ml) in EtOH (5 ml) was refluxed for 8 h, and then the solution was concentrated under reduced pressure. H_2O (20 ml) and CH_2Cl_2 (20 ml) were added to the residue, and the aq. solution was neutralized with $KHCO_3$ to give a precipitate of **3e** (1.64 g, 73%). An analytical sample was obtained by recrystallization from iso-PrOH. The data are listed in Table I.

4,5-Pentamethylene-2(1*H*)-pyrimidine Hydrochloride (3h)——A solution of 2-formylcycloheptaneone **1h** (22.9 g, 0.16 mol) in AcOH (8 ml) was added to a solution of urea (10.9 g, 0.18 mmol) in AcOH (14 ml), and the reaction mixture was allowed to stand overnight at room temperature. The product was filtered off to give the ureido-derivative (8.9 g, 30%). A mixture of the ureido derivative (5.0 g, 2.8 mmol) and NaOH (4 g, 0.1 mol) in H_2O (100 ml) was refluxed for 5 min, and then filtered. Conc. HCl (10 ml) was added to the filtrate, and the solution was concentrated under reduced pressure. The residue was extracted with hot EtOH (40 ml × 2), and the EtOH solution was concentrated to yield **3h** (3.67 g, 67%). An analytical sample was obtained by recrystallization from EtOH. The data are recorded in Table I.

General Procedure for the Preparation of 2-Chloropyrimidine Derivatives 4a—e, g, h——A solution of 2(1*H*)-pyrimidinone **3** (10 mmol) in $POCl_3$ (10 ml) was refluxed for 4 h, and concentrated under reduced pressure. The residue was added to ice-water (10 ml), and the mixture was extracted with $CHCl_3$ (5 ml × 3). The $CHCl_3$ solution was dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to give the 2-chloropyrimidine derivative **4**. The yields and other data are given in Table II.

2-(4-Substituted 1-piperazinyl)pyrimidines 5b—e, g, h, 6a, c, g, h, 8i, j, and 10j, k; Typical Example: 2-(4-Benzyl-1-piperazinyl)-4-methyl-5,6-trimethylenepyrimidine 5a——A mixture of 2-chloro-4-methyl-5,6-trimethylenepyrimidine **4a** (0.84 g, 5 mmol) and 1-benzylpiperazine (0.88 g, 5 mmol) in iso-AmOH (10 ml) was refluxed for 7 h, and then cooled overnight to give the hydrochloride of **5a** (0.81 g, 47%). ^1H NMR (free base of **5a** in $CDCl_3$) δ: 2.08 (2H, m, CH_2), 2.20 (3H, s, 4-CH_3), 2.35—2.90 (8H, m, CH_2), 3.50 (2H, s, NCH_2Ph), 3.79 (4H, t, J=6 Hz, piperazinyl 2′-, 6′-H), 7.28 (5H, s, Ph). Other data are shown in Table III.

2-(1-Piperazinyl)pyrimidines 7b—e, g, h, and 11k; Typical Example: 4-Methyl-2-piperazinyl-5,6-trimethylenepyrimidine 7a——A mixture of 2-(4-benzyl-1-piperazinyl)-4-methyl-5,6-trimethylenepyrimidine **5a** (410 mg, 1.33 mmol) and 5% Pd/C (40 mg) in EtOH was stirred under a hydrogen atmosphere at 70 °C, and then the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to give **7a** (259 mg, 89%). ^1H NMR ($CDCl_3$–D_2O) δ: 2.02 (2H, m, CH_2), 2.26 (3H, s, 4-CH_3), 2.60—2.90 (4H, m, CH_2), 3.00 (4H, m, piperazinyl 3′,5′-H), 3.90 (4H, m, piperazinyl 2′,6′-H). Other data are given in Table III.

2-(4-Ethyl-1-piperazinyl)-4,5-tetramethylenepyrimidine 8k——A mixture of 2-(1-piperazinyl)-4,5-tetramethylenepyrimidine **7g** (436 mg, 2 mmol) and ethyl iodide (312 mg, 2 mmol) in EtOH (10 ml) was refluxed for 4 h, and then 10% aq. solution of K_2CO_3 (50 ml) was added. The mixture was extracted with $CHCl_3$ (50 ml × 3). The extract was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography. Elution with $CHCl_3$ and EtOH (95:5) gave an oil, **8k**. ^1H NMR ($CDCl_3$) δ: 1.11 (3H, t, J= 9 Hz, NCH_2CH_3), 1.60—2.05 (4H, m, CH_2), 2.30—2.90 (10H, m, CH_2 in 4,5-methylene, piperazinyl 3′,5′-H, and N-ethyl), 3.80 (4H, t, J=6 Hz, piperazinyl 2′,6′-H), 7.95 (1H, s, 4-H). Other data are given in Table III.

2-(4-Methyl-1-piperazinyl)-4,5-trimethylenepyrimidine 6f——Derivative **6f** was prepared in a manner similar to that described for **8k**. The data are reported in Table III.

2-(1-Piperazinyl)-4,5-trimethylenepyrimidine Hydrochloride 7f——A mixture of 2-(4-benzyl-1-piperazinyl)-4-chloro-5,6-trimethylenepyrimidine **16a** (1.11 g, 3.38 mmol), 5% Pd/C (0.1 g), and MgO (0.14 g) in EtOH (10 ml) was stirred at 60 °C under an H_2 atmosphere. The reaction mixture was filtered, and the solution was concentrated under reduced pressure to give the hydrochloride of **7f**. An analytical sample was obtained by recrystallization from iso-PrOH. ^1H NMR ($CDCl_3$) δ: 1.95—2.35 (2H, m, CH_2), 2.65—3.00 (4H, br t, CH_2), 3.15—3.50 (4H, m, piperazinyl 3′,5′-H), 4.10—4.40 (4H, m, piperazinyl 2′,6′-H), 8.10 (1H, s, 4-H). Other data are listed in Table III.

2-(1-Piperazinyl)pyrimidine Maleate 11j——A suspension of 2-(4-formyl-1-piperazinyl)pyrimidine **10j** (5.0 g,

24 mmol) in 10% HCl (50 ml) was refluxed for 3 h. The reaction mixture was made alkaline with 10% aq. NaOH solution, and then extracted with EtOAc. The organic solution was dried over anhydrous $MgSO_4$ and concentrated to give an oily free base, **11j** (1.2 g, 36%). The free base (200 mg, 1.2 mmol) and maleic acid (162 mg, 1.4 mmol) were dissolved in EtOH (5 ml), and the mixture was kept overnight at 5 °C to give needles of **11j**. The data are given in Table IV.

2-(4-Benzyl-1-piperazinyl)-4-methyl-5,6-tetramethylenepyrimidine 5c——Methylmagnesium iodide (prepared from Mg (0.24 g, 10 mmol) and MeI (1.42 g, 10 mmol)) in Et_2O (10 ml) was added to a solution of 2-(4-benzyl-1-piperazinyl)-4-chloro-5,6-tetramethylenepyrimidine **16b** (0.34 g, 1 mmol) and Ni(dppp)Cl_2 (30 mg) in Et_2O (20 ml) under an N_2 atmosphere, and the reaction mixture was refluxed for 5 h. After concentration of the mixture, the resulting viscous liquid was kept at 40 °C for 8 h to complete the reaction, and then 10% aq. NH_4Cl solution (10 ml) was added. The mixture was extracted with Et_2O (10 ml × 3). The extract was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography. Elution with *n*-hexane and EtOAc (3 : 1) gave an oil, **5c** (75 mg, 23%). ^1H NMR ($CDCl_3$) δ: 1.60—2.00 (4H, br m, 6, 7-H), 2.24 (3H, s, 4-CH_3), 2.30—2.80 (8H, br m, 5,8-H and piperazinyl 3′,5′-H), 3.53 (2H, s, >N–CH_2–Ph), 3.80 (4H, t, J=6 Hz, piperazinyl 2′,6′-H), 7.28 (5H, s, Ph). MS *m/e*: 322 (M^+, 16), 176 (100). Other data are given in Table III.

2,4-Dimethyl-5,6-tetramethylenepyrimidine 15m——Methylmagnesium iodide (prepared from MeI (2.13 g, 15 mmol) and Mg (0.36 g, 15 mmol)) in Et_2O (15 ml) was added to a mixture of 4-chloro-2-methylthio-5,6-tetramethylenepyrimidine **13m** (644 mg, 3 mmol) and Ni(dppp)Cl_2 (36 mg, 0.09 mmol) in Et_2O (15 ml), under an N_2 atmosphere and the mixture was refluxed for 8 h. A 10% aq. solution (50 ml) of NH_4Cl was added to the reaction mixture, and the whole was extracted with Et_2O (50 ml × 3). The extract was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography. Elution with *n*-hexane and EtOAc (1 : 1) gave an oil, **15m** (235 mg, 48%). ^1H NMR δ: 1.60—2.10 (4H, m, CH_2), 2.36 (3H, s, 4-CH_3) 2.61 (3H, s, 2-CH_3), 2.20—3.10 (4H, m, CH_2). MS *m/e*: 162 (M^+, 100). *Anal.* Calcd for $C_{10}H_{14}N_2$: C, 74.04; H, 8.70; N, 17.27. Found C, 74.14; H, 8.72; N, 17.15.

2,4-Dimethyl-5,6-trimethylenepyrimidine 15l——Compound **15l** was prepared in the same manner as described for **15m**, yield 34%. ^1H NMR δ: 2.05 (2H, m, CH_2), 2.29 (3H, s, 4-CH_3), 2.53 (3H, s, 2-CH_3), 2.50—3.05 (4H, m, CH_2).

Hypoglycemic Activity——Hypoglycemic activity of the compounds was tested in groups of seven unanesthetized male mice of the ICR strain (25—30 g), fasted for 18—24 h prior to the administration. The test drugs, suspended in a 1% tragacanth gum solution, was administered orally at a dose of 30 mg/kg; 15 min later the mice were intraperitoneally given 2-deoxy-D-glucose at a dose of 500 mg/kg. Blood samples were taken from the plexus of the opthalmic veins 1 h after the drug administration. The level of blood glucose was determined by the glucose oxidase procedure. Mice of the control group (glucose level; 100—120 mg/dl) were treated with the same dosage of the inducer, and it was found that the level of blood glucose rose to 300—350 mg/dl.

Hypoglycemic activity was calculated according to the following formula:

$$\text{Hypoglycemic activity } (\%) = (a-x)/(a-b) \times 100$$

a: glucose level of positive control group
(vehicle *p.o.* + 2-deoxy-D-glucose. *i.p.*)
b: glucose level of negative control group
(vehicle, *p.o.* + saline, *i.p.*)
x: glucose level of test group
(test compounds, *p.o.* + 2-deoxy-D-glucose, *i.p.*)

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