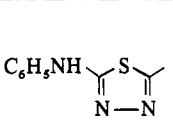
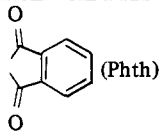
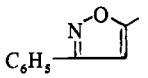
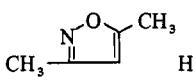
Table I

$RCH_2ON\langle^{A}_{B}$

No.	R	A	B	Salt	Method	% yield[a]	Recrystn[b] solvent	Mp, °C	Formula[g]	Antiinflam act, % inhib of edema
1		 (Phth)			C	72	E	222–223	$C_{17}H_{12}N_4O_3S$	
2		H	H	HCl[c]	D	90	E	188–190 dec	$C_9H_{10}N_4OS \cdot HCl$	29
3		Phth			C	60	E	132–133	$C_{12}H_8N_2O_4$	
4		Phth			C	66	E	206–208	$C_{18}H_{12}N_2O_4$	
5	C_6H_5	H	H	HCl	D	86	F	192–194 dec	$C_{10}H_{10}N_2O_2 \cdot HCl$[d]	55
6		Phth			C	70	E	143–145	$C_{14}H_{12}N_2O_4$	
7	CH_3	H	H	HCl	D	70	F	161–163 dec	$C_6H_{10}N_2O_2 \cdot HCl$[e]	24
8		Phth			C	50	E	146–148	$C_{13}H_9N_3O_3$	
9		H	H	2HCl	D	90	F	140–142 dec	$C_5H_7N_3O \cdot 2HCl$[f]	36

[a] Yield of once recrystallized material. [b] E, EtOH; F, MeOH-Et_2O. [c] Free base, mp 149–151°. [d] C: calcd, 52.99; found, 52.27. Nmr (DMF) δ 5.56 (s, 2 H), 7.32 (s, 1 H), 7.44–7.50 (m, 5 H). [e] Nmr (D_2O) δ 2.16 (s, 3 H), 2.31 (s, 3 H), 4.86 (s, 2 H). [f] C: Calcd, 30.32; found, 30.82. H: Calcd, 4.58; found, 5.18. Nmr (D_2O) δ 5.32 (s, 2 H), 8.75–8.82 (m, 3 H). [g] All compds were analyzed for C, H, N.

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Pyrimidine Derivatives and Related Compounds. 15.[1] Synthesis and Analgetic and Antiinflammatory Activities of 1,3-Substituted 5-Amino-6-methyluracil Derivatives

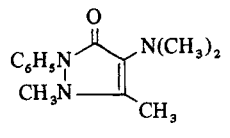
Shigeo Senda,* Kosaku Hirota, and Kazuo Banno

Gifu College of Pharmacy, Mitahora, Gifu, Japan.

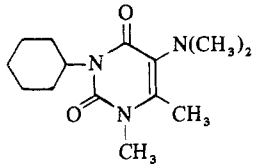
Received August 12, 1971

3-Alkyl-5-dimethylamino-6-methyl-1-phenyluracils (A), 1-alkyl-5-dimethylamino-6-methyl-3-phenyluracils (B) and their related compounds were synthesized and their acute toxicities and analgetic, antipyretic, and antiinflammatory activities were investigated. In the synthesis, substituted ureas were treated with diketene or ethyl acetoacetate, the 5 position of the resulting 1-substituted 6-methyluracils or 3-substituted 6-methyluracils was halogenated, and then the intermediate was refluxed in DMF with various amines to give 47 new 1,3-substituted 5-amino-6-methyluracil derivatives. The analgetic activities of group A (where 3-alkyl is Me or allyl) and group B (where 1-alkyl is Me, Et, or allyl) were of the same or higher order than that of aminopyrine combined with lower toxicity (0.5–0.25). Antiinflammatory activities of many of them were also comparable to or higher than that of benzydamine.

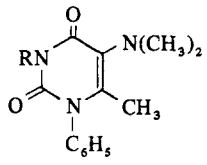
Senda, *et al.*, had previously synthesized[2] 3-cyclohexyl-5-dimethylamino-1,6-dimethyluracil (1) in which the pyrazolone ring of aminopyrine was expanded to a uracil ring. However, some difficulties were encountered in the synthesis of the uracil derivatives which have now been overcome. We have also investigated a relation between the pharmacological actions (analgetic, antipyretic, and antiinflammatory actions and acute toxicities) and chemical structures with particu-



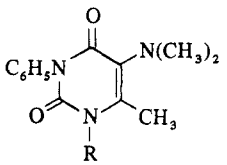
Aminopyrine



1



A



B

lar attention to 3-alkyl-5-dimethylamino-6-methyl-1-phenyluracils (A) and 1-alkyl-5-dimethylamino-6-methyl-3-phenyluracils (B).

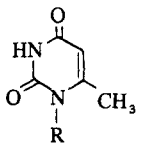
Chemistry. 1-Substituted 6-methyluracils [substituents: Me (**7**), cyclopentyl (**8**), cyclohexyl (**9**), *p*-ClC_6H_4 (**10**), *p*-$CH_3C_6H_4$ (**11**), and *p*-$CH_3OC_6H_4$ (**12**)] were synthesized (Table I) by a condensation of monosubstituted ureas with diketene followed by a ring closure similar to that used in the synthesis of 6-methyl-1-phenyluracil (**6**)[4] where phenylurea was condensed with diketene in AcOH and the resulting intermediate 1-acetoacetyl-3-phenylurea (**2**) was subjected to a ring closure. In the present study, it was possible to isolate and identify some of the intermediate 3-substituted 1-acetoacetylureas but, in general, heating without isolating such an intermediate was advisable.

When the resulting 1-substituted 6-methyluracils (**6–12**) and 3-substituted 6-methyluracils[5] [substituents: Ph (**13**), cyclopentyl (**14**), benzyl (**15**), and phenethyl (**16**)] were treated with alkylating agents (Me_2SO_4, RX), N-1 and N-3, respectively, were alkylated to give 1,3-disubstituted 6-methyluracils (**17–40**) (Table II). In these reactions 3-alkylation proceeded more easily than that at the 1 position of a pyrimidine ring.

Two methods were utilized for the introduction of secondary amines into position 5 of 1,3-substituted 6-methyluracils leading to compounds of the A and B series. The first involved nitration of the pyrimidine, reduction of this moiety, and subsequent alkylation of this amine. **9** and **20** afforded the corresponding 5-nitro compounds (**41**, **42**) in high yield. However where a Ph group was present in the 1 position (**17**) dinitration occurred (**43**). This method does present limitations and an additional reaction step compared with the second procedure. This latter method involves halogenation at the 5 position and replacement with the appropriate amine.

Chlorination of **6** and **13** by NaOCl gave the appropriate 5-chloro analogs (**44** and **45**) in poor yields (21–25%). Application of SO_2Cl_2 in the presence of $FeCl_3$ resulted in an

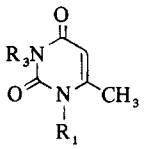
Table I. 1-Substituted 6-Methyluracils



Compd No.	R	Mp,[a] °C	Appearance (colorless)	Yield, %	Formula[b]
7	Me	228[c]	Prisms	56	$C_6H_8N_2O_2$
8	Cyclopentyl	228	Prisms	64	$C_{10}H_{14}N_2O_2$[d]
9	Cyclohexyl	241	Needles	72	$C_{11}H_{16}N_2O_2$
10	*p*-ClC_6H_4	291	Prisms	83	$C_{11}H_9ClN_2O_2$
11	*p*-$CH_3C_6H_4$	305	Needles	83	$C_{12}H_{12}N_2O_2$
12	*p*-$CH_3OC_6H_4$	270	Needles	45	$C_{12}H_{12}N_2O_3$

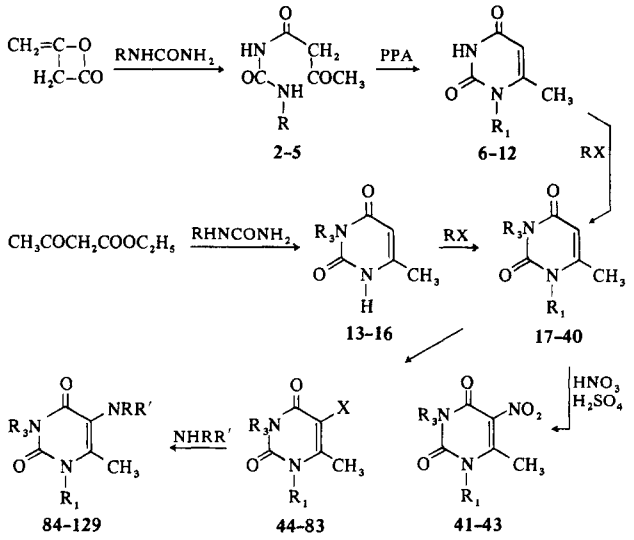
[a] All compds were recrystd from MeOH. [b] All compds were analzyed for C, H, N. [c] Lit.[3] mp 220°. [d] C: calcd, 61.83; found, 61.36.

Table II. 1,3-Disubstituted 6-Methyluracils



Compd No.	R_1	R_3	Mp, °C	Appearance (colorless)	Recrystn solvent	Yield, %	Formula[a]
17	Ph	Me	300	Needles	AcOH	79	$C_{12}H_{12}N_2O_2$
18	Me	Me	114[b]	Needles	H_2O	54	$C_7H_{10}N_2O_2$
19	Cyclopentyl	Me	146	Leaflets	MeOH-H_2O	95	$C_{11}H_{16}N_2O_2$
20	Cyclohexyl	Me	214	Needles	MeOH	95	$C_{12}H_{18}N_2O_2$
21	*p*-ClC_6H_4	Me	299	Leaflets	MeOH	63	$C_{12}H_{11}ClN_2O_2$
22	*p*-$CH_3C_6H_4$	Me	275	Needles	MeOH	40	$C_{13}H_{14}N_2O_2$
23	*p*-$CH_3OC_6H_4$	Me	234	Leaflets	MeOH	92	$C_{13}H_{14}N_2O_3$
24	Me	Ph	210	Needles	MeOH	73	$C_{12}H_{12}N_2O_2$
25	Me	Cyclopentyl	120	Leaflets	MeOH-H_2O	60	$C_{11}H_{16}N_2O_2$
26	Me	Cyclohexyl	137	Needles	MeOH-H_2O	70	$C_{12}H_{18}N_2O_2$
27	Me	$PhCH_2$	165	Prisms	MeOH	65	$C_{13}H_{14}N_2O_2$
28	Me	$PhCH_2CH_2$	135	Needles	MeOH	83	$C_{14}H_{16}N_2O_2$
29	Ph	Et	211	Prisms	MeOH	95	$C_{13}H_{14}N_2O_2$
30	Ph	*i*-Pr	182	Needles	MeOH	Trace	$C_{14}H_{16}N_2O_2$
31	Ph	*n*-Bu	186	Needles	MeOH	76	$C_{15}H_{18}N_2O_2$
32	Ph	$HOCH_2CH_2$	145	Needles	AcOEt	81	$C_{13}H_{14}N_2O_3$
33	Et	Ph	177	Needles	Ligroin	95	$C_{13}H_{14}N_2O_2$[c]
34	*n*-Bu	Ph	99	Needles	Ligroin	77	$C_{15}H_{18}N_2O_2$
35	$HOCH_2CH_2$	Ph	140	Needles	H_2O	53	$C_{13}H_{14}N_2O_3$
36	Ph	$EtOOCCH_2$	176	Needles	MeOH	85	$C_{15}H_{16}N_2O_4$
37	Ph	H_2NCOCH_2	254	Prisms	MeOH	63	$C_{13}H_{13}N_3O_3$
38	$EtOOCCH_2$	Ph	123	Needles	MeOH-H_2O	65	$C_{15}H_{16}N_2O_4$
39	Cyclopentyl	$EtOOCCH_2$	98	Prisms	Ligroin	64	$C_{14}H_{20}N_2O_4$
40	Cyclohexyl	$EtOOCCH_2$	132	Needles	MeOH-H_2O	58	$C_{15}H_{22}N_2O_4$

[a] All compds were analyzed for C, H, N. [b] Lit.[6] mp 110°. [c] N: calcd, 12.17; found, 12.88.



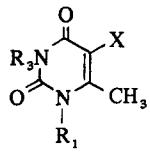
improved conversion (55–82%) as shown in Table III.

5-Bromination of the pyrimidine ring gave 1,3-substituted 5-bromo-6-methyluracils (**49–70**) (Table III) comparatively easily and in high yields by adding a quantitative amount of Br_2 in glacial AcOH. However, this method was not suitable for the halogenation of 6-methyluracil derivatives having 2-hydroxyethyl or alkenyl groups at the 1 or 3 position since various side reactions other than 5-halogenation took place. Thus we synthesized 1,3-substituted 5-halo-6-methyluracils (**71–78**) by the reaction of 5-halo-6-methyl-1-phenyluracils (**44, 65**) or 5-halo-6-methyl-3-phenyluracils (**45, 70**) with 2-chloroethanol, allyl bromide, or 2-cyclohexenyl bromide. When **63** and **64** (1- or 3-CH_2COOEt) were hydrolyzed in concd HCl, 5-bromo-3-carboxymethyl-6-methyl-1-phenyluracil (**79**) and 5-bromo-1-carboxymethyl-6-methyl-3-phenyluracil (**80**) were obtained, respectively. The Michael reaction of **65** with ethyl acrylate gave 5-bromo-3-ethoxycarbonylethyl-6-methyl-3-phenyluracil (**81**).

In the iodination of the 5 position of the pyrimidine ring, 5-iodo-3,6-dimethyl-1-phenyluracil (**82**) and 5-iodo-1,6-dimethyl-3-phenyluracil (**83**) were obtained from **17** and **24**, respectively, by a conventional route (Table III).

1,3-Substituted 5-halo-6-methyluracils (**44–83**), obtained by various halogenation methods, were then heated at 100° in a sealed tube with NH_3, or amines in DMF, to give

Table III. 1,3-Substituted 5-Halo-6-methyluracils



Compd No.	R_1	R_3	X	Mp, °C	Appearance (colorless)	Recrystn solvent	Method	Yield, %	Formula[a]
44	Ph	H	Cl	>300	Needles	AcOH	A	95	$C_{11}H_9ClN_2O_2$
45	H	Ph	Cl	257	Needles	MeOH	A	83	$C_{11}H_9ClN_2O_2$
46	Ph	Me	Cl	232	Needles	MeOH	A	73	$C_{12}H_{11}ClN_2O_2$
47	Me	Ph	Cl	158	Needles	Ligroin	A	73	$C_{12}H_{11}ClN_2O_2$
48	Me	Me	Cl	151	Needles	MeOH	A	67	$C_7H_9ClN_2O_2$
49	Ph	Me	Br	238	Needles	MeOH	B	85	$C_{12}H_{11}ClN_2O_2$
50	Me	Me	Br	138	Needles	MeOH	B	77	$C_7H_9BrN_2O_2$
51	Cyclopentyl	Me	Br	158	Needles	MeOH	B	91	$C_{11}H_{15}BrN_2O_2$
52	Cyclohexyl	Me	Br	240	Needles	MeOH	B	96	$C_{12}H_{17}BrN_2O_2$
53	*p*-ClC_6H_4	Me	Br	269	Needles	MeOH	B	88	$C_{12}H_{10}BrClN_2O_2$
54	*p*-$CH_3C_6H_4$	Me	Br	245	Needles	MeOH	B	71	$C_{13}H_{13}BrN_2O_2$
55	*p*-$CH_3OC_6H_4$	Me	Br	209	Needles	MeOH	B	85	$C_{13}H_{13}BrN_2O_3$
56	Me	Ph	Br	198	Leaflets	MeOH	B	89	$C_{12}H_{11}BrN_2O_2$
57	Me	Cyclopentyl	Br	174	Needles	MeOH	B	80	$C_{11}H_{15}BrN_2O_2$
58	Me	Cyclohexyl	Br	175	Needles	MeOH	B	65	$C_{12}H_{17}BrN_2O_2$
59	Me	$PhCH_2$	Br	135	Prisms	MeOH	B	91	$C_{13}H_{13}BrN_2O_2$
60	Me	$PhCH_2CH_2$	Br	117	Needles	MeOH	B	87	$C_{14}H_{15}BrN_2O_2$
61	Ph	Et	Br	209	Leaflets	MeOH	B	69	$C_{13}H_{13}BrN_2O_2$
62	Et	Ph	Br	165	Needles	MeOH	B	57	$C_{13}H_{13}BrN_2O_2$
63	Ph	$EtOOCCH_2$	Br	184	Prisms	MeOH	B	72	$C_{15}H_{15}BrN_2O_4$
64	$EtOOCCH_2$	Ph	Br	247	Needles	MeOH	B	76	$C_{15}H_{15}BrN_2O_4$
65	Ph	H	Br	293	Needles	AcOH	B	83	$C_{11}H_9BrN_2O_2$
66	Me	H	Br	264	Prisms	MeOH	B	57	$C_6H_7BrN_2O_2$
67	*n*-Bu	H	Br	164	Prisms	MeOH-H_2O	B	70	$C_9H_{13}BrN_2O_2$
68	Cyclopentyl	H	Br	185	Needles	MeOH	B	90	$C_{10}H_{13}BrN_2O_2$
69	Cyclohexyl	H	Br	261	Prisms	MeOH	B	92	$C_{11}H_{15}BrN_2O_2$
70	H	Ph	Br	281	Needles	MeOH	B	89	$C_{11}H_9BrN_2O_2$
71	Ph	$HOCH_2CH_2$	Br	188	Prisms	MeOH	C	96	$C_{13}H_{13}BrN_2O_3$
72	$HOCH_2CH_2$	Ph	Br	164	Needles	MeOH	C	69	$C_{13}H_{13}BrN_2O_3$
73	Ph	$CH_2=CHCH_2$	Cl	157	Needles	MeOH-H_2O	C	95	$C_{14}H_{13}ClN_2O_2$[c]
74	Ph	$CH_2=CHCH_2$	Br	175	Prisms	EtOH	C	81	$C_{14}H_{13}BrN_2O_2$
75	$CH_2=CHCH_2$	Ph	Cl	136	Needles	MeOH	C	45	$C_{14}H_{13}ClN_2O_2$
76	$CH_2=CHCH_2$	Ph	Br	136	Needles	EtOH-H_2O	C	72	$C_{14}H_{13}BrN_2O_2$
77	Ph	2-cyclohexenyl	Br	247	Needles	MeOH	C	Trace	$C_{17}H_{17}BrN_2O_2$
78	Ph	*i*-Pr	Br	230	Needles	MeOH	C	12	$C_{14}H_{15}BrN_2O_2$
79	Ph	$HOOCCH_2$	Br	252	Needles	EtOH	D	84	$C_{13}H_{11}BrN_2O_4$
80	$HOOCCH_2$	Ph	Br	192	Needles	EtOH	D	79	$C_{13}H_{11}BrN_2O_4$
81	Ph	$EtOOCCH_2CH_2$	Br	174	Prisms	MeOH	C	Trace	$C_{16}H_{17}BrN_2O_4$
82	Ph	Me	I	216	Needles[b]	MeOH	E	73	$C_{12}H_{11}IN_2O_2$
83	Me	Ph	I	235	Needles[b]	MeOH	E	83	$C_{12}H_{11}IN_2O_2$

[a] All Compds were analyzed for C, H, N. [b] Yellow crystal. [c] C: calcd, 60.77; found, 60.34.

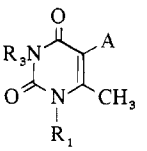
desired 1,3-substituted 5-amino-6-methyluracils (**84-129**) (Table IV).

Pharmacology. The resulting compounds were classified into 5-substituted 3-alkyl-6-methyl-1-phenyluracils (group A), 5-substituted 1-alkyl-6-methyl-3-phenyluracils (group B) and others (group C) and their acute toxicities [LD_{50} in mice (ip)], analgetic activities [according to Haffner's method with a threshold dose of morphine in mice (ip) and the phenylbenzoquinone writhing technique in mice (sc)], antipyretic activities [febrile rats by TTG—a pyrogen obtained from *Pseudomonas fluorescens,* Fujisawa Pharm. Co.—(po)], and antiinflammatory activities [rat hind paw edema induced by carrageenin (po)] were investigated (Table V). The 5-halouracil derivatives (groups A and B) were found to exhibit low acute toxicity, but, due to their insignificant pharmacological activities, these compounds were of little interest.

Acute toxicities of both groups A and B of 5-dialkylaminouracil derivatives were weak being 0.5 to 0.25 of that of aminopyrine. However **121** and **123** (group C) showed marked acute toxicities.

As to analgetic activities, **84**, **91**, **94**, and **99** (group A) and **101**, **102**, **108**, **111**, **112**, **114**, and **115** (group B) showed activity equal to or more pronounced than that of aminopyrine. As to antipyretic activities, **99** (group A), **101**, **102**, **107**, **108**, **113**, and **114** (group B), and **120**, **128**, and **129** (group C) gave marked results. As to antiinflammatory activities, **84** and **99** (group A) and **107** and **115** (group B) showed the same or more action than that of benzydamine.

Table IV. 1,3-Substituted 5-Amino-6-methyluracils



Compd No.	R_1	R_3	A	Mp[a] or bp (mm), °C	Appearance[b] (colorless)	Recrystn solvent	Yield, %	Formula[c]
84	Ph	Me	Me_2N	118	Prisms	Ligroin	77	$C_{14}H_{17}N_3O_2$
85	Ph	Me	Et_2N	89	Prisms	MeOH-H_2O	59	$C_{16}H_{21}N_3O_2$
86	Ph	Me	$(CH_2{=}CHCH_2)_2N$	93	Needles	PB	45	$C_{18}H_{21}N_3O_2$
87	Ph	Me	NH_2	251	Needles	MeOH	33	$C_{12}H_{13}N_3O_2$
88	Ph	Me	MeNH	129	Prisms	Ligroin	21	$C_{13}H_{15}N_3O_2$
89	Ph	Me	EtNH	110	Prisms	PB	38	$C_{14}H_{17}N_3O_2$
90	Ph	Me	*i*-PrNH	118	Needles	MeOH-H_2O	57	$C_{15}H_{19}N_3O_2$
91	Ph	Me	Pyrrolidinyl	124	Needles	MeOH-H_2O	85	$C_{16}H_{19}N_3O_2$
92	Ph	Me	Piperidyl	132	Needles	PB	92	$C_{17}H_{21}N_3O_2$
93	Ph	Me	Morpholinyl	147	Needles	MeOH-H_2O	33	$C_{16}H_{19}N_3O_3$
94	Ph	H	Me_2N	191	Needles	MeOH-H_2O	94	$C_{13}H_{15}N_3O_2$
95	Ph	Et	Me_2N	91	Needles	PB	91	$C_{15}H_{19}N_3O_2$
96	Ph	Et	Et_2N	173-175 (0.3)	Oil		62	$C_{17}H_{23}N_3O_2$
97	Ph	Et	Piperidyl	104	Needles	PB	96	$C_{18}H_{23}N_3O_2$
98	Ph	*n*-Bu	Me_2N	64	Needles	MeOH-H_2O	75	$C_{17}H_{23}N_3O_2$
99	Ph	$CH_2{=}CHCH_2$	Me_2N	180-183 (0.4)	Oil		66	$C_{16}H_{19}N_3O_2$
100	Ph	$HOCH_2CH_2$	Me_2N	148	Needles	MeOH-H_2O	78	$C_{15}H_{19}N_3O_3$
101	Me	Ph	Me_2N	135	Needles	Ligroin	87	$C_{14}H_{17}N_3O_2$
102	Me	Ph	Et_2N	121	Prisms	Ligroin	73	$C_{16}H_{21}N_3O_2$
103	Me	Ph	*n*-Bu_2N	99	Prisms	PE	17	$C_{20}H_{29}N_3O_2$
104	Me	Ph	$(CH_2{=}CHCH_2)_2N$	87	Needles	PE	23	$C_{18}H_{21}N_3O_2$
105	Me	Ph	NH_2	260	Prisms	MeOH	40	$C_{12}H_{13}N_3O_2$
106	Me	Ph	MeNH	152	Prisms	H_2O	34	$C_{13}H_{15}N_3O_2$
107	Me	Ph	*i*-PrNH	183	Needles	MeOH	92	$C_{15}H_{19}N_3O_2$
108	Me	Ph	*n*-BuNH	110	Needles	Ligroin	70	$C_{16}H_{21}N_3O_2$
109	Me	Ph	*s*-BuNH	151	Needles	MeOH-H_2O	66	$C_{16}H_{21}N_3O_2$[d]
110	Me	Ph	Pyrrolidinyl	162	Needles	MeOH-H_2O	84	$C_{16}H_{19}N_3O_2$
111	Me	Ph	Piperidyl	200	Prisms	MeOH	55	$C_{17}H_{21}N_3O_2$
112	Me	Ph	Morpholinyl	229	Needles	MeOH	47	$C_{16}H_{19}N_3O_3$
113	Et	Ph	Me_2N	190	Prisms	MeOH	95	$C_{15}H_{19}N_3O_2$
114	Et	Ph	Et_2N	110	Prisms	Ligroin	83	$C_{17}H_{23}N_3O_2$
115	$CH_2{=}CHCH_2$	Ph	Me_2N	139	Needles	MeOH-H_2O	93	$C_{16}H_{19}N_3O_2$
116	$HOCH_2CH_2$	Ph	Me_2N	197	Prisms	MeOH-H_2O	69	$C_{15}H_{19}N_3O_3$
117	*p*-ClC_6H_4	Me	Me_2N	144	Needles	MeOH-H_2O	45	$C_{14}H_{16}ClN_3O_2$
118	*p*-$CH_3C_6H_4$	Me	Me_2N	123	Needles	MeOH-H_2O	70	$C_{15}H_{19}N_3O_2$
119	*p*-$CH_3OC_6H_4$	Me	Me_2N	155	Needles	MeOH-H_2O	66	$C_{15}H_{19}N_3O_3$
120	Me	$PhCH_2$	Me_2N	185-195 (0.2)	Oil		60	$C_{15}H_{19}N_3O_2$
121	Cyclopentyl	Me	Me_2N	104	Leaflets	Ligroin	46	$C_{13}H_{21}N_3O_2$
122	Cyclopentyl	H	Me_2N	234	Needles	MeOH	34	$C_{12}H_{19}N_3O_2$
123	Cyclohexyl	Me	Me_2N	122	Needles	MeOH-H_2O	94	$C_{14}H_{23}N_3O_2$
124	Cyclohexyl	Me	Pyrrolidinyl	104	Leaflets	MeOH-H_2O	76	$C_{16}H_{25}N_3O_2$
125	Cyclohexyl	Me	Piperidyl	145	Needles	MeOH-H_2O	54	$C_{17}H_{27}N_3O_2$
126	Cyclohexyl	Me	Morpholinyl	137	Needles	MeOH-H_2O	59	$C_{16}H_{25}N_3O_3$
127	Cyclohexyl	H	Me_2N	189	Prisms	MeOH	59	$C_{13}H_{21}N_3O_2$
128	Me	Cyclopentyl	Me_2N	142	Prisms	Ligroin	64	$C_{13}H_{21}N_3O_2$
129	Me	Me	Me_2N	94	Needles	H_2O	81	$C_9H_{15}N_3O_2$

[a] HCl salt: **84** (mp 210°), **99** (mp 190-191°), **101** (mp 216°), **115** (mp 207°). [b] Recrystn solvent: PB (petr ether, bp 50-90°), PE (petr ether, bp 30-70°). [c] All compds were analyzed for C, H, N. [d] N: calcd, 14.62; found, 15.20.

Table V. Acute Toxicity and Analgetic, Antipyretic, and Antiinflammatory Activities of 1,3,5-Substituted 6-Methyluracils

Group	Compd No.	LD_{50}[a]	Analgetic activity [ED_{50}][b] Modified Haffner's[c] method	Analgetic activity [ED_{50}][b] PO writhing[d]	Antipyretic activity,[e] °C 100 mg/kg	Antipyretic activity,[e] °C 200 mg/kg	Antiinflammatory,[f] % 100 mg/kg	Antiinflammatory,[f] % 200 mg/kg
A	49	>2000	*Ca.* 300	73 (33-160)		−0.1		20
	74	>2000	>300	>300		5.8		50
	79	>2000	>300	180 (62-522)		5.8		20
	82	>2000	>300	*Ca.* 200-300		5.5		51
	84	815 (755-880)	98 (74-129)	56 (23-134)		−0.1		65
	85	830 (741-930)	172 (125-237)	>300		−0.4		46
	86	800 (702-912)	102 (54-194)	>300		5.9		46
	90	558 (507-614)	89 (48-165)	137 (69-274)		1.9		45
	91	1250 (1126-1388)	146 (97-219)	31 (12-76)		0.2		33
	92	>2000	245 (136-441)	35 (14-86)		1.0		37
	94	591 (563-624)	134 (71-255)	60 (15-241)		1.8		35
	95	510 (470-533)	63 (47-85)	146 (56-380)		−0.7		51
	96	845 (747-955)	98 (52-186)	140 (50-392)		0.7		53
	99	835 (758-918)	65 (47-89)	70 (32-155)	−0.7	−6.6		75
	100	1040 (953-1130)	215 (123-376)	54 (29-100)		0.8		36
B	56	393 (362-426)	170 (110-264)	130 (43-390)		1.5		41
	76	382 (347-420)	63 (35-113)	>300		0.2		48
	83	445 (412-480)	122 (64-232)	>300		7.6		48
	101	885 (763-1027)	102 (67-156)	46 (22-97)	−5.6	−7.7		44
	102	1100 (957-1265)	93 (73-119)	53 (23-121)	1.9	−5.0		45
	107	648 (620-677)	151 (117-198)	73 (37-142)		−4.6		64
	108	518 (491-547)	94 (75-118)	47 (24-94)		−5.5		48
	109	355 (319-381)	95 (52-173)	88 (39-198)		−0.5		58
	110	1460 (1304-1635)	214 (113-407)	>300		−0.2		32
	111	>2000	97 (54-175)	80 (37-172)		3.3		27
	112	1110 (965-1277)	71 (32-156)	59 (21-165)		2.6		35
	113	1100 (1000-1210)	136 (83-225)	77 (31-193)		−5.6		37
	114	660 (631-690)	79 (45-140)	95 (50-181)		−5.5		57
	115	644 (593-691)	42 (29-51)	45 (23-89)		−0.6	52	73
	116	>2000	170 (124-233)	130 (96-176)		2.0		31
C	1	785 (737-836)	146 (117-178)	72 (38-136)	−0.2	−1.8		36
	50	252 (230-276)	104 (67-161)	51 (30-87)		−3.2		57
	51	422 (380-468)	81 (51-130)	92 (51-166)		4.1		26
	52	>2000	84 (45-155)	56 (20-155)		2.7		22
	53	>2000	>300	>300		4.6		18
	54	>2000	>300	230 (96-522)		5.7		35
	55	>2000	225 (125-405)	*Ca.* 200-300		7.3		44
	57	945 (808-1106)	89 (51-156)	42 (18-97)		5.0		32
	59	719 (691-748)	85 (53-136)	85 (30-246)		6.4		37
	117	755 (696-819)	166 (95-307)	290 (95-882)		1.9		41
	119	1690 (1482-1927)	246 (144-417)	>300		11.0		41
	120	680 (582-796)	170 (112-258)	*Ca.* 300		−8.9		38
	121	33 (30-36)	50:5/6 (2/6 death)	11 (6-21)	5.4		6/7 death	
	123	125 (89-175)	100:2/5 (3/8 death)	19 (6-62)		4.3	2/6 death	38
	124	>2000	>300	>300		6.5		24
	125	>2000	*Ca.* 300	>300		2.8		22
	126	510 (460-566)	167 (118-237)	190 (66-551)		−0.2		44
	127	1540 (1426-1663)	204 (109-382)	55 (24-128)		2.8		38
	128	1220 (1156-1287)	128 (93-178)	62 (21-186)	−0.3	−5.1		55
	129	591 (542-644)	139 (99-195)	29 (12-73)		−5.6		37
	Aminopyrine	269 (255-284)	123 (89-170)	32 (20-52)	−4.1		69	86
	Benzydamine	109 (101-118)	45 (29-70)	13 (2-31)			52	67
	Phenylbutazone	419 (388-453)	122 (68-220)	96 (38-245)		0.1	(50 mg-62)	
	Aspyrine	400 (360-450)	300:1/2	49 (21-113)		−2.4		47

(cont 5.5-6.8)

[a] LD_{50} (mg/kg ip in female mice). [b] Analgetic activity, ED_{50} (mg/kg in male mice). [c] Haffner's method with a threshold dose of morphine in mice (ip). [d] The phenyl benzoquinone writhing technique in mice (sc). [e] Antipyretic activity (febrile rats by TTG) (mg/kg po in male rats). [f] Antiinflammatory (mg/kg po in male rats).

Experimental Section

6-Methyl-1-phenyluracil (6). Method A. A mixt of 8.4 g of diketene and 13.6 g of phenylurea was heated to reflux for 3 hr in 80 ml of AcOH, then AcOH was evapd, 60 ml of 10% NaOH was added to the residue, the mixt was filtered to remove insol matters, and the filtrate was acidified with HCl and filtered to give 6.6 g of the crude product, mp 278-281°. It was recrystd from AcOH to give needles of mp 281-283°, lit.[4a] mp 272-274°. The yield was 4.6 g (22.6%).

Method B. $Hg(AcO)_2$ (0.1 g) was further used in method A to give 8.3 g of the crude product (mp 281°). When this was mixed with 6 obtd by method A, no depression in mp was observed.

Method C. NEt_3 (5 drops) was also used in method A to give 15.0 g of the crude product (mp 281°). No mmp depression with 6 obtd by method A.

Method D. A mixt of 8.4 g of diketene, 13.6 g (0.1 mole) of phenylurea, and 0.1 g of $Hg(AcO)_2$ was kept overnight in 100 ml of AcOH and then AcOH is evapd. The resulting 1-acetoacetyl-3-phenylurea (2) was, without isolation from the reaction mixt, heated for 30 min on a water bath with 80-90 g of polyphosphoric acid (P_2O_5-H_3PO_4, 1:1) and cooled, a large amt of cold H_2O was added, and the mixt was filtered to give 16.2 g of the crude product, mp 272-278°. With 6 obtd by method A, no mmp depression took place.

1-Substituted 6-Methyluracils (7-12) (Table I). Method D was applied; thus, a mixt of 8.4-16.8 g (0.1-0.2 mole) of diketene, 0.1 mole of monosubstituted urea, and 0.1 g of $Hg(AcO)_2$ in 100 ml of

AcOH was allowed to stand overnight, then AcOH was evapd, the residue was heated for 30 min on a water bath with 80–90 g of polyphosphoric acid and cooled, a large amt of cold H_2O was added, the mixt was filtered, and the resulting crude product was recrystd. The intermediate 3-substituted 1-acetoacetylurea was, if desired, isolated by recrystg a part of the residue from MeOH–H_2O [substituents: cyclopentyl (3), mp 128°; *p*-$CH_3C_6H_4$ (4), mp 172°; *p*-$CH_3OC_6H_4$ (5), mp 146°] and was heated with polyphosphoric acid as mentioned above.

1,3-Disubstituted 6-Methyluracils (17–40) (Table II). Method A. 1-Substituted 6-methyluracil (**6–12**) or 3-substituted 6-methyluracil[5] (**13–16**) (0.1 mole) was dissolved in 45 ml of 10% NaOH soln and the mixt was stirred for 3 hr with 0.12 mole of Me_2SO_4 at room temp. When the reaction soln became almost neutral, it was filtered and the resulting crude product was recrystd.

Method B. 1-Substituted 6-methyluracil (**6, 8, 9**) or 3-phenyl-6-methyluracil (**13**) (0.1 mole) was dissolved in NaOEt soln (from 2.3 g of Na and 200 ml of abs EtOH), the mixt was heated to reflux for 3 hr with 0.12 mole of alkyl halides (*e.g.*, EtBr, *i*-PrBr, *n*-BuBr, 2-chloroethanol, ethyl chloroacetate, chloroacetoamide), the solvent was evapd, 100 ml of 10% NaOH soln was added to the residue, the mixt was filtered, and the resulting crude product was recrystd.

1-Cyclohexyl-6-methyl-5-nitrouracil (41). 9 (10.4 g) was gradually added to a stirring, cold (0–5°) mixt of 50 ml of concd H_2SO_4 and 50 ml of concd HNO_3, the mixt was allowed to react for 1 hr and poured over ice water, and the isolated mass was recrystd from MeOH to give 6.9 g (54.5%) of prisms, mp 235–237°. *Anal.* ($C_{11}H_{15}N_3O_4$) C, H, N.

1-Cyclohexyl-3,6-dimethyl-5-nitrouracil (42). **20** (11 g) was treated in a mixt of 50 ml of concd H_2SO_4 and 50 ml of concd HNO_3 above. Recrystn from MeOH gave 7.5 g (55.6%) of yellow needles, mp 156°. *Anal.* ($C_{12}H_{17}N_3O_4$) C, H, N.

3,6-Dimethyl-5-nitro-1-nitrophenyluracil (43). **17** (11 g) was treated in a mixt of 50 ml of concd H_2SO_4 and 50 ml of concd HNO_3. Recrystn from AcOH gave 8.5 g (55.6%) of yellow needles, mp 281°. *Anal.* ($C_{12}H_{10}N_4O_6$) C, H, N.

1,3-Substituted 5-Halo-6-methyluracils (44–83) (Table III). Method A. 1,3-Substituted 6-methyluracil (**6, 13, 17, 18, 24**) (0.1 mole) was added to 180 ml of 5% Ac_2O–AcOH, 60 mg of $FeCl_3$ was then added, and the mixt was heated to reflux for 3 hr with simultaneous dropwise addn of 15 g of SO_2Cl_2. After completion of the reaction, the mixt was allowed to cool, H_2O was added, and the ppt was filtered.

Method B. 1,3-Disubstituted 6-methyluracils (**17–29, 33, 36, 38**), 1-substituted 6-methyluracils (**6–9**), 6-methyl-3-phenyluracil (**13**), or 1-butyl-6-methyluracil[7] (0.1 mole) were added to 80 ml of AcOH, and 16 g of Br_2 and 30 ml of AcOH were gradually added with stirring until the mixt was decolorized. H_2O (300 ml) was added, and the resulting product was filtered, washed with H_2O, and recrystd.

Method C. To a soln of 2.3 g of Na in 200 ml of EtOH were added 0.1 mole of **44, 45, 65,** or **70** (Table III) and 0.11–0.12 mole of alkylating agent (*e. g.*, 2-chloroethanol, allyl bromide, 2-cyclohexenyl bromide, *i*-PrBr) and the mixt was heated to reflux for 3–5 hr on a water bath. After the reaction was over, EtOH was evapd, the residue was washed with H_2O, 30–50 ml of 10% NaOH soln was added, and the insol matter was collected, washed with H_2O, and recrystd.

Method D. To 50 ml of dioxane was added 10 g of **63** or **64** (Table III) and the mixt was heated to reflux with 20 ml of concd HCl. The product was filtered off, and recrystd from EtOH.

Method E. To 200 ml of AcOH were added 6.1 g (0.03 mole) of **17** or **24** and 3.8 g (0.03 mole) of I_2, fuming HNO_3 was dropped in gradually, and the mixt was allowed to react until the I_2 color disappeared. After the reaction, the mixt was poured over large quantity of H_2O, and the separated product was collected by filtration and recrystd from MeOH.

5-Chloro-6-methyl-1-phenyluracil (44). **6** (6.1 g) was added to 80 ml of Ac_2O, 2.6 ml of concd HCl and 11 ml of 10% NaClO soln were added successively and the mixt was allowed to react for 3 hr at below 60°. It was poured over ice H_2O, allowed to stand overnight and filtered, and the resulting mass was recrystd from AcOH to give 1.5 g (21.2%) of needles, mp >300°. No mmp depression with **44** obtd by method A.

5-Chloro-6-methyl-3-phenyluracil (45). **13** (6.1 g) was added to 80 ml of Ac_2O and the mixt was treated in the above chlorination. Recrystn from MeOH gave 1.8 g (25.3%) of a powder, mp 257°, no mmp depression with **45** obtd by method A.

5-Bromo-1,3,6-trimethyluracil (50). 1,3,6-Trimethyluracil (**18**) (4.2 g) in 80 ml of $CHCl_3$ was heated to reflux for 5 hr with 5.3 g of NBS. The soln was filtered, the resulting mother liquor was washed (H_2O) and evapd, and the residue was recrystd from H_2O to give 1.9 g (30.0%) of needles, mp 139°, no mmp depression with **50** obtd by method B.

5-Bromo-3-(2-ethoxycarbonylethyl)-6-methyl-1-phenyluracil (81). A mixt of 15 g of **65**, 10 g of ethyl acrylate, 50 ml of pyridine, and 50 ml of H_2O was heated to reflux for 5 hr and the reaction product was recrystd from MeOH to give 1.3 g (6.8%) of prisms, mp 173°; no mmp depression with **81** obtd by method C.

1,3-Substituted 5-Amino-6-methyluracils (84–129) (Table IV). To 50 ml of DMF were added 0.1 mole of 1,3-substituted 5-bromo-6-methyluracils (**49–59, 61, 62, 71, 72, 74, 76**), or 1-substituted 5-bromo-6-methyluracils (**65, 68, 69**), then 0.3–0.5 mole of amine (*e. g.*, NH_3, 40% aq soln of Me_2NH, Et_2NH, diallylamine, *n*-Bu_2NH, 30% aq soln of $MeNH_2$, $EtNH_2$, *i*-$PrNH_2$, *n*-$BuNH_2$, *sec*-$BuNH_2$, pyrrolidine, piperidine, morpholine) was added, and the mixt was heated at 100° for 8–10 hr in a sealed tube. When the bp of the amine was comparatively high, it was not necessary to use a sealed tube. After the reaction, DMF and an excess of amine were removed *in vacuo*, H_2O was added to the residue, the mixt was filtered, and the sepd product was recrystd. Instead of DMF, other solvents such as $HCONH_2$, MeCN, and DMSO can be used.

Acknowledgments. We want to offer our cordial thanks to Dr. K. Ohata and other staff-members of Research Laboratories, Nippon Shinyaku Co., Ltd., for their cooperation in carrying out the screening test for pharmacological activities.

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