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Pyrimidine Derivatives and Related Compounds. XIX.[1] Synthesis and Analgetic and Antiinflammatory Activities of 1,3-Substituted 5-Dimethylaminouracil Derivatives

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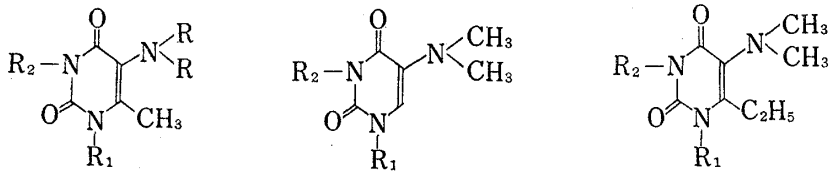
As a part of our studies on the structure-activity relationship of 1,3-disubstituted 5-dimethylamino-6-methyluracil derivatives, the authors have synthesized 1,3-disubstituted 5-dimethylaminouracils (B) and 1,3-disubstituted 5-dimethylamino-6-ethyluracils (C) and investigated their pharmacological activity. In the synthesis, 1,3-disubstituted uracils (**7**, **10**—**13**) were made to react with bromine and the resulting 5-bromouracils (**14**—**18**) were heated with dimethylamine in DMF to give compounds (B). Ethyl 3-oxovalerate was condensed with phenylurea to afford 6-ethyl-3-phenyluracil (**25**); 3-position of it was alkylated and 5-position was brominated and further dimethylaminated to give compounds (C). In the pharmacological tests, compound (C) showed nearly same analgetic action as that of compounds (A) while compounds (B) scarcely showed such an action. Both (B) and (C) did not exhibit antipyretic action.

In our previous paper,[3] we have synthesized a series of 1,3-disubstituted 5-dialkylamino-6-methyluracil derivatives (A) which are, in chemical structure, derived by expanding of a pyrazolone ring of aminopyrine to a 6-menbered ring, investigated the relation between their chemical structures and pharmacological actions, and found some of them showed activities as same as that of aminopyrine.

In the present study, we have synthesized 1,3-disubstituted 5-dimethylaminouracils (B) and 1,3-disubstituted 5-dimethylamino-6-ethyluracils (C) and investigated the influence of substituents on pharmacological activities. The compounds (B) are 6-demethylated derivatives of A, and the compounds (C) are derivatives of A, 6-methyl group of which is replaced with an ethyl group.



A B C

Chart 1

As to a method for synthesizing 1-phenyluracil (**10**) which is one of starting materials for 1,3-disubstituted 5-dimethylaminouracils (B), a hydrolysis-decarboxylation of 5-cyano-1-phenyluracil has been already reported by us.[4] We have attempted to find another method since the above method consists of many steps.

At first, we brominated 1-phenyl-5,6-dihydrouracil (**1**),[5] dehydrobrominated by heating the resulting 5,5-dibromo-1-phenyl-5,6-dihydrouracil (**2'**) in DMF and thought that the product

1) Part XVIII: S. Senda, K. Hirota, and K. Maeno, *Chem. Pharm. Bull.* (Tokyo), **21**, 1894 (1973).
2) Location: *492-36, Mitahora, Gifu.*
3) S. Senda, K. Hirota, and K. Banno, *J. Med. Chem.*, **15**, 471 (1972).
4) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1389 (1972).
5) N.W. Gabel and S.B. Binkley, *J. Org. Chem.*, **23**, 643 (1958).

was 5-bromo-1-phenyluracil (**3'**). It seemed, however, to be incorrect and the resulting product was presumed to be 1-(*p*-bromophenyl)uracil (**3**) because the product was not identical with **3'** prepared by bromination of 1-phenyluracil and showed an absorption of 5-proton at 5.7 ppm of the nuclear magnetic resonance (NMR) spectrum which meant the bromine atom was not at 5-position.

The monobromo compound was synthesized by another route in order to comfirm the position of the bromine atom. Thus, α-cyano-β-ethoxy-N-ethoxycarbonylacrylamide (**4**) was condensed with *p*-bromoaniline, the resulting β-(*p*-bromoanilino)-α-cyano-N-ethoxycarbonylacrylamide (**5**) was subjected to a ring closure by heating, and the resulting 1-(*p*-bromophenyl)-5-cyanouracil (**6**) was hydrolyzed and decarboxylated in 48% HBr to prepared **3** which was found to be identical with the monobromo compound obtained above. From the result, it was obvious that the dibromo compound obtained above was not 5,5-dibromo-1-phenyl-5,6-dihydrouracil (**2'**) but was 5-bromo-1-(*p*-bromophenyl)-5,6-dihydrouracil (**2**).

3 was then methylated with dimethyl sulfate and 1-(*p*-bromophenyl)-3-methyluracil (**7**) was obtained. Since a bromine atom was substituted in a phenyl group at 1-position of the uracil, the desired 1-phenyluracil derivatives could not be prepared by the above method.

Another method was therefore attempted. Thus 3-methyl-1-phenylbarbituric acid (**8**)[6] was refluxed in phosphorus oxychloride and the resulting 6-chloro-3-methyl-1-phenyl-

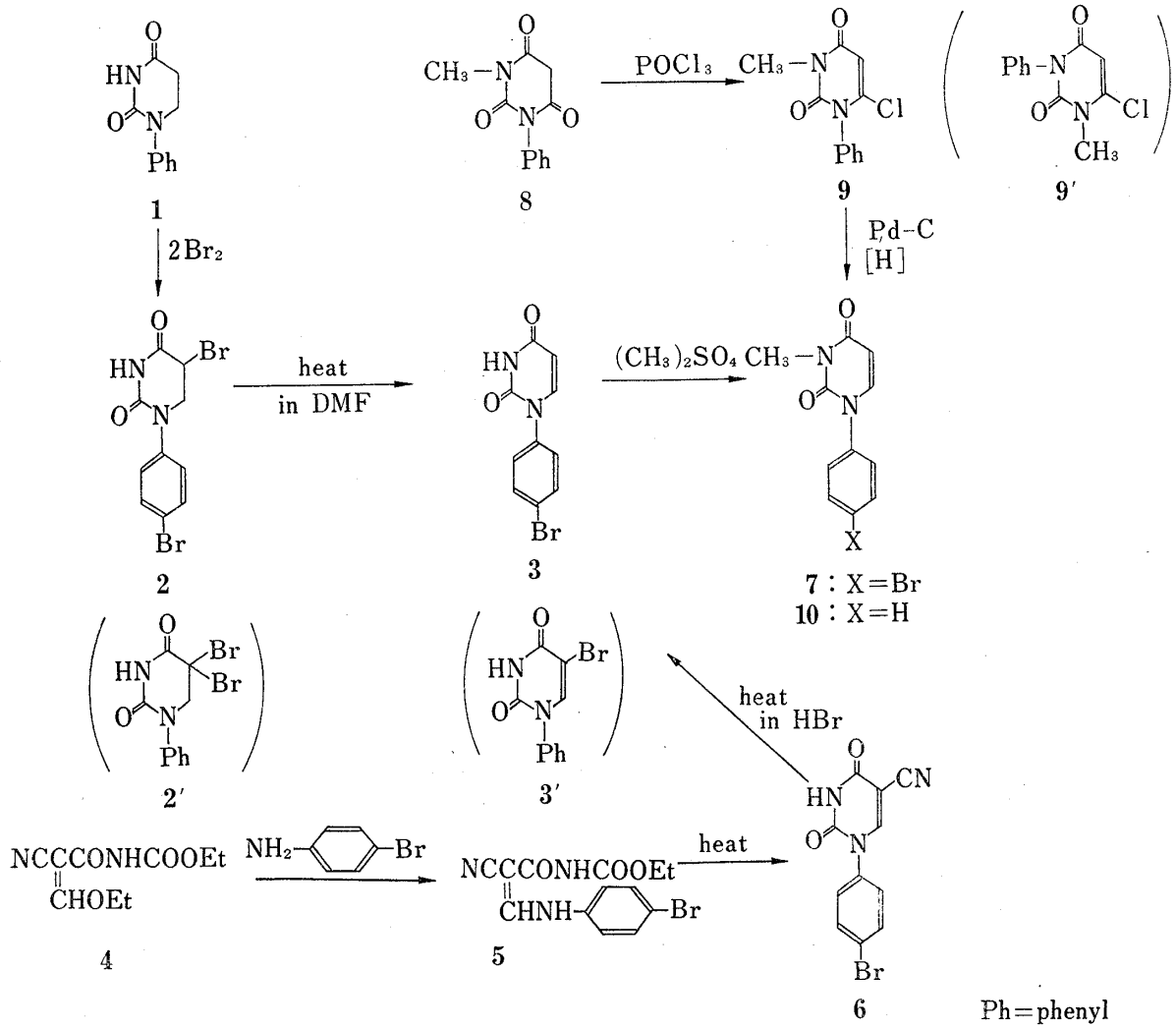


Chart 2

6) B. Hepner and S. Frenkenberg, *Chem. Ber.*, **65B**, 123 (1932).

uracil (**9**) [or 6-chloro-1-methyl-3-phenyluracil (**9'**)] was reduced with hydrogen in the presence of palladium-carbon whereupon dechlorination took place to give N-methyl-N'-phenyluracil in 81% yield. Since this compound was confirmed to be identical with 3-methyl-1-phenyluracil (**10**),[4] it was obvious that the main product upon heating of **8** with $POCl_3$ was not **9'** but **9**. Thus, a process of **8**→**9**→**10** was thought to be rational for the synthesis of 3-methyl-1-phenyluracil (**10**).

Compounds (**7**) and (**10**) obtained above and other 1,3-disubstituted uracils[4] [1-cyclohexyl-3-methyl (**11**); 1-methyl-3-phenyl (**12**); 1-methyl-3-cyclohexyl (**13**)] were treated with bromine in acetic acid to give 1,3-disubstituted 5-bromouracils (**14**—**18**) (Table I). The compound (**18**) was also prepared by methylating 5-bromo-1-cyclohexyluracil (**19**)[7] with dimethyl sulfate. The 1,3-disubstituted 5-bromouracils (**14**—**18**) were then condensed with dimethylamine to give 1,3-disubstituted 5-dimethylaminouracils (B) (**20**—**23**) (Table II).

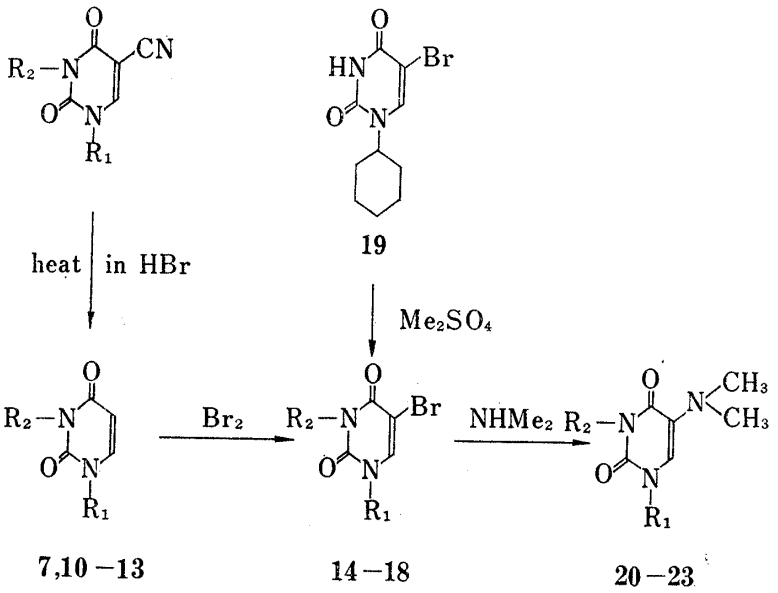


Chart 3

Synthesis of 1,3-disubstituted 5-dimethylamino-6-ethyluracils (C) was then attempted. Thus, ethyl propionylacetate was condensed with phenylurea in DMF–acetic anhydride, the resulting intermediate (**24**) was hydrolyzed in a solution of sodium hydroxide, and the reaction mixture was neutralized with HCl to give 6-ethyl-3-phenyluracil (**25**). The compound **25** was treated with dimethyl sulfate and the resulting 6-ethyl-1-methyl-3-phenyluracil (**26**) was brominated to give 5-bromo-6-ethyl-1-methyl-3-phenyluracil (**27**). The compound (**27**) was also prepared by methylating 5-bromo-6-ethyl-1-phenyluracil (**28**) which was yielded by bromination of **25**.

Refluxing of **28** with allyl bromide in ethanol in the presence of potassium carbonate gave 1-allyl-5-bromo-6-ethyl-1-phenyluracil (**29**). Treatment of **27** and **29** with dimethylamine gave desired 1,3-disubstituted 5-dimethylamino-6-ethyluracils (C) (**30** and **31**).

Pharmacology

As to pharmacological activities of compounds (B) and (C), acute toxicity [LD_{50} in mice (*i.p.*)], analgetic activity [Haffner's method with a threshold dose of morphine in mice (*i.p.*)][8] and antiinflammatory activity [rat hind paw edema induced by carrageenin (*p.o.*)][9] were tested (Table I).

7) T. Okano, S. Goya, and T. Takahashi, *Yakugaku Zasshi*, **88**, 1112 (1968).
8) H. Fujimura and K. Nakajima, *Bull. Inst. Chem. Res.* (Kyoto Univ.), **25**, 36 (1951).
9) C.A. Winter and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

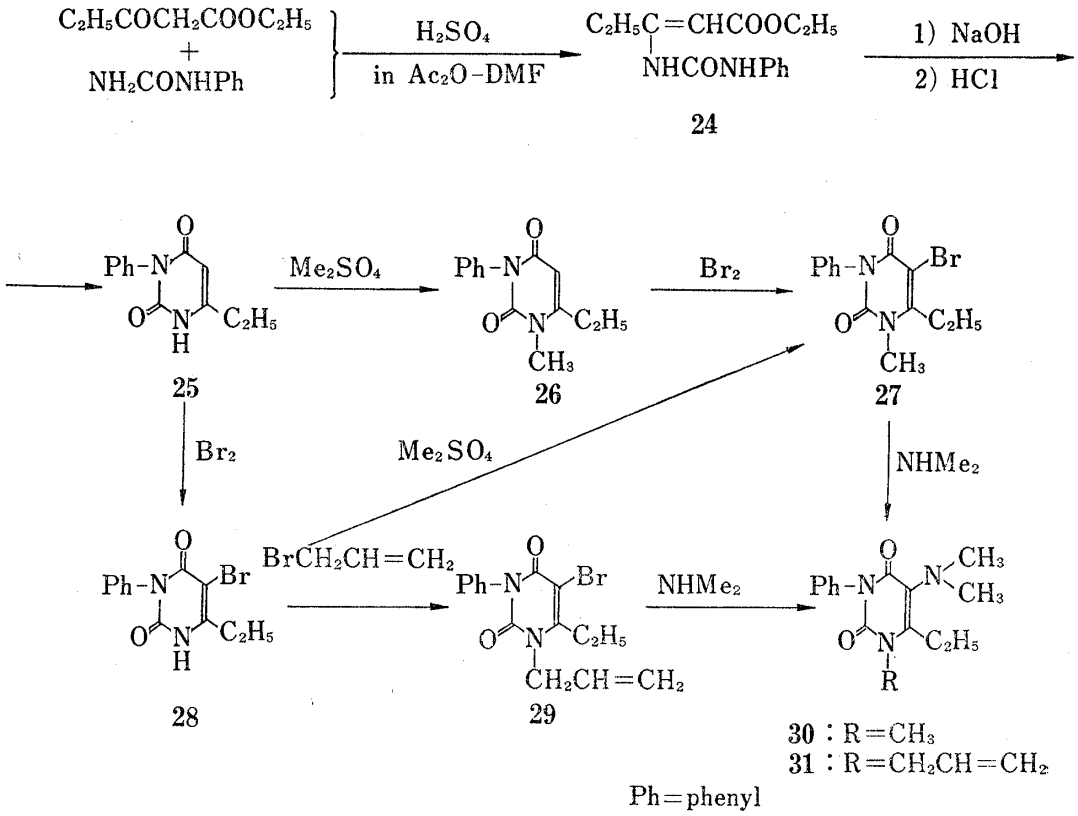
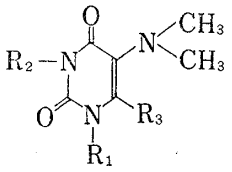


Chart 4

TABLE I. Acute Toxicity and Analgetic and Antiinflammatory Activities of 1,3,6-Substituted 5-Dimethylaminouracils



Group	Compd. No.	R_1	R_2	R_3	Acute toxicity[a] [LD_{50}] mg/kg	Analgetic activity[b] [ED_{50}] mg/kg	Antiinflammatory[c] 200 mg/kg (%)
B	**20**	*p*-BrC_6H_4	CH_3	H	375	—[d]	25
	21	C_6H_5	CH_3	H	540	—[d]	63
	22	CH_3	C_6H_5	H	1620	—[d]	26
	23	CH_3		H	442	—[d]	46
C	**30**	CH_3	C_6H_5	C_2H_5	844	100 (64—156)	50
	31	$CH_2CH=CH_2$	C_6H_5	C_2H_5	844	50 (23—110)	56
A	**32**[e]	$CH_2CH=CH_2$	C_6H_5	CH_3	644	42 (29— 51)	73
	aminopyrine				259	150 (112—201)	65(100mg)
	phenylbutazone				419	122 (68—220)	45(50mg)

a) in male mice (*i.p.*)
b) modified Haffner's method (Haffner's method with a threshold dose of morphine in male mice), (*i.p.*)[8]
c) carrageenin method (inhibitory effect (%) on the rat hind edema induced by carrageenin), (*p.o.*)[9]
d) This compound didn't exhibit analgetic activity (200 mg/kg).
e) The data of this compound were produced from lit[8].

As a result, 1,3-disubstituted 5-dimethylamino-6-ethyluracils (C) exhibited analgetic activity as same as those of compounds (A), while 1,3-disubstituted 5-dimethylaminouracils (B) scarcely showed analgetic activity. Yoshimura, *et al.*[10] studied the metabolism of aminopyrine *in vivo* and indicated that the methyl group at 3-position of the pyrazolone ring was oxidized to a hydroxymethyl group. From the facts discribed above, it seems that 6-methyl group of the uracil derivatives which corresponds to 3-methyl group of aminopyrine is related to the metabolism mechanism and plays a great role in appearance of an aminopyrine-like analgetic activity.

Compounds (B) and (C) scarcely showed antipyretic action while many of compounds (A) showed such an action. As to antiinflammatory activity, 1-phenyl compound (**21**) in group B and compounds (**30**) and (**31**) in group C exhibited the same activity as that of aminopyrine.

Experimental

5-Bromo-1-(*p*-bromophenyl)-5,6-dihydrouracil (2)——To a mixture of 47.5 g (0.25 mole) of 1-phenyl-5,6-dihydrouracil (1)[5] and 42.5 g of sodium acetate was added 300 ml of acetic acid. The mixture was refluxed with stirring while 80 g (0.5 mole) of bromine dissolved in 100 ml of acetic acid was added dropwise thereto. After a few minutes, the reaction solution was decolorized and evaporated *in vacuo*, then water was added to the residue. The precipitated product was filtered off and recrystallized from MeOH to give 54 g (62%) of colorless needles, mp 230°. *Anal.* Calcd. for $C_{10}H_8O_2N_2Br_2$: C, 34.51; H, 2.32; N, 8.05. Found: C, 34.66; H. 2.48; N, 8.05.

1-(*p*-Bromophenyl)uracil (3)——a) A solution of 52.2 g (0.15 mole) of 2 in 300 ml of DMF was refluxed for 2 hr. The reaction solution was distilled *in vacuo* and water was added to the residue. The precipitate was filtered off, washed with H_2O, and recrystallized from EtOH to give 31.2 g (78%) of colorless leaflets, mp 275—276°. *Anal.* Calcd. for $C_{10}H_7O_2N_2Br$: C, 44.97; H, 2.64; N, 10.49. Found: C, 45.20; H, 2.90; N, 10.38. NMR ($CDCl_3$) δ: 5.70 (1H, dd, J=7.5, 1.3 Hz, C_5-H), 7.42 and 7.74 (each 2H, each d, J=8.5 Hz, aromatic protons), 11.47 (1H, br, NH).

b) To 30 ml of 48% HBr was added 2.9 g (0.01 mole) of **6** and the mixture was refluxed for 10 hr. After the reaction, the precipitated product was filtered off, washed with H_2O, and recrystallized from EtOH to afford 2.5 g (93%) of 3, mp 277—278°. It was confirmed by infrared (IR) comparison to be identical with the compound (3) obtained above.

5-Bromo-1-phenyluracil (3′)——In 100 ml AcOH was dissolved 9.4 g (0.05 mole) of 1-phenyluracil[4] and 3.8 g of Br_2 was gradually added with stirring. Water was added thereto, and the resulting product was filtered, washed with H_2O, and recrystallized from MeOH to give 4.9 g (91%) of colorless crystals, mp 285°. *Anal.* Calcd. for $C_{10}H_7O_2N_2Br$: C, 44.95; H, 2.64; N, 10.48. Found: C, 45.07; H, 2.64; N, 10.48.

β-(*p*-Bromoanilino)-α-cyano-N-ethoxycarbonylacrylamide (5)——To 50 ml of EtOH were added 10.6 g. (0.05 mole) of α-cyano-β-ethoxy-N-ethoxycarbonylacrylamide (4)[11] and 8.6 g (0.05 mole) of *p*-bromoaniline. The mixture was stirred for 10 minutes at room temperature. The crude product was filtered off, washed with H_2O, and recrystallized from EtOH to give 15.5 g (91%) of colorless leaflets, mp 184—185°. *Anal.* Calcd. for $C_{13}H_{12}O_3N_3Br$: C, 46.17; H, 3.58; N, 12.43. Found: C, 46.16; H, 3.62; N, 12.46.

1-(*p*-Bromophenyl)-5-cyanouracil (6)——To 15 ml of tetralin was added 3.4 g of 5. The mixture was refluxed for 30 minutes, cooled on standing, and filtered off. The separated product was washed with ether and recrystallized from EtOH to give 2.8 g (96%) of colorless crystals, mp 265°. *Anal.* Calcd. for $C_{11}H_6O_2N_3Br$: C, 45.23; H, 2.07; N, 14.39. Found: C, 45.02; H, 2.17; N, 14.14.

1-(*p*-Bromophenyl)-3-methyluracil (7)——Into 400 ml of 1% NaOH aq. solution was dissolved 22.3 g (0.084 mole) of 3, 12.4 g of dimethyl sulfate was dropped there into with stirring. The precipitated product was filtered off, washed with H_2O, and recrystallized from MeOH to give 18 g (76%) of colorless needles, mp 189°. NMR ($CDCl_3$) δ: 3.38 (3H, s, N-CH_3), 5.88 (1H, d, J=7.9 Hz, C_5-H), 7.26 (1H, d, J=7.9 Hz, C_6-H), 7.22 and 7.63 (each 2H, each d, J=9.0 Hz, aromatic protons). *Anal.* Calcd. for $C_{11}H_9O_2N_2Br$: C, 47.00; H, 3.23; N, 9.97. Found: C, 47.22; H, 3.46; N, 9.89.

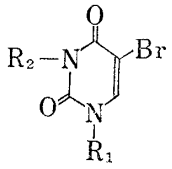
6-Chloro-3-methyl-1-phenyluracil (9)——To a mixture of 50 g (0.23 mole) of 1-Methyl-3-phenylbarbituric acid (8)[3] and 400 ml of $POCl_3$ was added 10 ml of H_2O. The mixture was refluxed for 1 hr, concentrated *in vacuo* to remove excess $POCl_3$, and the residue was poured over ice in a beaker. The precipitate was filtered off and washed with H_2O, EtOH, and ether to give 51 g of crude product. Recrystallization from EtOH gave yellow crystals, mp 273—275°. *Anal.* Calcd. for $C_{11}H_9O_2N_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.91; H, 3.93; N, 11.65.

10) H. Yoshimura, H. Shimeno, and H. Tsukamoto. *Yakugaku Zasshi*, **90**, 1405 (1970).
11) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1380 (1972).

3-Methyl-1-phenyluracil (10)——A mixture of 4.7 g of **9**, 400 ml of DMF, and 1.0 g of Pd-C was placed in an autoclave, stirred in the presence of hydrogen (10 atm) at room temperature for 5 hr. After the reaction, DMF was evaporated *in vacuo*, water was added to the residue. The precipitate was filtered off and recrystallized from ligroin to give 3.3 g (81%) of colorless needles, mp 133°. It was confirmed by IR comparison to be identical with an authentic sample of compound (**10**).[4]

1,3-Disubstituted 5-Bromouracils (14—18) (Table II)——In 100 ml of AcOH was dissolved 0.1 mole of 1,3-disubstituted uracil (**7**, **10**—**13**[4]), and 16 g of Br_2 was gradually added with stirring. Water was added thereto, and the resulting product was filtered, washed with H_2O, and recrystallized.

Table II. 1,3-Disubstituted 5-Bromouracils

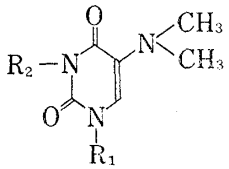


Compd. No.	R_1	R_2	mp (°C)	Recryst. solv.	Yield (%)	Formula		Analysis (%) C	H	N
14	*p*-BrC_6H_4	CH_3	217—218	EtOH	82	$C_{11}H_8O_2N_2Br_2$	Calcd.	36.70	2.24	7.78
							Found	36.88	2.36	7.87
15	C_6H_5	CH_3	204	MeOH	90	$C_{11}H_9O_2N_2Br$	Calcd.	47.00	3.59	9.97
							Found	47.24	3.58	9.73
16		CH_3	128—129	MeOH–H_2O	94	$C_{11}H_{15}O_2N_2Br$	Calcd.	46.01	5.27	9.76
							Found	45.83	5.17	9.60
17	CH_3	C_6H_5	244	MeOH	90	$C_{11}H_9O_2N_2Br$	Calcd.	47.00	3.59	9.97
							Found	47.04	3.60	10.05
18	CH_3		153—154	MeOH–H_2O	98	$C_{11}H_{15}O_2N_2Br$	Calcd.	46.01	5.27	9.76
							Found	46.19	5.32	9.52

5-Bromo-1-cyclohexyl-3-methyluracil (16)——In 130 ml of 5% aq. solution of NaOH was dissolved 40 g (0.15 mole) of 5-bromo-1-cyclohexyluracil (**19**),[7] and 20.2 g (0.16 mole) of dimethyl sulfate was added dropwise with stirring. After the reaction, the separate was filtered off and washed with H_2O to give 40 g of crude product. Recrystallization from MeOH–H_2O gave colorless leaflets of mp 128°. It was confirmed by IR comparison to be identical with the compound **16** obtained above.

1,3-Disubstituted 5-Dimethylaminouracils (20—23) (Table III)——To 30 ml of DMF were added 0.05 mole of 1,3-disubstituted 5-bromouracil (**14**, **15**, **17**, **18**) and 20 ml of 40% aq. solution of dimethylamine,

Table III. 1,3-Disubstituted 5-Dimethylaminouracils



Compd. No.	R_1	R_2	mp (°C)	Recryst. solv.	Yield (%)	Formula		Analysis (%) C	N	H
20	*p*-BrC_6H_4	CH_3	157—158	AcOEt	78	$C_{13}H_{14}O_2N_3Br$	Calcd.	48.17	4.36	12.96
							Found	48.37	4.48	12.75
21	C_6H_5	CH_3	125	ligroin	53	$C_{13}H_{15}O_2N_3$	Calcd.	63.66	6.16	17.13
							Found	63.92	6.37	17.13
22	CH_3	C_6H_5	197	MeOH	86	$C_{13}H_{15}O_2N_3$	Calcd.	63.66	6.16	17.13
							Found	63.25	6.03	17.20
23	CH_3		154	ligroin	93	$C_{13}H_{21}O_2N_3$	Calcd.	62.12	8.42	16.72
							Found	62.07	8.32	16.92

and the mixture was heated at 100° for 8 hr in a sealed tube. After the reaction, DMF was removed *in vacuo*, water was added to the residue. The resulting product was filtered off, washed with H_2O, and recrystallized.

6-Ethyl-3-phenyluracil (25)——To a mixture of 21.6 g (0.15 mole) of ethyl 3-oxovalerate,[12] 25 ml of DMF, 20 ml of Ac_2O, and 0.2 ml of conc. H_2SO_4 was added 13.6 g (0.1 mole) of phenylurea. The mixture was stirred until the phenylurea was in solution, allowed to stand at room temperature for 4 days, and then dissolved in 400 ml of 15% aq. solution of NaOH at 60° with stirring. The reaction solution was allowed to stand overnight at room temperature and acidified with conc. HCl. The precipitate was filtered off to give 20.2 g (95%) of crude product. Recrystallization from MeOH gave colorless needles of **25**, mp 212.° *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.45; H, 5.50; N, 12.60.

6-Ethyl-1-methyl-3-phenyluracil (26)——In 90 ml of 5% aq. solution of NaOH was dissolved 20.2 g of **25**, 12.3 g of dimethyl sulfate was added thereinto, and the mixture was stirred for 1 hr. When the reaction solution became neutral, the precipitate was filtered, and washed with H_2O to give 14.2 g (65%) of crude product. Recrystallization from MeOH gave colorless needles of **26**, mp 148°. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.65; H, 6.03; N, 12.45.

5-Bromo-6-ethyl-1-methyl-3-phenyluracil (27)——a) In 50 ml of AcOH was dissolved 11.5 g (0.05 mole) of **26**, and 8 g of Br_2 was gradually dropped with stirring. Water was added thereto and the resulting product was filtered off to give 13.4 g (87%) of crude crystals. Recrystallization from MeOH gave colorless needles of **27**, mp 174°. *Anal.* Calcd. for $C_{13}H_{13}O_2N_2Br$: C, 50.50; H, 4.24; N, 9.07. Found: C, 50.39; H, 4.22; N, 9.23.

b) In 10 ml of 5% aq. solution of NaOH was dissolved 1.5 g of **28**, and 0.9 g of dimethyl sulfate was treated as discribed in the preparation of **26**. Recrystallization from MeOH gave 0.9 g (56%) of mp 173°. It was confirmed by IR comparison to be identical with the compound (**27**) obtained above.

5-Bromo-6-ethyl-3-phenyluracil (28)——In 300 ml of AcOH was dissolved 49.5 g (0.23 mole) of **25**, and 27 g of Br_2 was treated as discribed in the preparation (a) of **27** to give 51.8 g (76%) of crude product. Recrystallization from MeOH gave colorless prisms of mp 227°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2Br$: C, 48.83; H, 3.76; N, 9.50. Found: C, 48.88; H, 3.81; N, 9.49.

1-Allyl-5-bromo-6-ethyl-3-phenyluracil (29)——In 480 ml of abs. EtOH were suspended 40 g (0.12 mole) of **28** and 25.2 g of K_2CO_3, 36.1 g of allyl bromide was added thereto. The mixture was refluxed with stirring for 10 hr. After the reaction, the precipitate was removed by filtration, the filtrate was evaporated *in vacuo*, and a small amount of ether was added to the residue. The crude product was filtered to give 37.5 g (93%) of mp 105—108°. Recrystallization from petroleum benzin gave colorless crystals of mp 114°. *Anal.* Calcd. for $C_{15}H_{15}O_2N_2Br$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.78; H, 4.63; N, 8.42.

5-Dimethylamino-6-ethyl-1-methyl-3-phenyluracil (30)——To 6.2 g (0.02 mole) of **27** were added 8.1 ml of 40% aq. solution of dimethylamine and 10 ml of DMF, and the mixture was treated as descrived in the preparation **20**—**23**. The crude product was recrystallized from ligroin to give 3.4 g (62%) of colorless prisms mp 127—128°. *Anal.* Calcd. for $C_{15}H_{19}O_2N_3$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.98; H, 6.98; N, 15.52.

1-Allyl-5-dimethylamino-6-ethyl-3-phenyluracil (31)——To 3.35 g (0.01 mole) of **29** were added 6 ml of 40% aq. solution of dimethylamine and 5 ml of DMF, and the mixture was treated as discribed in the preparation of **20**—**23**. The crude product was recrystallized from ligroin to give 2.4 g (83%) of colorless prisms, mp 132°. *Anal.* Calcd. for $C_{17}H_{21}O_2N_3$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.13; H, 6.91; N, 14.17.

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