[Chem. Pharm. Bull. 22(5)1179—1185(1974)]

UDC 547.854.4.04.09 : 615.276.011.5.015.11

Pyrimidine Derivatives and Related Compounds. XX.[1] Synthesis and Analgetic and Antiinflammatory Activities of 1,3-Disubstituted 5-Dialkylaminomethyluracil Derivatives

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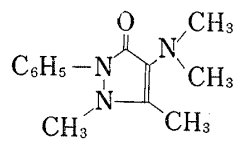
(Received September 17, 1973)

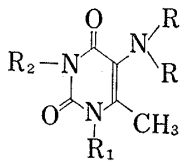
As a part of our studies on the structure-activity relationship of 1,3-disubstituted 5-dialkylamino-6-methyluracil derivatives, we have synthesized 1,3-disubstituted 5-dialkylaminomethyl-6-methyluracils (B). In the synthesis, 1,3-disubstituted 5-cyanouracils (**1**—**6**) were hydrogenated with Raney-cobalt followed by methylation to give the 5-dimethylaminomethyluracil compounds (**16**—**20**). The Mannich reaction of 1,3-disubstituted uracils (**23**—**26**, **33**) did not proceed, but halogenomethylation of them and subsequent amination gave the 5-dialkylaminomethyl compounds (**20**, **34**—**41**).

As to their pharmacological activities, analgetic, antipyretic and antiinflammatory activities and acute toxicity were tested. The compounds (B) showed only antiinflammatory activity.

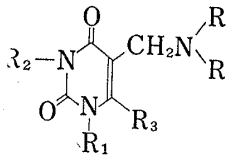
In our previous paper[1,3] was reported the synthesis of a series of 1,3-disubstituted 5-dialkylamino-6-methyluracils (A) which have chemical structures resembling that of aminopyrine (5-membered ring). Of those compounds, several ones, for example 1-alkyl-5-dimethylamino-6-methyl-3-phenyluracil and 3-alkyl-5-dimethylamino-6-methyl-1-phenyluracil, showed pharmacological activities equivalent or superior to those of aminopyrine. In the present paper, we have investigated the synthesis of 1,3-disubstituted 5-dialkylaminomethyl-6-methyluracil derivatives (B) in which a methylene group was inserted between the uracil ring and the dialkylamino group on the position 5, and the relationship between the chemical structure and pharmacological actions.



aminopyrine



A



B

Chart 1

For the synthesis of the 5-dialkylaminomethyluracil derivatives, reduction of 5-cyanouracil derivatives and then alkylation of the resulting 5-aminomethyl compounds were carried out.[4] Thus, among 1,3,6-substituted 5-cyanouracil derivatives [substituents: 1-cyclohexyl, 3-Me, 6-H (**1**); 1-Ph, 3-Me, 6-H (**2**); 1-Me, 3-cyclohexyl, 6-H (**3**); 1-Me, 3-Ph, 6-H (**4**); 1-cyclohexyl, 3-Me, 6-Me (**5**); 1-Ph, 3-Me, 6-Me (**6**)],[5] compounds **1** and **2** were hydrogenated catalytically in ethanolic ammonia at 60 atm and 100° with Raney nickel to give 1-cyclohexyl-3-methyl-

1) Part XIX: S. Senda, K. Hirota, and T. Asao, *Chem. Pharm. Bull.* (Tokyo), **22**, 189 (1974).
2) Location: *492-36, Mitahora, Gifu.*
3) S. Senda, K. Hirota, and K. Banno, *J. Med. Chem.*, **15**, 471 (1972).
4) S. Yamada and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **9**, 119 (1961).
5) S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1380 (1972).

5,6-dihydrothymine (**7**) and 3-methyl-1-phenyl-5,6-dihydrothymine (**8**) respectively instead of the desired 5-aminomethyluracil derivatives. These compounds (**7, 8**) showed no ultraviolet (UV) absorption characteristic of the uracil derivatives. The above structures were inferred by the fact that its nuclear magnetic resonance (NMR) spectrum shows a 3H doublet at 1.36 ppm ascribed to the 5-methyl group, a 1H multiplet at 2.70—3.08 ppm assigned from the 5-proton, and two 1H doublets coupled with each other at 3.66 and 3.73 ppm due to two protons at 6-position.

When Raney cobalt was employed in place of Raney nickel in the catalytic hydrogenation in ethanol of **1**, there was obtained 5-aminomethyl-1-cyclohexyl-3-methyluracil (**9**) in 20% yield with a by-product of the bis(5-pyrimidylmethyl)amine (**10**) in 31% yield. Formation of this bis-compound is considered to be due to the absence of ammonia. Catalytic hydrogenation with Raney cobalt in ethanolic ammonia converted 5-cyanouracil derivatives (**1—6**) into 5-aminomethyluracil derivatives (**9, 11—15**) (Table II) in good yields. Methylation of these products with formic acid and formalin gave 5-dimethylaminomethyluracil derivatives (**16—20**) (Table III).

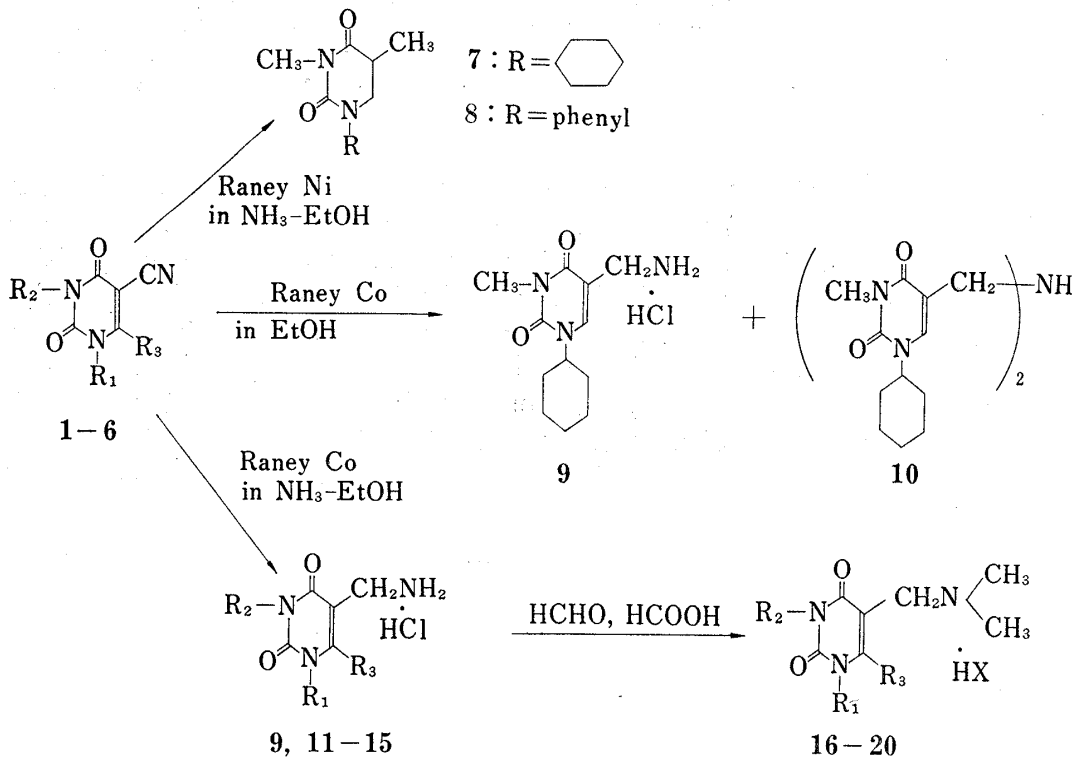


Chart 2

Meanwhile two other routes of introducing dialkylaminomethyl group onto the position 5 of uracil ring were studied by the Mannich reaction and by the halomethylation followed by amination.

The Mannich reaction of uracil derivatives has been reported[6] with those derivatives unsubstituted at 1- and 3-positions. The reaction with 1,3-disubstituted uracils did not proceed, however, and the starting materials were recovered unchanged. But 5-methyl-1-phenyluracil (**21**) with no substituent at 1-position, upon refluxing in ethanol with formalin and cyclohexylamine, gave 5-cyclohexylaminomethyl-6-methyl-3-phenyluracil (**22**) in a yield of 15%. This synthetic method, however, was concluded to inadequate for obtaining

6) J.H. Burckhalter, R.T. Seiwald, and H.C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960); M. Murakami, Y. Kawashima, N. Ito, and K. Yano, Ger. Offen, 1802922 (1969) [*Chem. Abstr.*, **71**, 61417 (1969)].

desired 5-dialkylaminomethyluracil derivatives because of a narrow applicability and low yields. For 5-halomethylation of 1,3-disubstituted uracils, four uracil derivatives [substituents: 1-Me, 3-Ph, 6-Me (**23**); 1-Ph, 3-Me, 6-Me (**24**); 1-Ph, 3-Bu, 6-Me (**25**); 1-cyclohexyl, 3-Me, 6-H (**26**)] were allowed to react with paraformaldehyde in a mixture of acetic acid and 40% HBr not to afford 5-chloromethyluracils, but bis(1,3-disubstituted 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidyl) methane (**27**—**30**) respectively (Table IV). In the case of **23**, small amounts of bis[(1,6-dimethyl-3-phenyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidyl)methyl] ether (**31**) and 1,6-dimethyl-5-hydroxymethyl-3-phenyluracil (**32**) were separated as by-products, whose structures were estimated by the NMR and infrared (IR) spectra. Formation of these compounds is probably due to too strong reaction conditions.

For preventing the formations of the bis(5-pyrimidyl)methane compounds (**27**—**30**) and the by-products **31** and **32**, the 1,3-disubstituted uracils (**23**—**26**) and 3-cyclohexyl-1,6-dimethyluracil (**33**) were heated with conc. HCl in aqueous formalin solution with passing HCl gas to give 1,3-disubstituted 5-chloromethyluracils, which upon reactions with secondary amines (dimethylamine, diethylamine, diallylamine, piperidine and morpholine) gave desired 1,3-disubstituted 5-dialkylaminomethyluracils (**20**, **34**—**41**) (Table V).

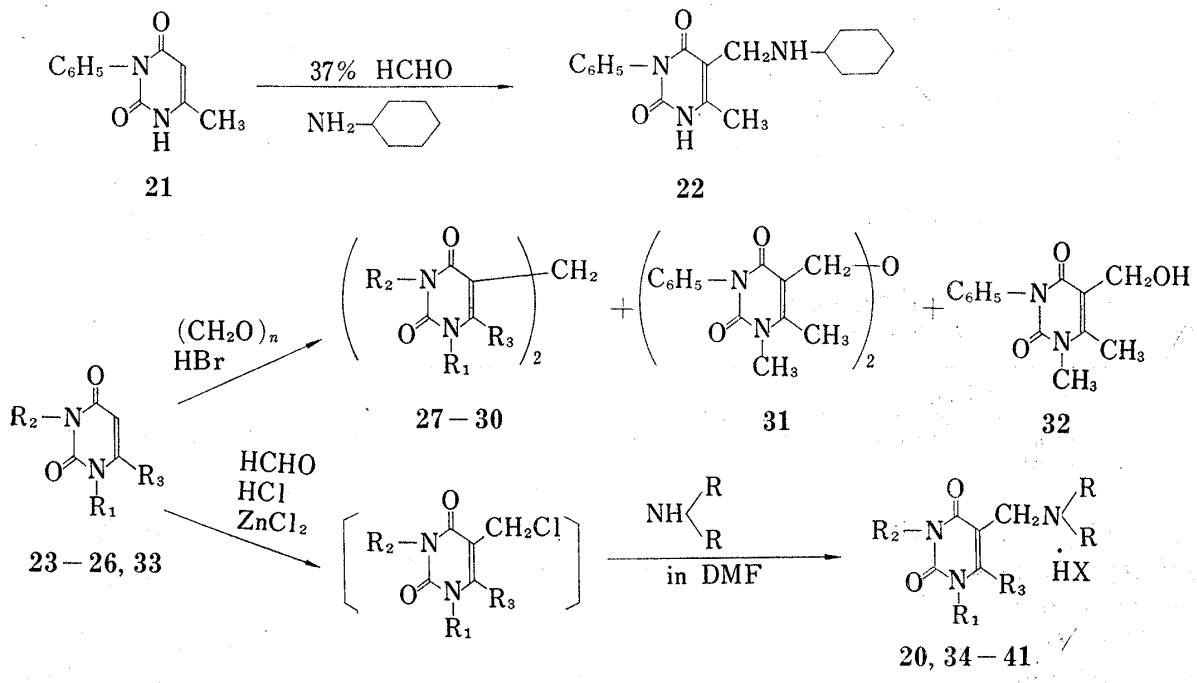


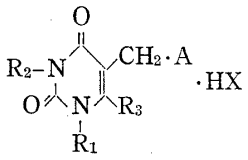
Chart 3

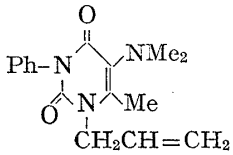
In reference to the pharmacological activities of 1,3-disubstituted 5-dialkylaminomethyluracils, analgetic activity [Haffner's method with a threshold dose of morphine in mice (*i.p.*)],[7] antipyretic activity [febrile rabbits by TTG No. 2- a pyrogen obtained from Pseudomonas fluorescens, Fujisawa Pharm. Co. (*i.p.*)],[8] antiinflammatory activity [rat kind paw edema induced by carrageenin (*p.o.*)][9] and acute toxicity [LD_{50} in mice (*i.p.*)] were tested (Table I).

In contrast to 1,3-disubstituted 5-dimethylamino-6-methyluracils (A), 1,3-disubstituted 5-dialkylaminomethyluracil derivatives (B) showed no analgetic activity at all and hardly revealed antipyretic activity except **38**. As to antiinflammatory activity, those compounds having no methyl group at 6-position on uracil ring showed higher activities than those having

7) H. Fujimura and K. Nakajima, *Bull. Inst. Chem. Res.* (Kyoto Univ.), **25**, 36 (1951).
8) Brownlee, *Quart. J. Pharm. Pharmcol.*, **10**, 609 (1937); *idem*, *ibid.*, **12**, 45 (1939).
9) C.A. Winter and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Table I. Acute Toxicity and Antipyretic and Antiinflammatory Activities of 1,3,6-Substituted 5-Dialkylaminomethyluracils



Compd. No.	R_1	R_2	R_3	A	X	Acute[a] toxicity LD_{50} (mg/kg)	Antipyretic[b] activity 50 (mg/kg)	Antiinflammatory[c] (%) 100	200 (mg/kg)
9		Me	H	NH_2	Cl	320	+0.70		41
16		Me	H	NMe_2	Cl	121	+0.40	46	
17	Ph	Me	H	NMe_2	Cl	630	+0.10		63
18	Me		H	NMe_2	Cl	237	+2.00		59
19		Me	Me	NMe_2	Cl	263	+0.57		32
20	Ph	Me	Me	NMe_2	Br	665	0.00		34
38	Ph	Me	Me		Cl	325	−4.53		48
40	Me		Me	NMe_2	Cl	273	−2.40		38
41	Me	Ph	Me	NMe_2	Cl	1380	−2.67		44
						640	−6.83	53	64
	Aminopyrine					270	−4.43	72	

a) in male mice (*i.p.*)
b) brownlee value (febrile rats by TTG No. 2, *i.p.*)[8]
c) carrageenin method, (inhibitory effect (%) on the rat paw edema induced by carrageenin in male rats, *p.o.*)[9]
Ph=phenyl

6-methyl group, that is, the 6-methyl group had the influence to reduce antiinflammatory activity. In general, the compounds of group B showed lower antiinflammatory activities than those of group A.

From the result, it seems essential to attach directly a dialkylamino group to 5-position on a uracil ring in order to keep antipyretic and analgetic activities of these uracil derivatives.

Experimental

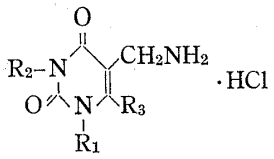
1-Cyclohexyl-3-methyl-5,6-dihydrothymine (7)——To 80 ml of EtOH saturated with ammonia were added 3 g of 5-cyano-1-cyclohexyl-3-methyluracil (1) and Raney Ni (prepared from 3 g of Al-Ni). The mixture was heated at 100° under 65 atm. of hydrogen in an autoclave with stirring for 3 hr. After the reaction, the Raney Ni was removed by filtration and the filtrate was evaporated. Petroleum ether was added to the residue and the resulting solid was filtered to give 2.2 g (73%) of a crude product, mp 50—65°. Recrystallization from ether–petroleum ether mixture gave colorless needles of mp 69—71°. *Anal.* Calcd. for $C_{12}H_{20}O_2N_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.29; H, 9.16; N, 12.57.

3-Methyl-1-phenyl-5,6-dihydrothymine (8)——To 80 ml of EtOH saturated with ammonia were added 3 g of 5-cyano-3-methyl-1-phenyluracil (2) and Raney Ni (prepared from 3 g of Al-Ni). The mixture was treated as described above to afford 1.5 g (49%) of a crude product, mp 65—68°. Recrystallization from petroleum ether gave colorless needles of mp 72—73°. *Anal.* Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.06; H, 6.69; N, 12.80. UV λ_{max}^{EtOH} 238 mμ. NMR ($CDCl_3$) δ: 1.36 (3H, d, J=7 Hz, 5-CH_3), 2.70—3.08 (1H, m, C_5-H), 3.27 (3H, s, N_3-CH_3), 3.66 and 3.73 (each 1H, each d, J=9.5 Hz and 6.5 Hz, C_6-H_2), 7.20—7.43 (5H, m, N_1-C_6H_5).

Reduction of 5-Cyano-1-cyclohexyl-3-methyluracil (1) with Raney-Co——To 100 ml of EtOH were added 6 g of 5-cyano-1-cyclohexyl-3-methyluracil (**1**) and Raney-Co (prepared from 3 g of Al-Co). The mixture was heated at 80° under 50 atm of hydrogen in an autoclave with stirring for 6 hr. The mixture was filtered and the filtrate was evaporated. The residue was dissolved into 30 ml of benzene and then 70 ml of petroleum ether was added thereto. The resulting precipitate was filtered and washed with ether to give 2.0 g (31%) of crude bis(1-cyclohexyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidylmethyl)amine (**10**). Recrystallization from EtOH afforded colorless prisms of mp 234—235°. *Anal.* Calcd. for $C_{24}H_{35}O_4N_5$: C, 63.00; H, 7.71; N, 15.31. Found: C, 63.18; H, 7.85; N, 15.42. The filtrate in the above procedure was evaporated, the residue was dissolved in 20 ml of acetone, and a few drops of conc. HCl were added thereto. The precipitate was filtered to give 1.3 g (20%) of crude 5-aminomethyl-1-cyclohexyl-3-methyluracil hydrochloride (**9**). Recrystallization from EtOH gave colorless needles of mp 285°. It was confirmed by IR to be identical with the compound **9** obtained below.

1,3,6-Substituted 5-Aminomethyluracils Hydrochloride (9,11—15) (Table II)——To 80 ml of EtOH saturated with ammonia were added 6 g of 1,3,6-substituted 5-cyanouracil (**1—6**)[5] and Raney-Co (prepared from 5 g of Al-Co). The mixture was stirred at 80° under 50 atm of hydrogen in an autoclave for 8 hr. After the reaction, the Raney-Co was removed by filtration and the filtrate was evaporated. The residue was dissolved into acetone. Upon addition of conc. HCl, the hydrochloride salt was filtered off and recrystallized.

Table II. 1,3,6-Substituted 5-Aminomethyluracils Hydrochloride



Compd. No.	R_1	R_2	R_3	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
9		Me	H	285	needles (EtOH)	95	$C_{12}H_{19}O_2N_3 \cdot HCl$	52.76 (52.88	7.35 7.49	15.38 15.19)
11	Ph	Me	H	297	needles (EtOH)	80	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.84 (54.00	5.28 5.47	15.70 15.50)
12	Me		H	226	needles ($CHCl_3$)	77	$C_{12}H_{19}O_2N_3 \cdot HCl$	52.76 (52.26	7.35 7.49	15.38 15.10)
13	Me	Ph	H	275	needles (MeOH–MeCN)	83	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.84 (53.25	5.28 5.64	15.70 15.36)
14		Me	Me	270	needles (MeOH–MeCN)	83	$C_{13}H_{21}O_2N_3 \cdot HCl$	54.36 (54.62	7.72 7.80	14.63 14.63)
15	Ph	Me	Me	269	plates (MeOH–MeCN)	82	$C_{13}H_{15}O_2N_3 \cdot HCl$	55.50 (55.16	5.73 6.09	14.94 14.85)

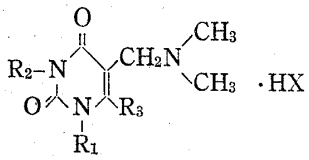
a) All compounds are colorless crystals.
Ph=phenyl

1,3,6-Substituted 5-Dimethylaminomethyluracils Hydrochloride (16—20) (Table III)——Into 50—100 ml of H_2O was dissolved 0.1 mole of 1,3,6-substituted 5-aminomethyluracil hydrochloride (**9**, **11**, **12**, **14** or **15**), and the solution was neutralized with 60 ml of 10% aq. solution of Na_2CO_3. 50 ml of 90% HCOOH and 40 ml of 37% formalin were added thereto, and upon standing for 1 hr, the mixture was heated at 80° for 3 hr. After the reaction, the mixture was concentrated *in vacuo*, 100 ml of acetone was added to the residue, and the insoluble paraformaldehyde was removed by filtration. 0.1 mole of conc. HCl or conc. HBr was added to the filtrate and the solution was evaporated *in vacuo*. Acetone was added to the residue and the resulting precipitate was filtered off.

5-Cyclohexylaminomethyl-6-methyl-3-phenyluracil (22)——Into 200 ml of EtOH were dissolved 10 g (0.05 mole) of 6-methyl-3-phenyluracil (**21**),[3] 5 ml of 37% formalin and 5.4 g of cyclohexylamine. The mixture was refluxed for 3 hr. After the reaction was over, it was evaporated *in vacuo*, and ether was added to the residue. The precipitate was filtered off and recrystallized from AcOEt to give 2.3 g of colorless crystals, mp 160°. *Anal.* Calcd. for $C_{18}H_{23}O_2N_3$: C, 68.98; H, 7.40; N, 13.41. Found: C, 68.89; H, 7.61; N, 12.97.

Bis(1,3,6-substituted 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidyl)methanes (27—30) (Table IV) and By-products (31, 32)——Into 30 ml of AcOH was dissolved 0.03 mole of 1,3,6-substituted uracil (**23—26**).[3]

Table III. 1,3,6-Substituted 5-Dimethylaminomethyluracils Hydrohalide

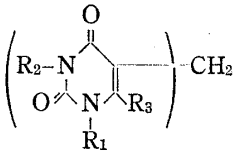


Compd. No.	R_1	R_2	R_3	X	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
16		Me	H	Cl	233	pills (MeOH–AcOEt)	99	$C_{14}H_{23}O_2N_3 \cdot HCl$	55.82 (56.06	8.03 8.26	13.95 14.00)
17	Ph	Me	H	Cl	236	plates (MeOH–AcOEt)	83	$C_{14}H_{17}O_2N_3 \cdot HCl$	56.84 (56.99	6.14 6.24	14.21 14.18)
18	Me		H	Cl	214	needles (MeCOEt)	84	$C_{14}H_{23}O_2N_3 \cdot HCl$	55.82 (55.99	8.03 8.32	13.95 13.83)
19		Me	Me	Cl	201	needles (MeOH–AcOEt)	92	$C_{15}H_{25}O_2N_3 \cdot HCl$	57.05 (57.20	8.30 8.52	13.31 13.35)
20	Ph	Me	Me	Br	240	needles (MeOH–AcOEt)	70	$C_{15}H_{19}O_2N_3 \cdot HBr$	50.95 (51.08	5.69 5.87	11.89 11.66)

a) All compounds are colorless crystals.
Ph=phenyl

Paraformaldehyde (1.0 g, 0.03 mole) and 48% HBr (30 ml) were added to the solution and the mixture was heated at 70° for 10 hr. The solvent was distilled off and acetone was added thereto. The precipitate was filtered and washed with H_2O to give a crude product of **27—30.** When a starting material was **23,** the acetone filtrate was purified by column chromatography using activated alumina and acetone to give **0.6** g **(7.8%)** of bis[(1,6-dimethyl-3-phenyl-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidyl)methyl] ether **(31)** and **1.0** g **(12.5%)** of 5-hydroxymethyl-1,6-dimethyl-3-phenyluracil **(32).** The compound **(31)** was recrystallized from MeOH to afford colorless prisms of mp 207—209°. *Anal.* Calcd. for $C_{26}H_{26}O_5N_4$: C, 65.41; H, 5.52; N, 11.81. Found: C, 65.64; H, 5.48; N, 11.82. NMR ($CDCl_3$) δ: 2.30 (3H, s, C_6–CH_3), 3.34 (3H, s, N_1–CH_3), 4.45 (2H, s, C_5–CH_2), 7.06—7.55 (5H, m, ph). Recrystallization of **32** from acetone gave colorless needles of mp 200°. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found; C, 63.19; H, 5.76; N, 11.18. NMR ($CDCl_3$) δ: 2.38 (3H, s, C_6–CH_3), 3.46 (3H, s, N_1–CH_3), 4.53 (2H, s, CH_2OH), 7.10—7.55 (5H, m, ph). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH).

Table IV. Bis(1,3,6-substituted 2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidyl)methanes

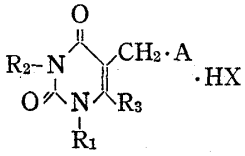


Compd. No.	R_1	R_2	R_3	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
27	Me	Ph	Me	>300	needles (AcOH)	81	$C_{25}H_{24}O_4N_4$	67.55 (67.47	5.44 5.36	12.61 12.56)
28	Ph	Me	Me	>300	needles (EtOH)	78	$C_{25}H_{24}O_4N_4$	67.55 (67.41	5.44 5.65	12.61 12.74)
29	Ph	Bu	Me	180—182	needles (MeOH)	28	$C_{31}H_{36}O_4N_4$	70.43 (70.69	6.86 6.77	10.60 10.65)
30		Me	H	291	prisms (AcOH–AcOEt)	65	$C_{23}H_{32}O_4N_4$	64.65 (64.65	7.62 7.53	13.08 13.16)

a) All compounds are colorless crystals.
Ph=phenyl

1,3,6-Substituted 5-Dialkylaminomethyluracils (20, 34—41) (Table V)——To 100 ml of conc. HCl was added 0.1 mole of 1,3,6-substituted uracil (23—26, 33), 25 ml of 37% formalin and 1.0 g of $ZnCl_2$. The mixture was heated at 70—75° for 5 hr with passing HCl gas. The solution was extracted with $CHCl_3$, the extract was washed with 100 ml of H_2O, 100 ml of 5% aq. solution of $NaHCO_3$, and 50 ml of H_2O, and then evaporated. The residue was dissolved into 60 ml of dimethyl formamide (DMF) and 0.1 mole of amine (dimethylamine, diethylamine, diallylamine, piperidine, or morphorine) was added thereto. The mixture was heated at 100° in a sealed tube for 2 hr. After the reaction, DMF was distilled off *in vacuo* and acetone was added to the residue to give crude crystals (**35, 36**). The acetone solution, unless crystallized, was made to pass HCl gas to afford the hydrochloride salt (**34, 37—41**). The crude product **20** was purified as the hydrogenbromide salt and confirmed by IR to be identical with the compound **20** obtained by reduction and methylation of **6**.

TABLE V. 1,3,6-Substituted 5-Dialkylaminomethyluracils



Compd. No.	R_1	R_2	R_3	A	X	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
20	Ph	Me	Me	NMe_2	Br	240	needles (MeOH–AcOEt)	28	$C_{15}H_{19}O_2N_3\cdot HBr$	50.95 (51.08	5.69 5.89	11.89 11.66)
34		Me	H		Cl	225—230	needles (acetone)	34	$C_{16}H_{25}O_3N_3\cdot HCl$	55.88 (55.73	7.63 7.74	12.23 12.06)
35	Ph	Me	Me	NEt_2	—	135	needles[b]	50	$C_{17}H_{23}O_2N_3$	67.75 (67.51	7.69 7.72	13.94 13.72)
36	Ph	Me	Me	$N(CH_2CH=CH_2)_2$	—	109—110	needles (acetone–H_2O)	50	$C_{19}H_{23}O_2N_3$	70.13 (70.05	7.12 7.31	12.91 12.76
37	Ph	Me	Me		Cl	263—265	needles (EtOH)	67	$C_{18}H_{23}O_2N_3\cdot HCl$	61.79 (61.60	6.91 7.00	12.01 11.80)
38	Ph	Me	Me		Cl	235—240	needles (acetone)	40	$C_{17}H_{21}O_3N_3\cdot HCl$	58.02 (57.89	6.30 6.54	11.94 11.85)
39	Ph	Bu	Me	NMe_2	Cl	180—182	prisms (acetone)	50	$C_{18}H_{25}O_2N_3\cdot HCl$	61.40 (61.20	7.45 7.20	11.94 11.83)
40	Me		Me	NMe_2	Cl	243	needles (MeOH–AcOEt)	50	$C_{15}H_{25}O_2N_3\cdot HCl$	57.05 (57.01	8.30 8.17	13.31 13.25)
41	Me	Ph	Me	NMe_2	Cl	263	prisms (MeOH–AcOEt)	32	$C_{15}H_{19}O_2N_3\cdot HCl$	58.13 (58.12	6.50 6.36	13.57 13.58)

a) All compounds are colorless crystals.
b) The compound **35** was purified by alumina-column chromatography with AcOEt.
Ph=phenyl

Acknowledgement The authors offer their sincere thanks to Dr. Katsuya Ohata and his coworkers of Nippon Shinyaku Research Laboratories for their cooperation in pharmacological experiments.