rated, and the residue was recrystallized. When the product was oily, HBr or MeBr was added and recrystallized (cf. Table V).

Summary

5-(2-Dimethylaminoacylamino)-1, 3, 6-trialkyluracils, which are analogous to Aminopropylon[3] in chemical structure, were synthesized and their pharmacological activities were tested (Table I). Quaternary ammonium salt of these compounds with methyl bromide showed remarkable increase in their toxicity, but, generally, they showed comparatively satisfactory results both in analgesic activity and toxicity.

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94. Shigeo Senda, Akio Suzui, and Makoto Honda: Uracil Derivatives and Related Compounds. IV. 5-Amino-1,3,6-trialkyluracil Derivatives. (2).

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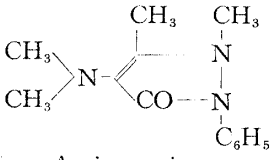
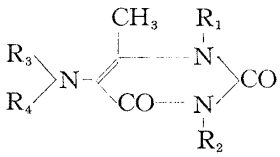
In continuation of the previous work,[1] 5-dialkylamino-1, 3, 6-trialkyluracils, which are analogous with aminopyrine in chemical structure, were synthesized and some interesting compounds were found after examining the relationship between their pharmacological activity and chemical structure.



Aminopyrine



5-Dialkylamino-1,3,6-trialkyluracil

5-Amino-3-cyclohexyl-1,6-dimethyluracil (I), 5-amino-3-cyclohexyl-1-ethyl-6-methyluracil (II), 5-amino-3-butyl-1,6-dimethyluracil (III), and 5-amino-1-butyl-3,6-dimethyluracil (IV), described in the previous report,[1] were treated with calcium oxide in methanol and alkylated with dimethyl sulfate, ethyl bromide, or allyl bromide, to afford 5-dialkylamino-1,3,6-trialkyluracils (V to X) (cf. Table II).

Ethylation of (I) with diethyl sulfate gave 3-cyclohexyl-5-ethylamino-1,6-dimethyluracil (XI) as a main product, while methylation of 3-cyclohexyl-5-formylamino-1,6-dimethyluracil (XII), prepared by the heating of (I) with formic acid or by the reduction of 3-cyclohexyl-1,6-dimethyl-5-nitrouracil with formic acid and zinc, and hydrolysis with hydrochloric acid gave 3-cyclohexyl-5-methylamino-1,6-dimethyluracil (XIII). Further alkylation of 5-monoalkylamino-1,3,6-trialkyluracils afforded 5-dialkylamino-1,3,6-trialkyluracils.

3-Cyclohexyl-5-(N-methyl-ethylamino)-1,6-dimethyluracil (XIV) was obtained by the methylation of (XI) or ethylation of (XIII), and treatment of (XIII) with allyl bromide gave 5-(N-methyl-allylamino)-3-cyclohexyl-1,6-dimethyluracil (XV).

3-Cyclohexyl-1, 6-dimethyl-5-dimethylaminouracil (V) was also prepared in another way. 3-Cyclohexyl-1,6-dimethyluracil in glacial acetic acid was treated with bromine or iodine and nitric acid to give 5-bromo- (XVI) or 5-iodo-3-cyclohexyl-1,6-dimethyluracil (XVII) in a good yield, and the product was condensed with dimethylamine.

To compare with sulpyrine, or Melubrin, sodium 3-cyclohexyl-1,6-dimethyluracil-5-aminomethanesulfonate (XVIII) or sodium N-methyl-3-cyclohexyl-1, 6-dimethyluracil-5-aminomethanesulfonate (XIX) was synthesized by the condensation of (I) or (XIII) with sodium hydrogen methanesulfonate.

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1) Part III: This Bulletin, **6**, 482(1958).

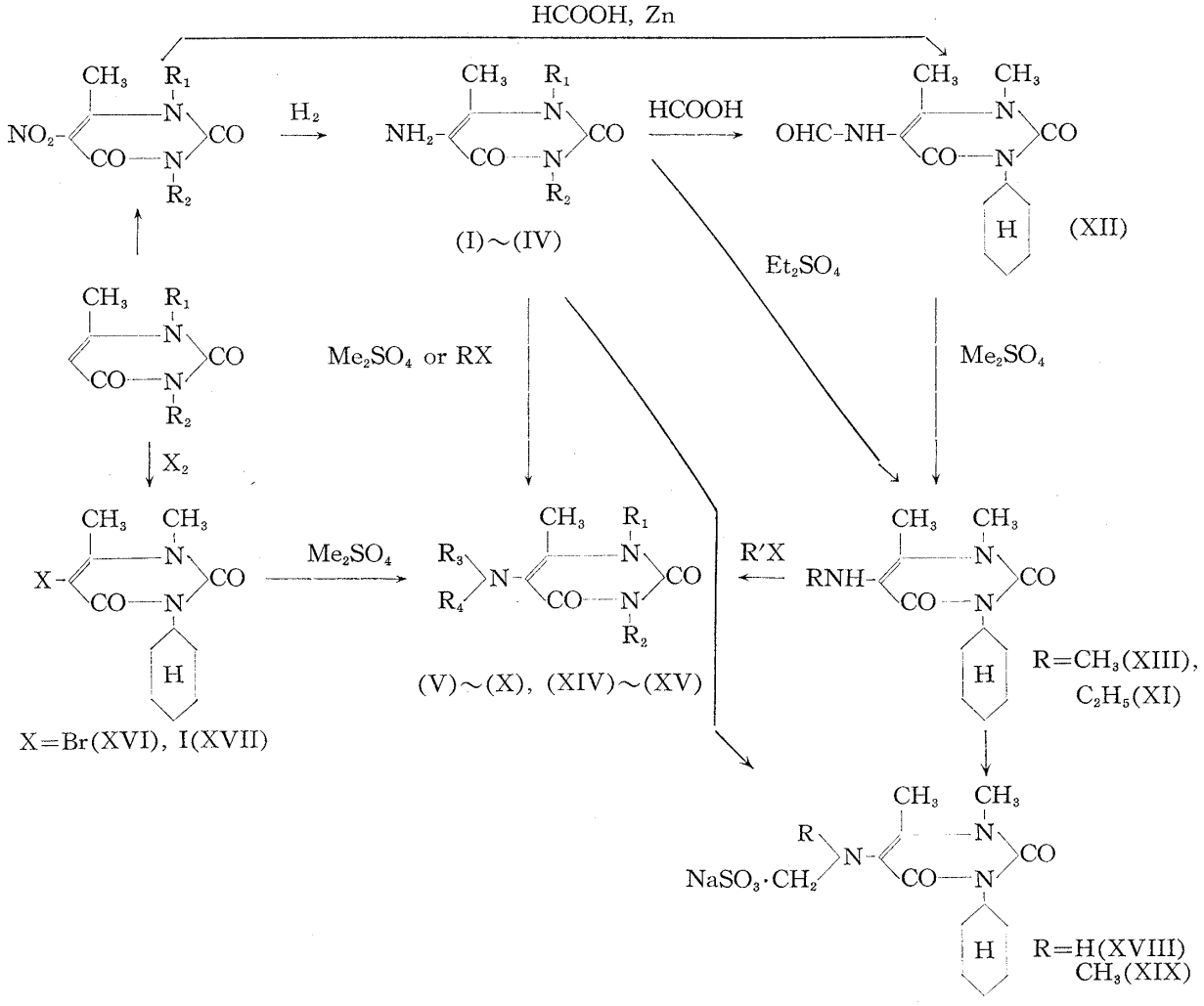
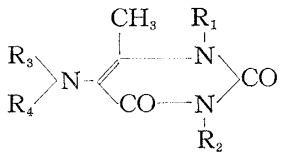


TABLE I.



No.	Compound R_1	R_2	R_3	R_4	LD_{50} (mg./10 g.i.p. in mice)	Antalgic effect ED 50 (modified Haffner method)[2]	Sedative effect (Cyclopane 0.25 mg. +sample 1 mg./10 g.i.p.) No. hypnotized mice/10 mice
(V)	CH_3	H	CH_3-	CH_3-	7.0 mg./10 g.	0.8 mg./10 g	5
(XIV)	CH_3	H	CH_3-	C_2H_5-	5.5	1.5	2
(VI)	CH_3	H	C_2H_5-	C_2H_5-	4.5	1.0	2
(VII)	CH_3	H	C_3H_5-	C_3H_5-	5.5	1.8	2
(IX)	CH_3	n-C_4H_9-	CH_3-	CH_3-	5.2	1.2	3
(X)	n-C_4H_9	CH_3-	CH_3-	CH_3-	2.4	0.5	6
(XVIII)	CH_3	H	H-	$NaSO_3CH_2$-	>20.0	>3.0	—
(XIX)	CH_3	H	CH_3-	$NaSO_3CH_2$-	>20.0	2.7	—
(I)	3-Cyclohexyl-1,6-dimethyluracil[1]				5.0	1.7	—
	aminopyrine				2.8	1.5	—

2) K. Ogiu, H. Fujimura, M. Matsumura, T. Uejima, T. Takahashi, S. Senda: Yakugaku Zasshi, **73,** 439(1953).

The pharmacological activity of these uracil derivatives will be described briefly. It is interesting that these compounds generally showed analgesic, hypothermic, antifebrile, and even tranquilizing actions with less toxicity than aminopyrine. When water-solubility of these compounds was increased by the introduction of $-CH_2SO_3Na$ group, the pharmacological activity other than hypothermic action decreased markedly, though the toxicity lesssened greatly, but these compounds did not show any better activity than sulpyrine and Melubrin.

Of the above compounds, 3-cyclohexyl-1, 6-dimethyl-5-dimethylaminouracil (V) clearly showed a better analgesic and antifebrile actions with less toxicity than aminopyrine in animal tests, and the compound itself showed a tranquilizing action. Further detailed examinations are now being made by Dr. Fujimura and others in the Department of Pharmacology, University of Kyoto.

The authors offer their cordial thanks to Dr. Etsuo Miyamichi, President of this College, for continually giving them encouragements. Thanks are also due to the cooperation of Dr. H. Fujimura and his colleagues in the Department of Pharmacology, University of Kyoto, for their pharmacological tests, and to Miss H. Iwata and others in the Analysis Center, University of Kyoto, for elemental analyses.

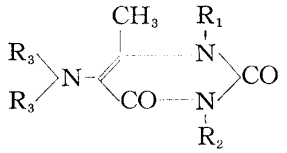
Experimental

5-Dialkylamino-1, 3, 6-trialkyluracil (V to X)—(a) One mole of each of 5-amino-1, 3, 6-trialkyluracils (I to IV) was dissolved in 5~6 volumes of MeOH, about 3 moles of well-powdered CaO and 2.4 moles of Me_2SO_4, EtBr, or allyl bromide was added, and the mixture was heated on a water bath for 6~8 hrs. After the reaction was completed, MeOH was evaporated and the residue was extracted with $CHCl_3$ or benzene. When the product solidified after distillation under a reduced pressure, it was recrystallized from petr. ether (cf. Table II).

(b) A mixture of 8 g. of (XVI) and 40 cc. of 10% MeOH solution of Me_2NH was heated in a sealed tube at 100° for 8 hrs. MeOH was evaporated and the residue was recrystallized from petr. ether to 2 g. (32%) of (V), recovering 0.5 g. of the starting material (XVI).

Table II.

5-Dialkylamino-1,3,6-trialkyluracil



No.	Compound R_1	Compound R_2	Compound R_3	Yield (%)	b.p.(m.p)	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(V)	CH_3	H	CH_3	85	$b.p._4$ 183~187 (103°)	prisms	$C_{14}H_{23}O_2N_3$	63.37	8.74	15.84	63.06	8.52	15.93
(VI)	CH_3	〃	C_2H_5	21	(95°)	〃	$C_{16}H_{27}O_2N_3$	65.49	9.28	14.32	65.24	9.04	15.49
(VII)	CH_3	〃	C_3H_5	78	$b.p._{3.5}$ 184~187° (64.5°)	〃	$C_{18}H_{27}O_2N_3$	68.11	8.57	13.24	68.03	8.68	13.31
(VIII)	C_2H_5	〃	CH_3	62	(113°)	〃	$C_{15}H_{25}O_2N_3$	64.48	9.02	15.04	64.20	8.99	15.32
(IX)*	CH_3	n-C_4H_9	CH_3	33	$b.p._4$ 145~148°	oil	$C_{12}H_{21}O_2N_3$	60.22	8.85	17.56	60.17	8.83	17.89
(X)	n-C_4H_9	CH_3	CH_3	80	$b.p._5$ 151~155°	oil	$C_{12}H_{21}O_2N_3$	60.22	8.85	17.56	59.85	9.01	17.62

* HCl salt of (IX): m. p. 130.5~134°, prisms.

3-Cyclohexyl-5-ethylamino-1,6-dimethyluracil (XI)—To a mixture of 10 g. of (I) and 60 cc. of MeOH, 6.5 g. of CaO and 16.6 g. of Et_2SO_4 were added and the mixture was refluxed for 2 hrs. MeOH was evaporated, the residue was extracted with $CHCl_3$, and distilled *in vacuo* to give 8.8 g. (79%) of (XI), $b.p._{3.5}$ 181~187°, which afforded 4.5 g. of colorless prisms, m. p. 122~123°, when recrystallized from petr. ether. *Anal.* Calcd. for $C_{14}H_{23}O_2N_3$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.31; H, 8.79; N, 16.01.

3-Cyclohexyl-5-formylamino-1,6-dimethyluracil (XII)—(a) A mixture of (I) and 100 cc. of 80% HCOOH was refluxed for 3 hrs., the mixture was evaporated to dryness, and the residue was washed with water. Recrystallization from ether afforded 31 g. (86%) of (XII) as colorless prisms, m. p. 159~159.5°. *Anal.* Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.72; H, 7.24; N, 15.99.

(b) A mixture of 10 g. of 3-cyclohexyl-1,6-dimethyl-5-nitrouracil and 100 cc. of 50% HCOOH was reduced with 20 g. of zinc dust with stirring and the solution was extracted with $CHCl_3$ to afford 2.5 g. of (XII), m. p. 159°.

3-Cyclohexyl-5-methylamino-1,6-dimethyluracil (XIII)—To a mixture of 27 g. of (XII), 7 g. of CaO, and 100 cc. of $CHCl_3$, 17 g. of Me_2SO_4 was dropped with heating and stirring. This was reacted for 3 hrs., the reaction mixture was filtered, washed with water, condensed, and the residue was heated with 40 cc. of 30% HCl for 3 hrs. After the hydrolysis, the solution was condensed *in vacuo* and the residue was recrystallized from Me_2CO or the mixed solution of MeOH and Et_2O to afford 22 g. of (XIII), colorless prisms, m.p. 211°. *Anal.* Calcd. for $C_{13}H_{21}O_2N_3 \cdot HCl \cdot H_2O$: C, 51.01; H, 7.83; N, 13.73. Found: C, 51.06; H, 7.86; N, 13.97.

3-Cyclohexyl-5-(N-methyl-ethylamino)-1,6-dimethyluracil (XIV)—A mixture of 4.9 g. of (XI), 1.1 g. of CaO, 2.8 g. of Me_2SO_4, and 50 cc. of MeOH was heated to reflux for 3 hrs. and treated same as in the case of (XI) to afford 3.3 g. of (XIV), colorless oil, b. p_4 175~180°, which became colorless prisms when recrystallized from petr. ether, m. p. 84~85°. *Anal.* Calcd. for $C_{15}H_{25}O_2N_3$: C, 64.48; H, 9.02; N, 15.04. Found: C, 64.13; H, 9.12; N, 15.28. (XIV) could also be obtained by the reaction of (XIII) with EtBr.

3-Cyclohexyl-5-(N-methyl-allylamino)-1, 6-dimethyluracil (XV)—A mixture of 7 g. of (XI), 1.7 g. of CaO, 4.7 g. of allyl bromide, and 50 cc. of MeOH in a sealed tube was heated at 100° for 10 hrs. and treated same as described in (XI) to afford 3.3 g. of (XV), colorless oil, b.p_3 188~190°. *Anal.* Calcd. for $C_{16}H_{25}O_2N_3$: C, 65.95; H, 8.65; N, 14.42. Found: C, 66.47; H, 8.57; N, 14.52.

5-Bromo-3-cyclohexyl-1,6-dimethyluracil (XVI)—To a mixture of 22.2 g. of 3-cyclohexyl-1, 6-dimethyluracil and 50 cc. of glacial AcOH, 17.6 g. of Br_2 was dropped, kept overnight, 450 cc. of water was added, and separated mass was collected and recrystallized from MeOH to afford 17 g. of (XVI), colorless needles, m. p. 174~175°. *Anal.* Calcd. for $C_{12}H_{17}O_2N_2Br$: C, 47.83; H, 5.69; N, 9.30. Found: C, 47.56; H, 5.56; N, 9.32.

3-Cyclohexyl-5-iodo-1,6-dimethyluracil (XVII)—To a mixture of 8.8 g. of 3-cyclohexyl-1, 6-dimethyluracil, 5.1 g. of iodine, and 50 cc. glacial AcOH, fuming HNO_3 was dropped gradually till the reaction solution decolorized, 50 cc. of water was added, and the separated mass was collected and recrystallized from MeOH to afford 7.2 g. of (XVII), colorless needles, m. p. 187~188°. *Anal.* Calcd. for $C_{12}H_{17}O_2N_2I$: C, 41.39; H, 4.92; N, 8.05. Found: C, 41.46; H, 4.92; N, 8.03.

Sodium 3-Cyclohexyl-1, 6-dimethyluracil-5-aminomethanesulfonate (XVIII)—A mixture of 5.4 g. of (I), 3.1 g. of sodium formaldehyde bisulfite, and 100 cc. of MeOH was refluxed for 2 hrs., about half volume of MeOH was evaporated, ether was added, and the separated mass was recrystallized from MeOH to afford 1.3 g. of (XVIII), colorless prisms, m.p. 116°(decomp.). *Anal.* Calcd. for $C_{13}H_{26}O_5N_3NaS$: N, 11.89. Found: N, 12.13.

Sodium N-Methyl-3-cyclohexyl-1, 6-dimethyluracil-5-aminomethanesulfonate (XIX)—A mixture of 5 g. of (XIII), 2.7 g. of sodium formaldehyde bisulfite, and 100 cc. of MeOH was treated same as described in (XVIII) to afford 3.5 g. of (XIX), colorless needles, m. p. 163°(decomp.). *Anal.* Calcd. for $C_{14}H_{22}O_5N_3NaS$: N, 11.44: Found: N, 11.10.

Summary

5-Dialkylamino-1,3,6-trialkyluracils, which were analogous with aminopyrine in chemical structure, were synthesized systematically and their phamacological actions were investigated. It is interesting that 5-dimethylamino-3-cyclohexyl-1, 6-dimethyluracil (V) showed analgesic, hypothermic, antifebrile, and moreover tranquilizing actions with less toxicity than aminopyrine.

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95. Shigeo Senda, Makoto Honda, Kyoji Maeno, and Hajime Fujimura: Uracil Derivatives and Related Compounds. V.[1] Alkyluracil Derivatives.

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As shown in the preceding paper,[1] examination of the pharmacological activity of 5-dialkylamino-1, 3, 6-trialkyluracils, which are analogous to aminopyrine in their chemical structure, showed that they had analgesic and antifebrile actions. Since these uracil derivatives also showed sedative activity — aminopyrine has no such an activity — the uracil derivatives were further investigated from the point of sedation.

The relationship between chemical structure and pharmacological action in these uracil derivatives might be presented as follows: The uracil ring may be regarded as an expansion of the five-membered pyrazolone ring to a six-member by introduction of one more carbonyl group between the two nitrogen atoms in the pyrazolone ring, or it may also be regarded as having been formed by dehydration between 5- and 6-positions of the barbital ring.

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1) Part IV: This Bulletin, **6**, 487(1958).