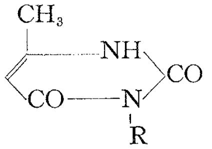
2-Methylthio-4-alkoxy-6-methylpyrimidines (IX to XII) (cf. Table I)—2-Methylthio-4-chloro-6-methylpyrimidine (VII) was dissolved in two volumes of the corresponding dehydrated alcohol and sodium alkoxide (containing equivalent amount of Na) was added gradually to this solution. The reaction occurred vigorously and inorganic salt separated out. The alcohol was evaporated, the residue was extracted with ether, and ether residue was distilled *in vacuo.*

3-Ethyl-6-methyluracil (XIII)—A mixture of 30 cc. of 20% HCl and 3 g. of (VIII) was boiled for 3 hrs., evaporated to dryness, and the residue was recrystallized from water to afford 2 g. of (XIII) as colorless granules, m. p. 193°. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.41; H, 6.55; N, 18.09.

Hydrolysis of Alkylated Derivatives of (VI): Formation of (XIII) to (XV) (cf. Table II)—The alkylated derivative of (VI) was dissolved in 10 volumes of 20% HCl, boiled for 3 hrs., evaporated to dryness *in vacuo,* and the residue was extracted with $CHCl_3$. 6-Methyluracil (XVI) was obtained from the residue after extraction. $CHCl_3$ extract was recrystallized from water to give 3-alkyl-6-methyluracils (XIII)～(XV).

TABLE II.



3-Alkyl-6-methyluracil

Compd. No.	R	m.p.(°C)	Yield(%)	(Yield (%) of 6-methyluracil[b])	Formula	Anal. (%) Calcd. C	H	N	Found C	H	N
(XIII)[a]	C_2H_5	193	47	(45)	$C_7H_{10}O_2N_2$	54.53	6.54	18.17	54.31	6.63	18.11
(XIV)	n-C_3H_7	183～184	37	(51)	$C_8H_{12}O_2N_2$	57.13	7.19	16.66	56.85	7.39	16.48
(XV)	n-C_4H_9	176～177	37	(50)	$C_9H_{14}O_2N_2$	59.32	7.74	15.37	59.78	7.72	15.38

a) Found by admixture to be identical with the compound obtained by the hydrolysis of (VIII).

b) Converted to 1, 3, 6-trimethyluracil (m.p. 111°; cf. K. Schmedes: Ann., **441**, 196(1925)) and by the mixed melting point test.

Hydrolysis of 2-Methylthio-4-alkoxy-6-methylpyrimidines (IX to XII)—To 30 cc. of 20% HCl, 3 g. of one of the compounds (IX to XII) was added, the mixture was boiled for 2 hrs., evaporated to dryness, and the residue was recrystallized from MeOH to give 1.0～1.5 g. of (XVI), decomposing above 300°. *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.47; H, 4.63; N, 22.31.

Summary

The methylation of 6-methyl-2-thiouracil with dimethyl sulfate gave 3, 6-dimethyl- and 1, 6-dimethyl-2-methylthio-4-pyrimidone. The alkylation of 6-methyl-2-methylthio-4-pyrimidone with alkyl halide, however, gave both 3-alkyl-6-methyl-2-methylthio-4-pyrimidone and 4-alkoxy-6-methyl-2-methylthiopyrimidine. The compounds obtained above were hydrolyzed to afford 3-alkyl-6-methyluracils and 6-methyluracil. 4-Alkoxy-6-methyl-2-methylthiopyrimidine was also synthesized from 4-chloro-6-methyl-2-methylthiopyrimidine and sodium alkoxide.

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93 **Shigeo Senda, Akio Suzui, Makoto Honda, and Hajime Fujimura:**

Uracil Derivatives and Related Compounds. III.[1)]

5-Amino-1, 3, 6-trialkyluracil Derivatives. (1).

(*Gifu College of Pharmacy* and Institute for Chemical Research, University of Kyoto***)

Uracil base is related to nucleoproteins which are important as a constituent of nervous tissue. Uracil derivatives used as pharmaceutics are rather restricted, there being 6-methyl-2-thiouracil as antithyroid, and, recently, 6-amino-1,3-dialkyluracils as diuretics.

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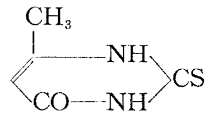
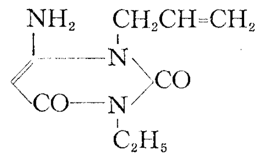
* Kokonoe-cho 3, Gifu (千田重男, 鈴井明男, 本田 真).

** Yoshida Konoe-cho, Sakyo-ku, Kyoto (藤村 一).

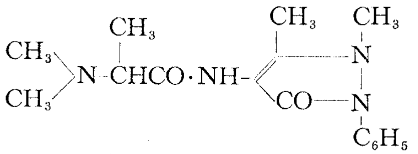
Past studies mainly concerned preparation of intermediates for the synthesis of pharmaceutics of pyrimidine and purine derivatives.

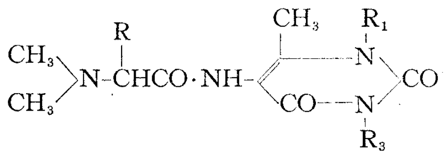
As previously reported,[1,2] examinations were made to develop a new utilization of uracil derivatives as pharmaceutics fixing the -NH-CO- group in the uracil ring and avoiding the transformation into pyrimidine ring by the introduction of various hydrocarbon groups into the nitrogen atoms at 1- and 3- positions of the uracil ring.


6-Methyl-2-thiouracil

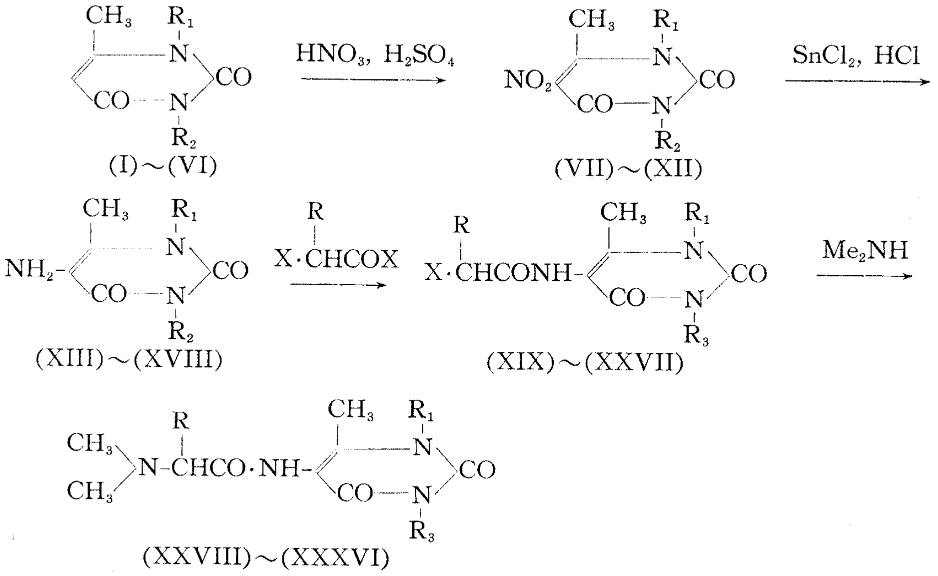

Aminometradine

Takahashi and Senda[3] previously synthesized 4-(2-dimethylaminopropionylamino)antipyrine (Aminopropylon) as a new analgesic. Based on the fact that the pyrazolone ring, fundamental skeleton of Aminopropylon, is analogous to 1,3,6-trialkyluracil in chemical structure, the present series of studies was undertaken in an attempt to obtain 5-dimethylaminoacylamido-1,3,6-trialkyluracils and also to investigate the relationship between their pharmacological activity and chemical structure.


Aminopropylon


5-Dimethylaminoacylamino-1,3,6-trialkyluracil

Following six compounds were used as the starting 1,3,6-trialkyluracils: 1,3,6-Trimethyluracil (I),[4] 3-cyclohexyl-1,6-dimethyluracil (II), 3-cyclohexyl-1-ethyl-6-methyluracil (III), and 1,6-dimethyl-3-phenyluracil (IV), were reported previously,[1,2] and 1-butyl-3,6-dimethyluracil (V) and 3-butyl-1,6-dimethyluracil (VI) were prepared by the butylation of 3,6-dimethyluracil and 1,6-dimethyluracil, respectively.



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[1] Part I: This Bulletin, **6**, 476(1958).

[2] Part II: This Bulletin, **6**, 479 (1958).

[3] T. Takahashi, S. Senda: Yakugaku Zasshi, **72**, 614(1952).

[4] K. Schmedes: Ann., **441**, 196(1925).

1,3,6-Trialkyluracils (I～VI) were nitrated with conc. sulfuric acid and fuming nitric acid to give 1,3,6-trialkyl-5-nitrouracils (VII～XII) (cf. Table II). By the nitration of (IV), nitro group was introduced also into the *para* position of the phenyl group, and 1,6-dimethyl-5-nitro-3-(*p*-nitrophenyl)uracil (X) was obtained. The introduction of a nitroso group into 4-position of antipyrine occurred easily, but on the contrary, this reaction for these uracil derivatives was difficult.

These nitro compounds (VII～XII) were reduced with stannous chloride and hydrochloric acid, and 5-amino-1,3,6-trialkyluracils (XIII～XVIII) were obtained in good yields (cf. Table III).

Further, (XIII～XVIII) in chloroform was treated with 2-chloroacetyl chloride, 2-bromopropionyl bromide, or 2-bromobutyryl bromide in the presence of potassium carbonate to afford 5-(2-haloacylamino)-1,3,6-trialkyluracils (XIX ～ XXVII) (cf. Table IV). The products were condensed with Me_2NH to give 5-(2-dimethylaminoacylamido)-1, 3, 6-trialkyluracils (XXVIII～XXXVI) (cf. Table V).

The pharmacological activity of the above compounds was as follows: The toxicity of these uracil derivatives was comparatively weak. The larger the acyl group in the side-chain (in the order of $R=H<CH_3<C_2H_5$), the stronger the toxicity. When $R_1=R_2=CH_3$, the compounds were all water-soluble, but when $R_1=CH_3$, R_2=cyclohexyl and R_1=*n*-C_4H_9, $R_2=CH_3$, such solubility in water vanished. Hence, HBr or MeBr was added to those compounds to form a salt, and made crystalline and water-soluble to be ready for pharmacological tests, but the quaternary ammonium salt with MeBr showed a remarkable increase in toxicity. The analgesic activity was tested by the modified Haffner method[5] and it was found that ED_{50} of the compounds (XXIX) to (XXXII) was the same as or superior to that of Aminopropylon. The synergetic action with Cyclopane (Cyclopane 0.25 mg. + sample 1 mg./10 g., intraperitoneal, in mice) was also tested but its sedative action was hardly recognized. Further experiments are now being carried out by Dr. H. Fujimura and others of the Institute for Chemical Research, University of Kyoto.

The authors offer their cordial thanks to Dr. Etsuo Miyamichi, President of Gifu College of Pharmacy, for his continued encouragement. Thanks are also due to the members of the Analysis Center, University of Kyoto, for analytical data.

Experimental

1-Butyl-3,6-dimethyluracil (V)—To ethanolic KOH solution (39.4 g. of KOH in 550 cc. of EtOH), 76.6 g. of 3,6-dimethyluracil and 120 g. of BuBr were added, refluxed for 19 hrs., concentrated, and the residue was extracted with $CHCl_3$. The residue was distilled *in vacuo* to give 62 g. (58%) of (V) as light yellow oil, b.p_4 164～170° (m.p. 41°). *Anal.* Calcd. for $C_{10}H_{16}O_2N_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.32; H, 8.16: N, 14.30.

3-Butyl-1,6-dimethyluracil (VI)—To ethanolic KOH solution (23.4 g. of KOH in 358 cc. of EtOH), 56 g. of 1,6-dimethyluracil and 63.6 g. of BuBr were added, the mixture was refluxed for 13 hrs., and treated as above to give 45 g. (64%) of (VI) as light yellow oil, b.p_6 174～186° (m.p. 56°). *Anal.* Calcd. for $C_{10}H_{16}O_2N_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 60.99; H, 7.94; N, 14.38.

1,3,6-Trialkyl-5-nitrouracils (VII to XII)—To the acid mixture of 100 cc. each of conc. H_2SO_4 and fuming nitric acid (*d* 1.48), 50 g. of the compound (I～VI) was added gradually with stirring and cooling at 0° to 5°. The reaction mixture was poured carefully into ice, the separated product was washed with water, and recrystallized from MeOH. The compound (XI) (R_1=*n*-C_4H_9, $R_2=CH_3$) was oily, hence the reduction of (XI) was carried out without further purification (cf. Table II).

1,3,6-Trialkyl-5-aminouracils (XIII to XVIII)—To 100 cc. of conc. HCl, 0.1 mole of the compound (VII～XII) and 0.4～0.5 mole of $SnCl_2$ were added and the mixture was heated cautiously with shaking. When the nitro compound, the starting material, dissolved completely, solution was neutralized by addition of 30% NaOH solution and the solution extracted with 200 cc. of $CHCl_3$ (cf. Table III).

5-(2-Haloacylamino)-1,3,6-trialkyluracils (XIX to XXVII)—To a solution of 0.1 mole of the compound dissolved in 5 volumes of dehyd. $CHCl_3$, 0.2 mole of anhyd. K_2CO_3 and 0.1 mole of haloacyl halide were added, the mixture was refluxed on a water bath for 1 hr., the solvent was distilled off, the residue was washed with water, and recrystallized. The compound (XXIV) ($R_1=CH_3$, R_3= cyclohexyl, $R=C_2H_5$, X=Br) was oily, and so it was used as a starting material for the next reaction without further purification (cf. Table IV).

5-(2-Dimethylaminoacylamino)-1,3,6-trialkyluracils (XXVIII to XXXVI)—To the benzene solution of 0.3～0.4 mole of dimethylamine, 0.1 mole of (XIX to XXVII) was added, placed in a sealed tube, and heated at 100° for 5 hrs. The separated salt of dimethylamine was removed, the solvent was evapo-

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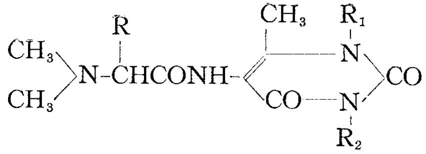
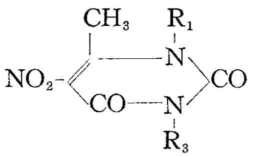
[5] K. Ogiu, H. Fujimura, M. Matsumura, T. Uejima, T. Takahashi, S. Senda: Yakugaku Zasshi, **73**, 439(1953).

TABLE I.



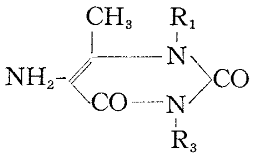
No.	Compound R₁	Compound R₂	R (salt)	LD$_{50}$ (mg./10 g i.p. in mice)	Analgesic effect (modified Haffner method[5]) sample (mg.)	(positive %)
(XXVIII)	CH_3	CH_3	H	ca. 20.	2.	(50)
(XXIX)	〃	〃	CH_3	ca. 20.	0.54	(50)
(XXX)	〃	〃	C_2H_5	5.4	0.60	(50)
(XXXI)	〃		H (HBr)	8.8	0.70	(50)
(XXXII)	〃	〃	CH_3 (HBr)	ca. 4.0	0.56	(50)
(XXXIII)	〃	〃	C_2H_5 (CH_3Br)	0.7	0.2	(20)
(XXXIV)	n-C_4H_9	CH_3	H (CH_3Br)	ca. 1.5	0.5	(40)
(XXXV)	〃	〃	CH_3	5.4	0.90	(50)
	Aminopropylon			11.	1.0	(50)

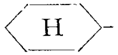
TABLE II.



No.	Compound R₁	R₃	m. p. (°C) (decomp.)	Appearance	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(VII)	CH_3	CH_3	150	yellow plates	93	$C_7H_9O_4N_3$	42.21	4.55	21.10	41.90	4.76	20.92
(VIII)	〃		138	yellow prisms	95	$C_{12}H_{17}O_4N_3$	53.92	6.41	15.72	53.58	6.68	15.65
(IX)	C_2H_5	〃	133～135	yellow plates	90	$C_{13}H_{19}O_4N_3$	55.50	6.81	14.94	55.20	7.01	14.77
(X)	CH_3		(248)	yellow prisms	75	$C_{12}H_{10}O_6N_4$	47.06	3.29	18.30	46.92	3.19	18.53
(XII)	〃	n-C_4H_9	78	yellow plates	18	$C_{10}H_{15}O_4N_3$	49.78	6.27	17.42	50.45	6.18	17.61

TABLE III.

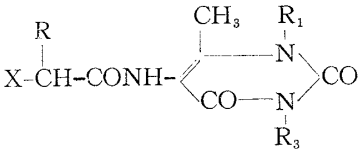


No.	Compound R₁	R₃	m. p. (°C)	Appearance	Yield (%)	Recrystn. solvent	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(XIII)	CH_3	CH_3	167	colorless needles	87	EtOH	$C_7H_{11}O_2N_3$	49.69	6.55	24.84	49.63	6.37	24.62
(XIV)	〃		159	colorless prisms	88	50% MeOH	$C_{12}H_{19}O_2N_3$	60.73	8.07	17.71	60.81	8.21	17.88
(XV)	C_2H_5	〃	122～124	〃	50	Et_2O	$C_{13}H_{21}O_2N_3$	62.12	8.42	16.72	62.07	8.51	16.94

(XVI)*	CH_3	-NH_2	213	〃	37	EtOH	$C_{12}H_{14}O_2N_4$	58.52	5.73	22.75	58.51	5.41	22.62
(XVII)	n-C_4H_9	CH_3	96~97	〃	76	Et_2O	$C_{10}H_{17}O_2N_3$	56.86	8.11	19.98	56.99	8.20	19.98
(XVIII)	CH_3	n-C_4H_9	49	〃	88	petr. ether	$C_{10}H_{17}O_2N_3$	56.86	8.11	19.98	57.01	8.16	20.12

(* $SnCl_2 \cdot 2H_2O$ 10 moles)

TABLE IV.



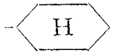
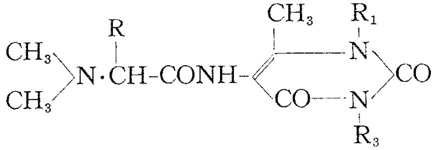
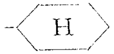
No.	Compound R_1	R_3	R	X	m.p.(°C)	Appearance (colorless)	Yield (%)	Recryten. solvent	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(XIX)	CH_3	CH_3	H	Cl	174	needless	77	50% MeOH	$C_9H_{12}O_3N_3Cl$	44.01	4.77	17.11	43.86	5.03	17.41
(XX)	〃	〃	CH_3	Br	216	〃	92	〃	$C_{10}H_{14}O_3N_3Br$	39.46	4.61	13.82	39.63	4.64	13.88
(XXI)	〃	〃	C_2H_5	〃	195	plates	44	〃	$C_{11}H_{16}O_3N_3Br$	41.52	5.03	13.24	40.88	5.33	13.41
(XXII)	〃		H	Cl	164	prisms	92	〃	$C_{14}H_{20}O_3N_3Cl$	53.57	6.43	13.39	53.58	6.57	13.27
(XXIII)	〃	〃	CH_3	Br	173	〃	90	〃	$C_{15}H_{22}O_3N_3Br$	48.34	5.91	11.28	48.17	6.05	11.33
(XXV)	n-C_4H_9	CH_3	H	Cl	94	needles	85	petr. ether	$C_{12}H_{18}O_3N_3Cl$	50.03	6.29	14.60	49.94	6.96	14.88
(XXVI)	〃	〃	CH_3	Br	106	〃	87	〃	$C_{13}H_{20}O_3N_3Br$	45.04	5.82	12.13	45.21	5.96	12.63
(XXVII)	〃	〃	C_2H_5	〃	88	prisms	92	〃	$C_{14}H_{22}O_3N_3Br$	46.63	6.16	11.66	47.48	6.30	11.78

TABLE V.



No.	Compound R_1	R_3	R(salt)	m.p.(°C)	Appearance (colorless)	Yield (%)	Recrystn. solvent	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(XXVIII)	CH_3	CH_3	H	118	plates	72	Me_2CO-Et_2O	$C_{11}H_{18}O_3N_4$	51.97	7.14	22.03	52.22	6.90	22.14
(XXIX)	〃	〃	CH_3	119~121	prisms	86	〃	$C_{12}H_{20}O_3N_4$	53.71	7.51	20.88	53.79	7.27	21.24
(XXX)	〃	〃	C_2H_5	125	needles	55	CS_2-ligroine	$C_{13}H_{22}O_3N_4$	55.30	7.85	19.85	55.24	7.56	20.07
(XXXI)	〃		H(HBr)	225	prisms	20	Me_2CO-Et_2O	$C_{16}H_{27}O_3N_4Br$	47.59	6.75	13.89	47.61	6.51	14.13
(XXXII)	〃	〃	CH_3(HBr)	185	〃	35	〃	$C_{17}H_{29}O_3N_4Br$	48.86	7.01	13.42	48.67	7.21	13.48
(XXXIII)	〃	〃	C_2H_5(CH_3Br)	240	needles	28	〃	$C_{19}H_{33}O_3N_4Br$	51.18	7.47	12.57	51.09	7.18	12.69
(XXXIV)	n-C_4H_9	CH_3	H(CH_3Br)	109	prisms	15	〃	$C_{15}H_{27}O_3N_4Br \cdot H_2O$	43.96	7.14	13.69	43.78	7.17	14.01
(XXXV)	〃	〃	CH_3	116	〃	85	Et_2O-petr. ether	$C_{15}H_{26}O_3N_4$	58.04	8.44	18.05	57.82	8.35	18.22
(XXXVI)	〃	〃	C_2H_5	101	〃	65	〃	$C_{16}H_{28}O_3N_4$	59.23	8.70	17.27	59.50	8.72	17.62

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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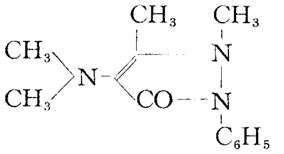
UDC 547.854.4

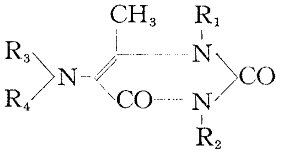
94. **Shigeo Senda, Akio Suzui, and Makoto Honda:** Uracil Derivatives and Related Compounds. IV. 5-Amino-1,3,6-trialkyluracil Derivatives. (2).

(*Gifu College of Pharmacy**)

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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* Kokonoe-cho, Gifu (千田重男, 鈴井明男, 本多 貞)

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