colorless prisms, m. p. 223～225°.

(iii) A mixture of 0.7 g. of cyclohexylurea and 1.3 g. of (IV) was boiled in MeOH-KOH solution (0.6 g. of KOH and 50 cc. of MeOH) and acidified with HCl. The separated mass was collected and recrystallized from MeOH to afford 0.6 g. of (VI) as colorless prisms, m.p. 225°. Both compounds obtained in (ii) and (iii) were found by admixture to be identical with (VI) obtained in (i).

1-[3-(3-Cyclohexylureido)crotonoyl]-3′-phenylurea (VII)—A mixture of phenylurea (0.68 g.) and 1.27 g. of (IV) in EtOH-KOH (0.56 g. of KOH in 50 cc. of EtOH) was refluxed on a water bath, cooled, and acidified with HCl. The separated product was collected, washed with water, and recrystallized from 50% MeOH to give 0.9 g. of (VII) as colorless needles, m.p. 178°. *Anal.* Calcd. for $C_{18}H_{24}O_3N_4$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.53; H, 6.96; N, 16.33.

1,6-Dimethyl-3-cyclohexyluracil (VIII)—To NaOH solution (27.7 g. of NaOH in 270 cc. of H_2O) was added 110 g. of (VI), and 86.5 g. of Me_2SO_4 was dropped gradually under stirring and cooling. When the reaction mixture became acidic, the separated mass was collected, washed with water, and recrystallized from 50% MeOH to give 116 g. of (VIII) as colorless plates, m.p. 139°. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.02; N, 12.82.

1-Ethyl-3-cyclohexyl-6-methyluracil (IX)—To NaOH solution (5.6 g. of NaOH in 28 cc. of H_2O) was added 15 g. of (VI), and ethylated with 21.6 g. of Et_2SO_4 to give 16 g. of (IX) as colorless needles (from petr. ether), m.p. 109～112°. *Anal.* Calcd. for $C_{13}H_{20}O_2N_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.35; H, 8.73; N, 11.73.

3,6-Dimethyluracil (XI)—To 13 g. of ethyl acetoacetate and 7.4 g. of methylurea in 2.5 cc. of dehyd. EtOH 2 drops of conc. HCl was added and the mixture was treated as for (II). A part of the crude product was recrystallized from petr. ether to give ethyl 3-(3-methylureido)crotonate (X) as colorless prisms, m. p. 49°. *Anal.* Calcd. for $C_8H_{14}O_3N_2$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.57; H, 7.82; N, 14.83.

The crude (X) was hydrolyzed with NaOH solution (5 g. of NaOH in 60 cc. of water), acidified with HCl, and the separated mass was recrystallized from water to give 6.4 g. of (XI) as colorless needles, m. p. 262°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.40; H, 5.66; N, 20.30.

Summary

All of the compounds derived from the condensation of monosubstituted ureas (substituents: phenyl, cyclohexyl, methyl) and ethyl acetoacetate were 3-substituted 6-methyluracil derivatives. In the case of phenylurea, the hydrolysis of the condensation product gave 1-[3-(3-phenylureido)crotonoyl]-3-phenylurea without the formation of a uracil ring, and when the condensation product was methylated, the ring closure occurred to afford 1,6-dimethyl-3-phenyluracil. In the case of cyclohexylurea or methylurea, 5-alkyl-6-methyluracil was obtained in a good yield via ethyl 3-(3-alkylureido)crotonate.

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92 **Shigeo Senda and Akio Suzui:** Uracil Derivatives and Related Compounds. II.[1]

Alkylation of 6-Methyl-2-thiouracil Derivatives.

(*Gifu College of Pharmacy**)

The present study was carried out to investigate the alkylation reaction of 6-methyl-2-thiouracil derivatives in detail and also to use the alkyluracils so obtained as the intermediate for pharmaceutics.

Methylation of 6-methyl-2-thiouracil[2] (I) with 2 moles of dimethyl sulfate afforded 2-methylthio-3,6-dimethyl-4-pyrimidone[3] (II) in a good yield and a small amount of 1,6-dimethyl-2-methylthio-4-pyrimidone (III) as a by-product. The hydrolysis of (II) or (III)

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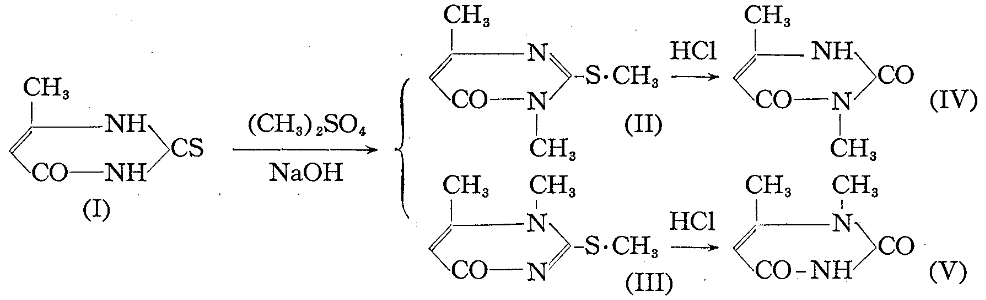
[1] Part I: This Bulletin, **6**, 476 (1958).

[2] Org. Syntheses, Coll. Vol. II, 422 (1948).

[3] H. L. Wheeler, McFarland: Am. Chem. J., **42**, 105 (1911).

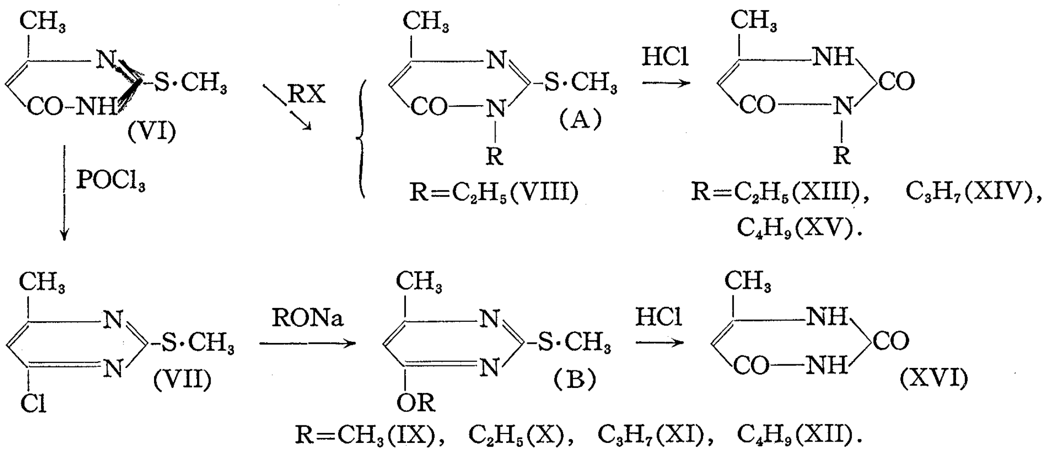
with 20% hydrochloric acid gave 3,6-dimethyluracil[1] (IV) or 1,6-dimethyluracil (V).



Treatment of 2-methylthio-6-methyl-4-pyrimidone[4] (VI) with ethyl bromide in ethanolic solution of potassium hydroxide gave the ethylated compound (b.p$_5$ 123$\sim$140°) of (VI). This was fractionally distilled, and from the fraction of b.p$_5$ 120$\sim$128° and b.p$_5$ 128$\sim$137°, crystals of m.p. 40° and m.p. 54° were respectively obtained. The results of elemental analyses showed that both were compounds formed by substitution of one hydrogen atom in (VI) with one ethyl, and from the results of infrared spectral analysis the compound of m.p. 54° (I.R. $\nu_{\mathrm{c=o(ring)}}$ 5.99 μ) was thought to be of N-alkylpyrimidone type (A) and the compound of m.p. 40° (I.R. $\nu_{\mathrm{pyrimidine}}$ 6.32 and 6.47 μ), to be a 4-alkoxypyrimidine type (B).

The same alkylation of (VI) with propyl bromide or butyl bromide as described above gave the oily propyl or butyl derivative of (VI). The separation of these products into (A) and (B) did not materialize but from the results of elemental analyses and infrared spectra, they were thought to be a mixture of (A) and (B) types. (Propyl derivative of (VI): I.R. $\lambda_{\mathrm{c=o(ring)}}$ 5.94 μ, $\lambda_{\mathrm{pyrimidine}}$ 6.38 and 6.48 μ; butyl derivative of (VI): I.R. $\lambda_{\mathrm{c=o(ring)}}$ 5.94 μ, $\lambda_{\mathrm{pyrimidine}}$ 6.38 and 6.48 μ).

The reaction of 2-methylthio-4-chloro-6-methylpyrimidine[5] (VII), obtained by the chlorination of (VI) with phosphoryl chloride, with various kinds of sodium alkoxide gave the compounds of 4-alkoxyprimidine type (B) such as 2-methylthio-4-methoxy-6-methylpyrimidine[6] (IX), 2-methylthio-4-ethoxy-6-methylpyrimidine (X), 2-methylthio-4-propoxy-6-methylpyrimidine (XI), and 2-methylthio-4-butoxy-6-methylpyrimidine (XII). The compound (X) was identical with the compound of m.p. 40° obtained by the ethylation of (VI). The hydrolysis of (B)-type compounds (IX to XII) with 20% hydrochloric acid gave 6-methyluracils, (XVI), and of (A) type compound (VIII), 3-ethyl-6-methyluracil (XIII).



The hydrolysis of previously mentioned propyl and butyl derivatives of (VI) respectively gave 6-methyluracil and 3-propyl-6-methyluracil (XIV), or 6-methyluracil and 3-butyl-6-

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[4] G. Poetsch: Ann., **448**, 97(1926); H. L. Wheeler: Am. Chem. J., **29**, 486(1898).

[5] H. L. Wheeler, McFarland: *Ibid.*, **42**, 435(1911).

[6] T. Matsukawa, K. Shirakawa: Yakugaku Zasshi, **71**, 935(1951).

methyluracil (XV). These experimental results agreed with the consideration from the infrared absorption spectra that the above-mentioned compounds are the mixture of both (A) and (B) types.

The authors offer their cordial thanks to Dr. Etsuo Miyamichi, President of this College, for his continual encouragement. Thanks are also due to the Analysis Center of the University of Kyoto for analytical data and to the Institue of Polytechnic of Osaka City University for infrared absorption spectra.

Experimental

2-Methylthio-3,6-dimethyl-4-pyrimidone (II) and 1,6-Dimethyl-2-methylthio-4-pyrimidone (III)—To a mixture of 20% NaOH solution (80 g. of NaOH in 320 cc. of H_2O) and 130 g. of 4-methyl-2-thiouracil (I), 253 g. of Me_2SO_4 was added dropwise with stirring at 50～60°. When the reaction solution became weakly acid, the separated product was collected and 105 g. of crude (II), m.p. 87°, was obtained. The mother liquor was extracted 3 times with 100 cc. of benzene and from this extract, further 11.7 g. of crude (II) was obtained. These were combined and recrystallized from water to afford 103 g. of (II) as colorless needles, m.p. 94°. *Anal.* Calcd. for $C_7H_{10}ON_2S$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.38; H, 5.86; N, 16.38.

The mother liquor after the extraction with benzene was extracted 3 times with 100 cc. of $CHCl_3$ and 6.6 g. of crude (III), m.p. 203°, was obtained. This was recrystallized from acetone to afford 3.5 g. of (III) as colorless needles, m.p. 207°. *Anal.* Calcd. for $C_7H_{10}ON_2S$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.38; H, 5.86; N, 16.49.

3,6-Dimethyluracil (IV)—A mixture of 200 cc. of 20% HCl and 20 g. of (II) was boiled for 2 hrs. and the separated product was recrystallized from water to afford 9 g. of (IV) as colorless needles, m.p. 262°. Further 6.9 g. of the product was obtained by concentration of the mother liquor of reaction solution. This compound was confirmed by the mixed melting point test.[1)]

1, 6-Dimethyluracil (V)—A mixture of 1.1 g. of (III) and 11 cc. of 20% HCl was boiled for 2 hrs, and the separated product was recrystallized from water to give 0.8 g. of (V) as colorless plates, m.p. 220°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.47; H, 5.82; N, 19.76.

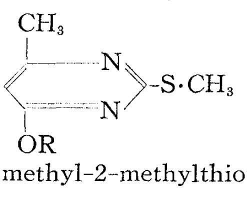
Alkylation of 2-Methylthio-6-ethyl-4-pyrimidone (VI)—(a) Ethylation, and separation of (VIII) and (X): A mixture of 32 g. of (VI) and 65 g. of EtBr was added to ethanolic KOH solution (11.2 g. of KOH in 90 cc. of EtOH) and the mixture was refluxed for 7 hrs. When the reaction solution became weakly acid, the separated inorganic salt was filtered off, EtOH was evaporated, and the residue was extracted with ether. Ethereal residue was distilled *in vacuo* to afford 21 g. of colorless oil, $b.p_7$ 123～140°. This was fractionally distilled *in vacuo* and the fractions of $b.p_5$ 120～128° and $b.p_5$ 128～137° were obtained. From the former fraction, (X) was obtained as colorless prisms, m.p. 40° *Anal.* Calcd. for $C_8H_{12}ON_2S$: C, 52.13; H, 6.57; N, 15.21. Found: C, 52.49; H, 6.79; N, 15.45.

From the latter fraction, (VIII) was obtained as colorless prisms, m.p. 54～55° *Anal.* Calcd. for $C_8H_{12}ON_2S$: C, 52.13; H, 6.57; N, 15.21. Found: C, 52.17; H, 6.27; N, 15.32.

(b) Propylation: A mixture of 28 g. of (VI) and 34.5 g. of PrBr in ethanolic KOH solution (10 g. of KOH in 85 cc. of EtOH) was refluxed for 12 hrs., and treated similarly as described in (a) to give 19 g. of colorless oil, $b.p_7$ 132～145°. *Anal.* Calcd. for $C_9H_{14}ON_2S$: C, 54.49; H, 7.12; N, 14.13. Found: C, 54.31; H, 7.10; N, 14.31.

(c) Butylation: A mixture of 32 g. of (VI) and 42.5 g. of BuBr in ethanolic KOH solution (11.2 g. of KOH in 90 cc. of EtOH) was refluxed for 9 hrs. and treated similarly as described in (a) to give 25 g. of colorless oil, $b.p_7$ 145～160°. *Anal.* Calcd. for $C_{10}H_{16}ON_2S$: C, 56.55; H, 7.60; N, 13.20. Found: C, 56.22; H, 7.33; N, 13.25.

TABLE I.



4-Alkoxy-6-methyl-2-methylthiopyrimidine

No.	R	(VII)	RONa	(Na)	b.p. (°C/mm.Hg)	Yield (%)	Formula	Anal. (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(IX)	CH_3	14 g.	40 cc.	(1.9 g.)	104～112/5	10.8 g (79%)	$C_7H_{10}ON_2S$	49.37	5.92	16.46	49.47	6.03	16.21
(X)	C_2H_5	8.7 g.	40 cc.	(1.15 g.)	113～116/5[a)]	9.0 g (70%)	$C_8H_{12}ON_2S$	52.13	6.57	15.21	52.47	6.79	15.41
(XI)	n-C_3H_7	8.7 g.	40 cc.	(1.15 g.)	130～137/9	8.0 g (81%)	$C_9H_{14}ON_2S$	54.49	7.12	14.13	54.28	6.83	14.20
(XII)	n-C_4H_9	8.7 g.	40 cc.	(1.15 g.)	130～136/9	9.0 g (84%)	$C_{10}H_{16}ON_2S$	56.55	7.60	13.20	56.22	7.27	13.26

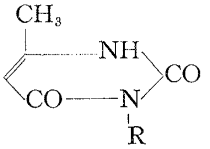
a) m. p. 40°, colorless prisms, found by admixture to be identical with the compound of m. p. 40° obtained by the ethylation of 2-methylthio-6-methyl-4-pyrimidone (VI)

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).

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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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