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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UDC 547.854.4

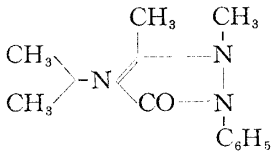
95. Shigeo Senda, Makoto Honda, Kyoji Maeno, and Hajime Fujimura: Uracil Derivatives and Related Compounds. V.[1] Alkyluracil Derivatives.

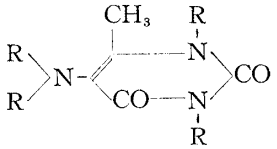
(*Gifu College of Pharmacy,* and Institute for Chemical Research, University of Kyoto***)

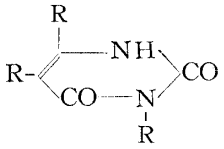
As shown in the preceding paper,[1] examination of the pharmacological activity of 5-dialkylamino-1, 3, 6-trialkyluracils, which are analogous to aminopyrine in their chemical structure, showed that they had analgesic and antifebrile actions. Since these uracil derivatives also showed sedative activity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

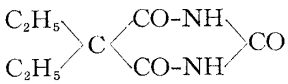
The relationship between chemical structure and pharmacological action in these uracil derivatives might be presented as follows: The uracil ring may be regarded as an expansion of the five-membered pyrazolone ring to a six-member by introduction of one more carbonyl group between the two nitrogen atoms 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.

* 3-chome, Kokonoe-cho, Gifu (千田重男, 本多 真, 前野恭治)
** Yoshida Konoe-cho, Sakyo-ku, Kyoto (藤村 一)
1) Part IV: This Bulletin, **6**, 487(1958).


Aminopyrine

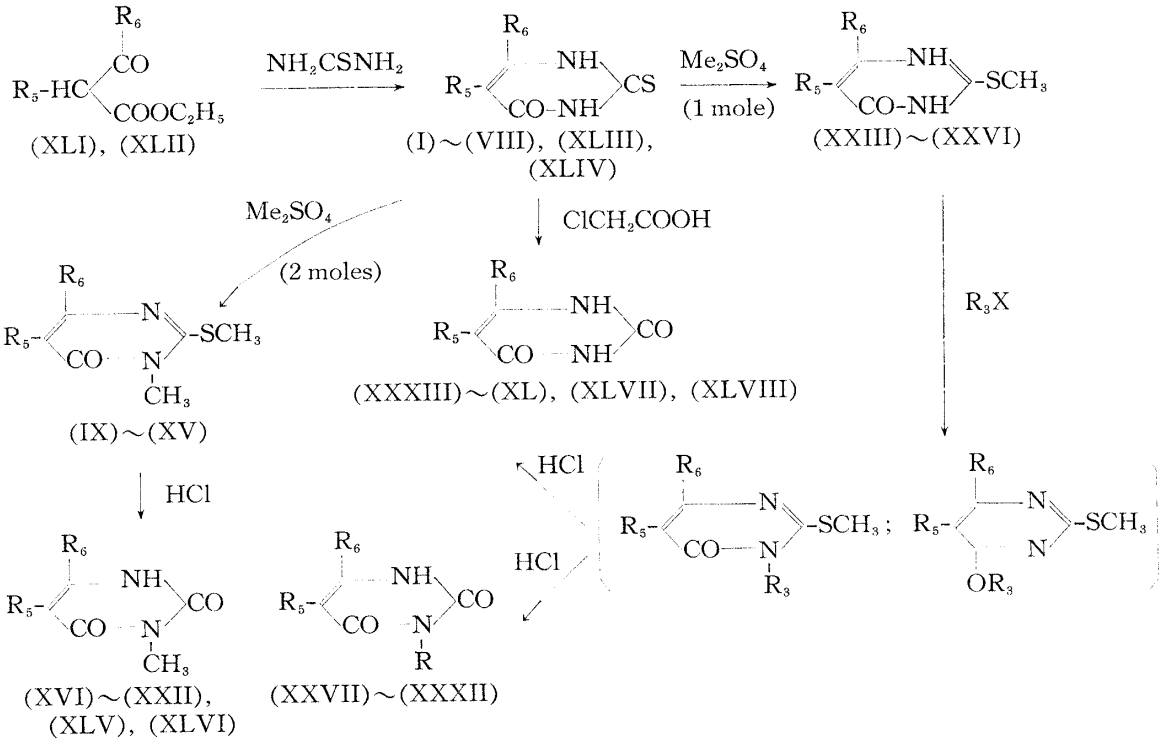

5-Dialkylamino-1, 3, 6-trialkyluracil


3, 5, 6-Trialkyluracil


Barbital

Systematic synthesis of various kinds of 5, 6-dialkyl-2-thiouracils, 5, 6-dialkyluracils, and 3, 5, 6-trialkyluracils, which are analogous to barbital in their chemical structure, was carried out and a relationship between pharmacological activity and chemical structure of these compounds was examined.

5-Alkyl-6-methyl-2-thiouracils (alkyl: CH_3(I)[2], C_2H_5(II)[3], *n*-C_3H_7(III)[4], C_3H_5(IV)[5], *n*-C_4H_9(V)[6], *iso*-C_4H_9(VI)[7], *n*-C_5H_{11}(VII)[8], *iso*-C_5H_{11}(VIII)[9]) were obtained by the condensation of ethyl alkylacetoacetate, thiourea, and sodium ethoxide under heating, methylated with 2 moles of dimethyl sulfate to give 5-alkyl-3, 6-dimethyl-2-methylthio-4-pyrimidones (alkyl: CH_3(IX), C_2H_5(X), C_3H_7(XI), C_3H_5(XII), C_4H_9(XIII), C_5H_{11}(XIV), *iso*-C_5H_{11}(XV)) (cf. Table IV). The product was then boiled with 20% hydrochloric acid to afford 5-alkyl-3,6-dimethyluracils (alkyl: CH_3(XVI), C_2H_5(XVII), C_3H_7(XVIII), C_3H_5(XIX), C_4H_9(XX), C_5H_{11}(XXI), *iso*-C_5H_{11}(XXII)) with evolution of methanethiol (cf. Table V). Of these compounds, (XVI) and (XVIII) had already been synthesized by the methylation of 5, 6-dimethyluracil[10] and 6-methyl-5-propyluracil,[11] respectively. The present method, however, gave better yield.



2) Y. F. Chi, Y. S. Kao: J. Am. Chem. Soc., **58**, 769(1936).
3) B. Johnson, Bailey: *Ibid.*, **35**, 1010(1913).
4) Y. F. Chi: *Ibid.*, **60**, 1721(1938).
5) B. Johnson, A. Hill: *Ibid.*, **36**, 3681(1914).
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7) A. Jurand: Nature, **162**, 896(1948).
8) L. Mont: Gazz. chim. ital., **78**, 638(1948).
9) K. A. Jensen, K. Kjeruff-Jensen: Acta Pharmacol. Toxicol. **1**, 280(1945)(C. A. **40** 7386(1946)).
10) R. Behrend: Ann., **378**, 305(1911).
11) Yuoh Foung Chi, Shao Wei, Mei Seng Liang: J. Am. Chem. Soc., **61**, 3373(1939).

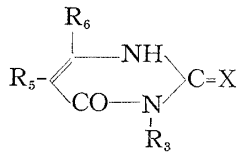
5-Alkyl-6-methyl-2-thiouracils (V to VIII) were then treated with 1 mole of dimethyl sulfate to obtain 5-alkyl-6-methyl-2-methylthio-4-pyrimidones (5-alkyl: C_4H_9(XXIII), *iso*-C_4H_9(XXIV), C_5H_{11}(XXV), *iso*-C_5H_{11}(XXVI)) (cf. Table VI). (XXIII) was treated with ethyl or allyl bromide, and then heated with 20% hydrochloric acid to give 3-alkyl-5-butyl-6-methyluracils (alkyl: C_2H_5(XXVII), *n*-C_3H_7(XXVIII)). Compounds (XXIII) to (XXVI) were treated with butyl bromide and similarly hydrolyzed to give 5-alkyl-3-butyl-6-methyluracils (alkyl: *n*-C_4H_9(XXIX), *iso*-C_4H_9(XXX), *n*-C_5H_{11}(XXXI), *iso*-C_5H_{11}(XXXII)).

In these reactions, 5-alkyl-6-methyluracils (alkyl: *n*-C_4H_9(XXXIII), *iso*-C_4H_9(XXXIV), *n*-C_5H_{11}(XXXV), *iso*-C_5H_{11}(XXXVI)), which had no butyl substituted in nitrogen at 3-position, were obtained as a by-product (cf. Table VII). It is assumed that these compounds were formed from 4-alkoxypyrimidine-type obtained as the intermediates during butylation of (XXIII to XXVI). These kinds of 5-alkyl-6-methyluracils (alkyl: CH_3(XXXVII),[2] C_2H_5(XXXVIII),[3] C_3H_7(XXXIX),[4] C_3H_5(XL)[5]) can also be prepared by boiling 5-alkyl-6-methyl-2-thiouracils (I to IV) with aqueous solution of monochloroacetic acid.

In order to synthesize the uracil derivatives with ethyl or propyl group in 6-position, ethyl 2-butyl-3-oxovalerate (XLI) and ethyl 2-butyl-3-oxocaproate (XLII), obtained from ethyl 3-oxovalerate and ethyl 3-oxocaproate, were condensed with thiourea to afford 6-alkyl-5-butyl-2-thioureas (alkyl: C_2H_5 (XLIII), *n*-C_3H_7(XLIV)). (XLIII) and (XLIV) were methylated with 2 moles of dimethyl sulfate similarly as already described and hydrolyzed directly with hydrochloric acid to give 6-alkyl-5-butyl-3-methyluracils (alkyl: C_2H_5(XLV), *n*-C_3H_7(XLVI)) (cf. Table V). By desulfurization of (XLIII) and (XLIV) on boiling with aqueous solution of monochloroacetic acid, 6-alkyl-5-butyluracils (alkyl: C_2H_5 (XLVII), C_3H_7(XLVIII)) were obtained.

The relationship between chemical structure and pharmacological activity is illustrated in Tables I to III. The strongest sedative action was observed when the alkyl groups, R_3

TABLE I. Acute Toxicity



Compound				LD_{50} (mg./10 g. mice, i. p.)	
X	R_3	R_5	R_6		
S	H	—	CH_3	3～2.5	R_5 (C_3H_5>CH_3, C_2H_5, *n*-C_3H_7)
S	H	*n*-C_4H_9	—	2.5～1.4	R_6 (*n*-C_3H_7>C_2H_5>CH_3)
O	—	*n*-C_4H_9	CH_3	1.8～0.8>	R_3 (C_3H_5>C_2H_5, *n*-C_4H_9)
O	H	—	CH_3	4～1.4	R_5 (CH_3, C_2H_5>C_3H_5>*n*-C_3H_7>*n*-C_4H_9)
O	CH_3	—	CH_3	2.4～0.8>	R_5 (CH_3>C_2H_5>*n*-C_3H_7>C_3H_5, *n*-C_4H_9)
O	C_4H_9	—	CH_3	1.5～0.5	R_5 (*n*-C_5H_{11}>*n*-C_4H_9>*iso*-C_4H_9, *iso*-C_5H_{11})
O	H	*n*-C_4H_9	—	1.4～1.0	R_6 (CH_3>C_2H_5>*n*-C_3H_7)
O	CH_3	*n*-C_4H_9	—	1.8～0.8	R_6 (*n*-C_3H_7>C_2H_5>CH_3)

TABLE II. Analgesic Effect

Compound				ED_{50} (modified Haffner method[12]) (mg.)	
X	R_3	R_5	R_6		
S	H	—	CH_3	1<	R_5 (CH_3, C_2H_5<*n*-C_3H_7<C_3H_5)
S	H	*n*-C_4H_9	—	1<	R_6 (*n*-C_3H_7<C_2H_5, CH_3)
O	—	*n*-C_4H_9	CH_3	0.5～1	R_3 (*n*-C_4H_9<C_2H_5<CH_3, C_3H_5)
O	H	—	CH_3	1<	R_5 (*n*-C_4H_9<*n*-C_3H_7, C_2H_5<CH_3<C_3H_5)
O	CH_3	—	CH_3	1<	R_5 (C_2H_5, *n*-C_3H_7<CH_3, C_3H_5<*n*-C_4H_9)
O	*n*-C_4H_9	—	CH_3	0.35～1	R_5 (*iso*-C_4H_9<*n*-C_4H_9, *iso*-C_5H_{11}, <*n*-C_5H_{11})
O	H	*n*-C_4H_9	—	0.8～1	R_6 (*n*-C_2H_7<C_2H_5, CH_3)
O	CH_3	*n*-C_4H_9	—	0.7～1	R_6 (*n*-C_2H_7, C_2H_5<CH_3)

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

TABLE III. Sedative Effect

Compound X	R_3	R_5	R_6	No. of hypnotized mice (No./10 mice)	(sample 1.5 mg. +cyclopane 0.25 mg./10 g. i. p.)
S	H	—	CH_3	3/0	R_5 (n-C_3H_7, C_2H_5 > CH_3, C_3H_5)
S	H	n-C_4H_9	—	3/0	R_6 (C_2H_5 > CH_3, n-C_3H_7)
O	—	n-C_4H_9	CH_3	9/4	R_3 (n-C_4H_9* > C_2H_5 > CH_3, C_3H_5)
O	H	—	CH_3	4/0	R_5 (n-C_4H_9 > n-C_3H_7, C_2H_5, C_3H_5, CH_3)
O	CH_3	—	CH_3	7/1	R_5 (n-C_3H_7 > n-C_4H_9 > C_2H_5, CH_3, C_3H_5)
O	n-C_4H_9	—	CH_3	10/5	R_5 (*iso*-C_4H_9** > n-C_4H_9* > *iso*-C_5H_{11})
O	H	n-C_4H_9	—	4/2	R_6 (CH_3 > C_2H_5 > n-C_3H_7)
O	CH_3	n-C_4H_9	—	9/4	R_6 (n-C_3H_7 > C_2H_5 > CH_3)

* 5 in 10 mice (sample 2 mg.)
** 8 in 10 mice (sample 2 mg.), 3 in 10 mice (sample 1 mg.).

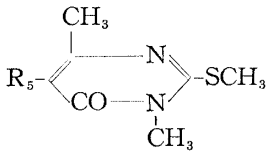
and R_5, were butyl and, as was expected, the compounds of this kind showed stronger sedative action than 5-dialkylamino-1,3,6-trialkyluracils. A more detailed examinations will be carried out by Dr. Fujimura and his co-workers in the near future.

The authors offer their cordial thanks to Dr. E. Miyamichi, President of the Gifu College of Pharmacy, and to Dr. K. Ogiu, Professor of Kyoto University, for their continued encouragements. Thanks are also due to Miss H. Iwata and others in the Analysis Center, University of Kyoto, for elemental analytical data.

Experimental

5-Alkyl-3,6-dimethyl-2-methylthio-4-pyrimidone (IX to XV)—To a mixture of 0.1 mole of 5-alkyl-6-methyl-2-thiouracil and 5% NaOH solution (0.3 mole NaOH), 0.3 mole of Me_2SO_4 was dropped gradually, the mixture was heated on a water bath for 30 mins., allowed to cool, and the separated mass was collected and recrystallized from MeOH (cf. Table IV).

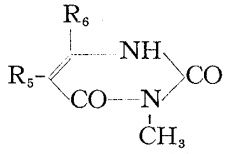
TABLE IV.



Compound No.	R_5	m.p.*(°C)	Yield(%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(IX)	CH_3	85~86	47	$C_8H_{12}ON_2S$	52.17	6.57	15.21	52.09	6.60	15.39
(X)	C_2H_5	114~116	50	$C_9H_{14}ON_2S$	54.54	7.12	14.13	54.34	7.30	14.15
(XI)	n-C_3H_7	85~86	68	$C_{10}H_{16}ON_2S$	56.57	7.60	13.20	56.15	7.58	13.41
(XII)	C_3H_5	86	70	$C_{10}H_{14}ON_2S$	57.11	6.71	13.33	57.05	6.60	13.44
(XIII)	n-C_4H_9	71	37	$C_{11}H_{18}ON_2S$	58.39	8.02	12.38	58.29	7.84	12.50
(XIV)	n-C_5H_{11}	56~56.5	77	$C_{12}H_{20}ON_2S$	59.98	8.39	11.66	60.26	8.18	11.71
(XV)	*iso*-C_5H_{11}	Oil, $b.p_9$ 164~166°	92	$C_{12}H_{20}ON_2S$	59.98	8.39	11.66	60.10	8.60	11.82

* colorless needles.

TABLE V.

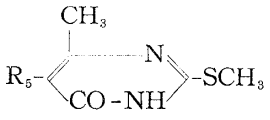


Compound No.	R_5	R_6	m. p.	Appearance	Yield(%)	Formula	Calcd. (%) C	H	N	Found. (%) C	H	N
(XVI)	CH_3	CH_3	220	Colorless needles	73	$C_7H_{10}O_2N_2$	54.53	6.54	18.17	54.34	6.72	18.35
(XVII)	C_2H_5	〃	229	〃	43	$C_8H_{12}O_2N_2$	57.13	7.19	16.66	56.65	7.11	16.86
(XVIII)	n-C_3H_7	〃	198	〃	60	$C_9H_{14}O_2N_2$	59.32	7.74	15.37	59.35	7.88	15.62
(XIX)	C_3H_5	〃	214	〃	30	$C_9H_{12}O_2N_2$	59.98	6.71	15.55	59.72	6.67	15.78
(XX)	n-C_4H_9	〃	134	〃	80	$C_{10}H_{16}O_2N_2$	61.20	8.22	14.28	61.22	8.26	14.31
(XXI)	n-C_5H_{11}	〃	139	〃	64	$C_{11}H_{18}O_2N_2$	62.83	8.63	13.32	62.91	8.66	13.51
(XXII)	*iso*-C_5H_{11}	〃	138	〃	64	$C_{11}H_{18}O_2N_2$	62.83	8.63	13.32	62.63	8.82	13.62
(XLV)	n-C_4H_9	C_2H_5	103~105	Colorless plates	55	$C_{11}H_{18}O_2N_2$	62.83	8.63	13.32	62.53	8.88	13.58
(XLVI)	n-C_4H_9	n-C_3H_7	94~96	Colorless needles	34	$C_{12}H_{20}O_2N_2$	64.25	8.99	12.49	63.74	8.98	12.67

5,6-Dialkyl-3-methyluracils (XVI to XXII, XLV, and XLVI)—A mixture of 0.1 mole of 5,6-dialkyl-3-methyl-2-methylthio-4-pyrimidone and 5 volumes of 20% HCl was boiled for 2~4 hrs., the separated mass was collected, washed with water, and recrystallized from MeOH and water (cf. Table V).

5-Alkyl-6-methyl-2-methylthio-4-pyrimidone (XXIII to XXVI)—To a mixture of 0.1 mole of 5-alkyl-6-methyl-2-thiouracil and 5% NaOH solution (0.12 mole NaOH), 1.2 moles of Me_2SO_4 was dropped gradually, at 50~60° during 5 hrs., and the mixture was allowed to cool. The separated mass was collected and recrystallized from MeOH (cf. Table VI).

TABLE VI.



Compound No.	R_5	m. p.*(°C)	Yield(%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(XXIII)	*n*-C_4H_9	158	57	$C_{10}H_{16}CN_2S$	56.59	7.60	13.20	56.86	7.74	13.31
(XXIV)	*iso*-C_4H_9	135~136	55	$C_{10}H_{16}ON_2S$	56.59	7.60	13.20	56.91	7.71	13.45
(XXV)	*n*-C_5H_{11}	154	74	$C_{11}H_{18}ON_2S$	58.39	8.02	12.38	58.12	8.24	12.50
(XXVI)	*iso*-C_5H_{11}	126.5	76	$C_{11}H_{18}ON_2S$	58.39	8.02	12.38	58.39	8.01	12.49

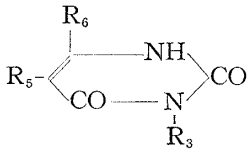
* Colorless needles

3,5-Dialkyl-6-methyluracils (XXVII to XXXII) and 5,6-Dialkyluracils (XXXIII to XXXVI, XLVII, and XLVIII)—(a) To a mixture of 0.1 mole of (XXIII) and 5% ethanolic KOH (KOH: 0.12 mole), 0.15 mole of alkyl halide was added and the whole was refluxed till the reaction mixture became neutral (8~10 hrs.). After the reaction, the inorganic salt was filtered off, EtOH was evaporated, the residue was boiled with 5 volumes of 20% HCl for 2 hrs, allowed to cool, and the separated mass was recraystallized from MeOH and water.

(b) To a mixture of 0.1 mole of sodium and 20 volumes of anhyd. EtOH, 0.1 mole of (XXIII~XXVI) was dissolved, refluxed with the addition of 0.15 to 0.2 mole of *n*-BuBr for 9~15 hrs., and then treated as in (a). The separated product was extracted with benzene and from the benzene solution, 5-alkyl-3-butyl-6-methyluracils (XXIX~XXXII), while from the benzene-insoluble part, 5-alkyl-6-methyluracils (XXXIII~XXXVI) were obtained, respectively. These compounds were recrystallized from MeOH and water.

(c) To 0.1 mole of 5,6-dialkyl-2-thiouracil, 5 volumes of water and 0.15 mole of monochloroacetic acid were added, boiled for 3~4 hrs., and the separated product was recrystallized from MeOH and water (cf. Table VII).

TABLE VII.



Compound No.	R_3	R_5	R_6	m.p. (°C)	Appearance	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
(XXVII)	C_2H_5	*n*-C_4H_9	CH_3	95~96	Colorless needles	24[a]	$C_{11}H_{18}O_2N_2$	62.83	8.63	13.22	62.80	8.82	13.41
(XXVIII)	C_3H_5	〃	〃	115	〃	17[a]	$C_{12}H_{18}O_2N_2$	64.84	8.16	12.60	65.04	8.26	12.68
(XXIX)	*n*-C_4H_9	〃	〃	77	〃	9[a] (53)[b]	$C_{13}H_{22}O_2N_2$	65.51	9.31	11.76	65.29	9.35	11.91
(XXX)	〃	*iso*-C_4H_9	〃	80~81*	〃	38[b]	$C_{13}H_{22}O_2N_2$	65.51	9.31	11.76	65.57	9.38	11.87
(XXXI)	〃	*n*-C_5H_{11}	〃	61~63**	〃	33[b]	$C_{14}H_{24}O_2N_2$	66.63	9.59	11.10	66.93	9.75	11.17
(XXXII)	〃	*iso*-C_5H_{11}	〃	107~108	〃	38[b]	$C_{14}H_{24}O_2N_2$	66.63	9.59	11.10	66.36	9.68	11.25
(XXXIII)	H	*n*-C_4H_9	〃	243	〃	7[b]	$C_9H_{14}O_2N_2$	59.32	7.74	15.37	59.50	7.70	15.61
(XXXIV)	〃	*iso*-C_4H_9	〃	244	〃	21[b]	$C_9H_{14}O_2N_2$	59.32	7.74	15.37	59.56	7.95	15.39
(XXXV)	〃	*n*-C_5H_{11}	〃	234	〃	20[b]	$C_{10}H_{16}O_2N_2$	61.20	8.22	14.28	61.22	8.42	14.41
(XXXVI)	〃	*iso*-C_5H_{11}	〃	247	〃	19[b]	$C_{10}H_{16}O_2N_2$	61.20	8.22	14.28	61.36	8.37	14.33
(XLVII)	〃	*n*-C_4H_9	C_2H_5	213	Colorless plates	57[c]	$C_{10}H_{16}O_2N_2$	61.20	8.22	14.28	60.92	8.35	14.35
(XLVIII)	〃	〃	*n*-C_3H_7	186	〃	48[c]	$C_{11}H_{18}O_2N_2$	62.83	8.63	13.32	62.30	8.44	13.52

a, b, c: Synthetic method (a), (b), or (c).
* b. p_6 203~205°
** b. p_{16} 230~240°

Ethyl 2-Butyl-3-oxovalerate (XLI)—Under stirring, 5.8 g. (0.25 mole) of Na was dissolved in 130 cc. of anhyd. EtOH, 35.5 g. (0.25 mole) of ethyl 3-oxovalerate was added, 38.4 g. (0.28 mole) of *n*-BuBr was dropped, and refluxed for 6 hrs. EtOH was evaporated, the residue was extracted with benzene, and distilled *in vacuo* to afford 28.5 g. (0.25 mole) of (XLI), b. p_6 103~110°.

Ethyl 2-Butyl-3-oxocaproate (XLII)—Starting from 40 g. (0.25 mole) of ethyl 3-oxocaproate, the same reaction as for (XLI) gave 31 g. (57%) of (XLII), b. p_{13} 126～133°.

5-Butyl-6-ethyl-2-thiouracil (XLIII)—To a mixture of 3.1 g. (0.135 mole) of Na and 60 cc. of anhyd. EtOH, 25 g. (0.125 mole) of (XLI) and 11 g. (0.145 mole) of thiourea were added, and the whole was refluxed for 10 hrs. EtOH was evaporated, water was added to the residue, acidified with AcOH, and the separated product was recrystallized from MeOH and water to give 13.7 g. (52%) of (XLIII), colorless plates, m. p. 185.5°. *Anal.* Calcd. for $C_{10}H_{16}ON_2S$: C, 56.57; H, 7.60; N, 13.20. Found: C, 56.86; H, 7.38; N, 13.38.

5-Butyl-6-propyl-2-thiouracil (XLIV)—Thirty-one g. (0.145 mole) of (XLII) was treated as for (XLIII) to afford 14.5 g. (44%) of (XLIV), colorless plates, m. p. 147～153°. *Anal.* Calcd. for $C_{11}H_{18}ON_2S$: C, 58.37; H, 8.02; N, 12.38. Found: C, 58.08; H, 8.00; N, 12.41.

Summary

Various kinds of 5, 6-dialkyl-2-thiouracils, 5, 6-dialkyluracils, and 3, 5, 6-trialkyluracils (alkyl: CH_3, C_2H_5, C_3H_7, C_4H_9, *iso*-C_4H_9, C_5H_{11}, *iso*-C_5H_{11}), which were analogous with barbital in their chemical structures, were synthesized systematically, and relationship between pharmacological action and chemical structure was investigated. The compounds of this series showed sedative rather than analgesic action, and 3, 6, 5-trialkyluracils (R_3, R_5: C_4H_9, R_6: CH_3) showed a comparatively strong sedative action.

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96. Eiji Ochiai und Takenari Nakagome: Über die Umlagerung von 5-Nitroisochinolin-N-Oxyd mittels Tosylchlorids.[1]

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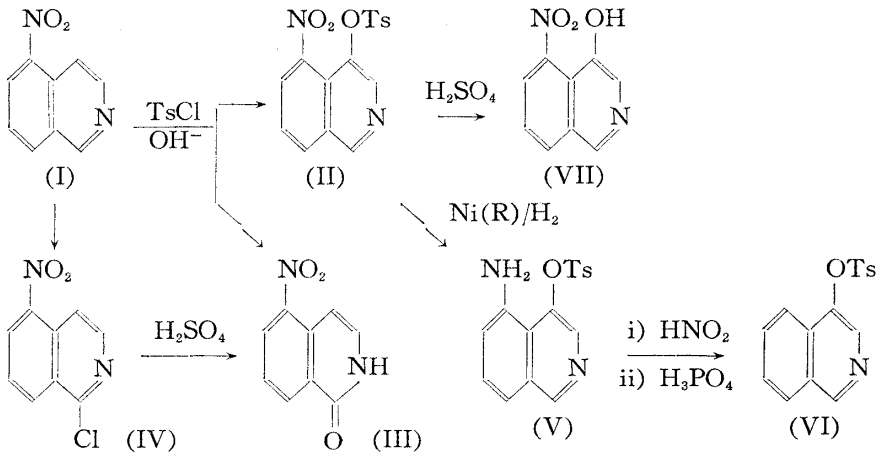
Es wurde schon gezeigt, dass Isochinolin-N-oxyd beim Behandeln mit Tosylchlorid nach Schotten-Baumann in 4-Tosyloxyisochinolin übergeht und daneben eine kleine Menge Isocarbostyril ergibt.[2] Wir haben nun festgestellt, dass sich 5-Nitroisochinolin-N-oxyd (I) gegen Tosylchlorid ganz analog wie beim Isochinolin-N-oxyd verhält. Es entstand dabei nämlich 4-Tosyloxy-5-nitroisochinolin (II) und 5-Nitroisocarbostyril (III) mit der Ausbeute von 50～60% und 15～40% bzw. der Theorie. (III) wurde mit dem durch Verseifen von 1-Chlor-5-nitroisochinolin (IV) mit verd. Schwefelsäure erhaltenen Präparat identfiziert. Die Konstitution von (II) wurde durch Überführung in 4-Tosyloxyisochinolin (VI) festgestellt. (II) wurde nämlich durch katalytische Reduktion in das entsprechende Aminoderivat (V) übergeführt



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1) CXXVI. Mitt. über "Polarisation der heterozyklischen Ringe mit aromatischem Charakter."

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