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Pyrimidine Derivatives and Related Compounds. XXII.[1] Synthesis and Pharmacological Properties of 7-Deazaxanthine Derivatives

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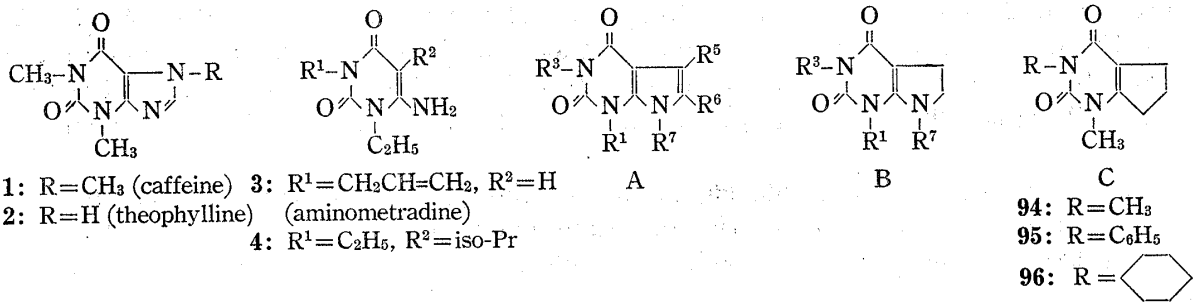
For investigation of the structure-activity relationship of xanthine derivatives, 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (A), which belong to 7-deazaxanthine derivatives, were prepared from the corresponding 6-aminouracils and chloroacetaldehyde, and then were catalytically reduced to give 2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]-pyrimidines (B). A new method for synthesis of compounds (A) was found by heating 6-hydrazinouracil derivatives with aldehydes or ketones.

Diuretic, cardiac, and central nervous system stimulating activities of compounds (A and B) were tested to be compared with those of caffeine. Compounds (A and B) showed caffeine-like activities.

Xanthine derivatives such as caffeine (**1**) and theophylline (**2**) have been used as a diuretic cardiotonica for a long time. 6-Aminouracil derivatives such as 3-allyl-6-amino-1-ethyluracil (**3**: Aminometradine)[3] and 6-amino-1,3-diethyl-5-isopropyluracil (**4**)[4] had once been used as a synthetic diuretic drug.

In the present paper, 7-deazaxanthines such as 2,4-dioxo-1,2,3,4-tetrahydropyrrolo-[2,3-*d*]pyrimidines (A) and 2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidines (B) were synthesized and their diuretic, cardiac, and central nervous system (CNS) stimulating activities were tested to investigate their structure-activity relationship. It is because theoretically the chemical structares of A are derived by a replacement of the nitrogen atom at 7-position of xanthine ring with a methine group and those of B are derived by a ring-closure between 6-amino group and 5-alkyl group of 5-alkyl-6-aminouracil compounds.

In this connection, diuretic, cardiac, and CNS stimulating activities of 2,4-dioxo-1,2,3,4,6,7-hexahydro-5H-cyclopenta[*d*]pyrimidines (C),[5] namely, those of 7,9-dideaza-8,9-dihydroxanthine derivatives, were also tested in order to research a role of the nitrogen atom at 9-position of 7-deazaxanthines and the 6-amino group of uracils on their pharmacological properties.



1: R=CH_3 (caffeine) **3**: R^1=$CH_2CH{=}CH_2$, R^2=H A B C

2: R=H (theophylline) (aminometradine)

4: R^1=C_2H_5, R^2=iso-Pr

94: R=CH_3

95: R=C_6H_5

96: R=

Chart 1

1) Part XXI: S. Senda, K. Hirota, and O. Otani, *Yakugaku Zasshi*, **94**, 571 (1974).
2) Location: *492-36, Mitahora, Gifu.*
3) V. Papesch and E.F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951).
4) W. Stoll, Ger. Patent 938846 (1956) [*Chem. Abstr.*, **53**, 6273 (1959)]; W. Stoll, Jap. Patent 244973 (1958).
5) S. Senda, K. Hirota, and K. Maeno, *Chem. Pharm. Bull.* (Tokyo), **21**, 1894 (1973).

Chemistry

Up to now, some syntheses of 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines or 7-deazaxanthines have been reported.[6] According to the method of Noell and Robins,[6b] 6-aminouracils (I) were heated with chloroacetaldehyde in the presence of sodium acetate so that a ring closure took place to give 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (II: **5**—**20** in Table I). Methylation of II with dimethyl sulfate in an aqueous solution of sodium hydroxide gave 7-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (III: **21**—**27** in Table I). When these pyrrolo[2,3-*d*]pyrimidine derivatives (II and III) were reduced in ethanol at 50—60 atm and 100—120° in the presence of Pd-C, 2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidines (IV: **28**—**42** in Table II) were prepared. The 1-allyl groups of **13** and **14** were further reduced by the above mentioned catalytic reduction to give the corresponding 1-propyl compounds (**34**, **35**). 1-Benzyl-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**17**) was reduced and debenzylated under the same conditions described above to yield **29**.

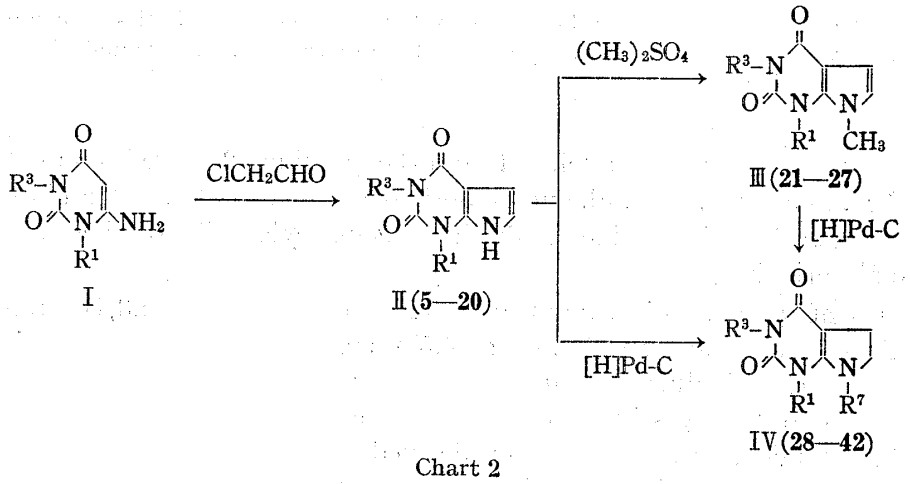


Chart 2

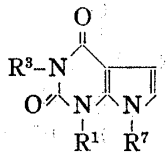
Then the authors investigated[7] a new method for synthesis of 5-substituted or 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine derivatives (VIII) by heating 6-hydrazinouracil derivatives (V: **43**—**46**) with aldehydes or ketones. Thus 1,3-disubstituted 6-hydrazinouracil (V) was refluxed in ethanol or xylene with acetaldehyde, propionaldehyde, butyraldehyde, valeraldehyde or methyl ethyl ketone and the resulting hydrazones (VI: **47**—**59** in Table III) were refluxed for 2—3 hours in ethylene glycol or tetraline to give 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (VII: **60**—**64**, **76**, **82** in Table IV) with an evolution of ammonia (Method A). When 6-hydrazinouracil derivatives (V: **43**—**46**) were refluxed in ethylene glycol or tetraline with aldehydes or ketones, the desired products (VII: **63**—**90** in Table IV) were obtained without isolation of the intermediates (VI) (Method B).

Pyrrolo[2,3-*d*]pyrimidines (**89**, **90**) having a ethoxycarbonylmethyl group at 5-position were hydrolyzed in an aqueous solution of sodium hydroxide to give 5-carboxymethyl derivatives (**91**, **92**), and the hydrolysis of **89** in hydrochloric acid gave the decarboxylated compound (**64**).

6) *a*) R.K. Robins and G.H. Hitchings, Brit. Patent 812366 (1959) [*Chem. Abstr.*, **54**, 592 (1960)]; *b*) C.W. Noell and R.K. Robins, *J. Heterocycl. Chem.*, **1**, 34 (1964); *c*) E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, **30**, 655 (1965); *d*) H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972).

7) A part of this work has been reported in a communication: S. Senda and K. Hirota, *Chemistry Lett.*, 1972, 367.

TABLE I. 1,3,7-Trisubstituted 2,4-Dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines

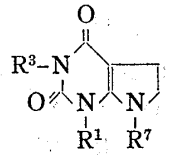


Compd. No.	R^1	R^3	R^7	mp (°C) Recryst. solvent	Yield (%)	UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-3}$)	Formula		Analysis (%) C	H	N
5	H	H	H	>300[a] DMF	53	[b]	$C_6H_5O_2N_3$	Calcd.	47.68	3.34	27.81
								Found	47.44	3.51	27.49
6	Me	Me	H	300[c] H_2O	54	243(6.7) 275(6.7)	$C_8H_9O_2N_3$	Calcd.	53.62	5.06	23.45
								Found	53.89	5.22	23.68
7	Et	H	H	>300 H_2O	65	241(7.5) 274(6.7)	$C_8H_9O_2N_3$	Calcd.	53.62	5.06	23.45
								Found	53.69	5.28	23.30
8	Et	Me	H	234—236 H_2O	56	243(6.9) 274(6.9)	$C_9H_{11}O_2N_3$	Calcd.	55.95	5.74	21.75
								Found	56.03	5.81	21.97
9	Et	Et	H	203 H_2O	58	243(7.7) 275(7.5)	$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
								Found	57.86	6.38	20.44
10	*n*-Pr	H	H	295 EtOH	70	241(8.1) 274(7.4)	$C_9H_{11}O_2N_3$	Calcd.	55.95	5.74	21.75
								Found	56.02	5.71	21.64
11	*n*-Pr	Me	H	207—209 H_2O	65	243(6.0) 274(6.1)	$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
								Found	58.07	6.13	20.55
12[d]	*n*-Pr	*n*-Pr	H								
13	$CH_2CH=CH_2$	H	H	>300 EtOH	58	241(6.4) 274(6.3)	$C_9H_9O_2N_3$	Calcd.	56.54	4.75	21.98
								Found	56.71	4.89	21.86
14	$CH_2CH=CH_2$	Me	H	219 AcOEt	51	243(6.9) 274(7.4)	$C_{10}H_{11}O_2N_3$	Calcd.	58.53	5.40	20.48
								Found	58.79	5.69	20.40
15	*n*-Bu	H	H	275 EtOH–H_2O	11	241(7.2) 275(6.6)	$C_{10}H_{13}O_2N_3 \cdot H_2O$[e]	Calcd.	53.32	6.71	18.66
								Found	53.22	6.66	19.11
16	*n*-Bu	Me	H	165 AcOEt	17	243(6.2) 274(6.3)	$C_{11}H_{15}O_2N_3$	Calcd.	59.71	6.83	18.99
								Found	59.99	6.79	18.76
17	CH_2Ph	Me	H	196 EtOH–H_2O	42	244(6.1) 276(7.4)	$C_{14}H_{13}O_2N_3$	Calcd.	65.87	5.13	16.42
								Found	66.04	5.38	16.68
18	Ph	H	H	>300 EtOH–H_2O	36	242(6.7) 276(6.5)	$C_{12}H_9O_2N_3$	Calcd.	63.43	3.99	18.49
								Found	63.30	4.38	18.04
19	Ph	Me	H	280 MeOH–H_2O	82	240(5.0) 278(6.4)	$C_{13}H_{11}O_2N_3$	Calcd.	64.72	4.60	17.43
								Found	64.74	4.79	17.63
20	*p*-MePh	Me	H	235 H_2O	31	239(7.4) 278(9.1)	$C_{14}H_{13}O_2N_3$	Calcd.	65.87	5.13	16.46
								Found	65.51	5.32	16.22
21	Me	Me	Me	265—266 EtOH	68	247(5.5) 277(5.1)	$C_9H_{11}O_2N_3$	Calcd.	55.95	5.74	21.75
								Found	55.91	5.74	21.90
22	Et	Me	Me	215—217 H_2O	75	248(7.4) 277(6.8)	$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
								Found	57.99	6.45	20.43
23	Et	Et	Me	160—163 H_2O	71	248(7.3) 277(6.8)	$C_{11}H_{15}O_2N_3$	Calcd.	59.71	6.83	18.99
								Found	59.81	7.03	19.02
24	$CH_2CH=CH_2$	Me	Me	162 H_2O	78	248(6.4) 277(6.3)	$C_{11}H_{13}O_2N_3$	Calcd.	60.26	5.98	19.15
								Found	60.35	6.10	19.13
25	CH_2Ph	Me	Me	190—191 EtOH–H_2O	69	247(6.0) 278(6.6)	$C_{15}H_{15}O_2N_3$	Calcd.	66.90	5.61	15.61
								Found	66.62	5.88	15.66
26	Ph	Me	Me	277 MeOH	74	246(5.2) 279(5.8)	$C_{14}H_{13}O_2N_3$	Calcd.	65.87	5.13	16.46
								Found	65.95	5.34	16.50
27	*p*-MePh	Me	Me	276 EtOH–H_2O	77	243(7.2) 278(8.4)	$C_{15}H_{15}O_2N_3$	Calcd.	66.90	5.61	15.61
								Found	66.97	5.83	15.74

Ph=phenyl

a) lit.[6a] mp 330° *b*) J. Davoll, *J. Chem. Soc.*, **1960**, 131, UV $\lambda_{max}^{H_2O\ (pH\ 6.8)}$ mμ ($\varepsilon \times 10^{-3}$): 243 (7.1), 275 (6.3) *c*) lit.[6b] mp 292—294° *d*) This compound was not purified and reduced directly to give **36** (in Table II). *e*) H_2O was confirmed by IR spectra.

TABLE II. 1,3,7-Trisubstituted 2,4-Dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidines



Compd. No.	R^1	R^3	R^7	mp (°C) Recryst. solvent	Yield (%)	UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-3}$)	Formula		Analysis (%) C	H	N
28	H	H	H	>300[a] EtOH	13	239(5.3) 280(12.2)	$C_6H_7O_2N_3$	Calcd.	47.05	4.61	27.44
								Found	46.83	4.59	27.11
29	H	Me	H	285—286 H_2O	60	243(1.5) 282(13.0)	$C_7H_9O_2N_3$ H_2O[b]	Calcd.	45.40	5.99	22.65
								Found	45.33	5.96	22.68
30	Me	Me	H	283 EtOH	66	243(2.1) 284(17.9)	$C_8H_{11}O_2N_3$	Calcd.	53.03	6.12	23.19
								Found	53.09	6.21	23.08
31	Et	H	H	>300 H_2O	50	236(3.2) 284(17.8)	$C_8H_{11}O_2N_3$	Calcd.	53.03	6.12	23.19
								Found	53.25	6.31	23.33
32	Et	Me	H	258 H_2O	74	243(2.0) 284(17.2)	$C_9H_{13}O_2N_3$	Calcd.	55.37	6.71	21.53
								Found	55.61	6.49	21.66
33	Et	Et	H	191—192 H_2O	64	240(2.6) 285(17.5)	$C_{10}H_{15}O_2N_3$	Calcd.	57.40	7.23	20.08
								Found	57.69	7.30	20.18
34	*n*-Pr	H	H	285—287 H_2O	51 (65)[c]	236(2.8) 285(16.8)	$C_9H_{13}O_2N_3$	Calcd.	55.37	6.71	21.53
								Found	55.24	6.68	21.56
35	*n*-Pr	Me	H	181—182 H_2O	60 (65)[d]	238(2.8) 284(17.8)	$C_{10}H_{15}O_2N_3$	Calcd.	57.40	7.23	20.08
								Found	57.34	7.07	20.29
36	*n*-Pr	*n*-Pr	H	170—172 AcOEt	26	244(2.0) 286(16.8)	$C_{12}H_{19}O_2N_3$	Calcd.	60.73	8.02	17.71
								Found	60.82	8.04	17.65
37	*n*-Bu	H	H	243—244 H_2O	76	233(2.4) 283(16.5)	$C_{10}H_{15}O_2N_3 \cdot 1/2H_2O$[b]	Calcd.	55.03	7.39	19.25
								Found	55.02	7.36	19.10
38	*n*-Bu	Me	H	151—152 H_2O	76	243(1.9) 285(15.4)	$C_{11}H_{17}O_2N_3$	Calcd.	59.17	7.68	18.82
								Found	59.48	7.87	18.55
39	Ph	H	H	292—293 H_2O	74	287(19.4)	$C_{12}H_{11}O_2N_3$	Calcd.	62.87	4.84	18.33
								Found	62.86	5.04	18.31
40	Ph	Me	H	270—272 EtOH	75	287(17.8)	$C_{13}H_{13}O_2N_3$	Calcd.	64.18	5.39	17.28
								Found	64.15	5.21	17.36
41	*p*-MePh	Me	H	228—229 H_2O	40	286(19.9)	$C_{14}H_{15}O_2N_3$	Calcd.	65.35	5.88	16.33
								Found	65.36	5.94	16.53
42	Ph	Me	Me	205 H_2O	60	298(17.8)	$C_{14}H_{15}O_2N_3$	Calcd.	65.35	5.88	16.33
								Found	65.30	5.74	16.54

Ph=phenyl
a) V. G. Granik and R. G. Glushkov, *Khim.-Farm. Zh.*, **1** (5), 16 (1967) [*Chem. Abstr.*, **68**, 12941 (1968)], mp >300°
b) H_2O was confirmed by IR spectra. *c*) prepared from **13** *d*) prepared from 14

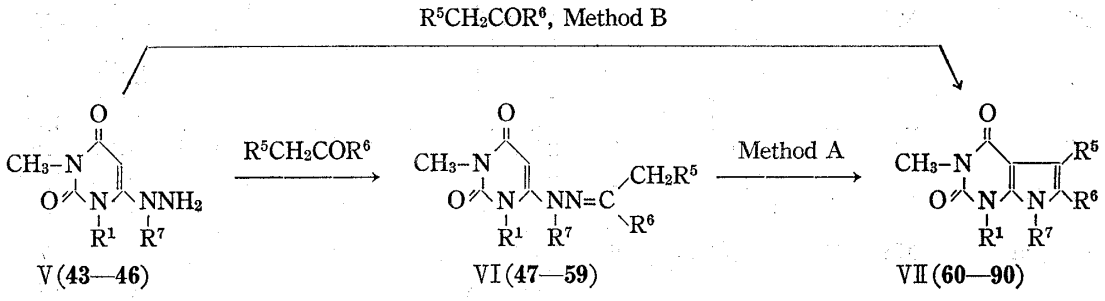
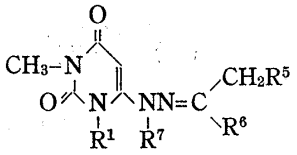


Chart 3

The 5,6-double bond of such 5,6-disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]-pyrimidines (VII) were generally resistant to catalytic reductions except **64** which was reduced to give 1,3,5,6-tetramethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (**93**).

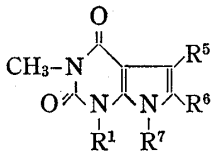
TABLE III. 1-Substituted 6-Alkylenehydrazino-3-methyluracils



Compd. No.	R^1	R^5	R^6	R^7	mp (°C) Recryst. solvent	Yield (%)	Formula		Analysis (%) C	H	N
47	Me	Me	H	H	203 EtOH	86	$C_9H_{14}O_2N_4$	Calcd.	51.42	6.71	26.65
								Found	51.26	6.84	26.55
48	Me	Et	H	H	179 EtOH	83	$C_{10}H_{16}O_2N_4$	Calcd.	53.55	7.16	24.99
								Found	53.34	6.96	25.17
49	Me	*n*-Bu	H	H	158 AcOEt	83	$C_{12}H_{20}O_2N_4$	Calcd.	57.11	7.99	22.21
								Found	57.26	8.12	22.07
50	Me	Ph	H	H	168 AcOEt	91	$C_{14}H_{16}O_2N_4$	Calcd.	61.75	5.92	20.58
								Found	61.92	6.14	20.81
51	Me	H	Me	H	146 xylene	87	$C_9H_{14}O_2N_4$	Calcd.	51.42	6.71	26.65
								Found	51.37	6.79	26.76
52	Me	Me	Me	H	132—134 AcOEt	61	$C_{10}H_{16}O_2N_4$	Calcd.	53.55	7.19	24.99
								Found	53.47	7.00	25.05
53	Me	CH_2COOMe	Me	H	140 ligroin	63	$C_{12}H_{18}O_4N_4$	Calcd.	51.05	6.43	19.85
								Found	51.34	6.62	20.00
54	Me	Me	Me	Me	78—79 PE[a]	41	$C_{11}H_{18}O_2N_4$	Calcd.	55.44	7.61	23.52
								Found	55.42	7.63	23.19
55	Ph	Et	Me	H	107—108 ligroin	42	$C_{16}H_{20}O_2N_4$	Calcd.	63.98	6.71	18.65
								Found	64.08	6.78	18.89
56	Me	H	H	H	210—212 MeOH	82	$C_8H_{12}O_2N_4$	Calcd.	48.97	6.17	28.56
								Found	48.80	6.31	28.53
57	Me	H	Ph	H	203 EtOH	78	$C_{14}H_{16}O_2N_4$	Calcd.	61.75	5.92	20.58
								Found	61.78	6.25	20.76
58	Me	COOEt	Me	H	119—120 BuOH	85	$C_{12}H_{18}O_4N_4$	Calcd.	51.05	6.43	19.85
								Found	51.27	6.53	19.77
59	Ph	$CH_2NCH_2CH_2$ (Me)	H		196 AcOEt	81	$C_{17}H_{21}O_2N_5$	Calcd.	62.36	6.47	21.39
								Found	62.29	6.41	21.20

Ph=phenyl
a) PE: petroleum ether (bp 50—90°)

TABLE IV. 1,5,6,7-Tetrasubstituted 3-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines



Compd. No.	R^1	R^5	R^6	R^7	mp (°C) Recryst. solvent	Yield (%) Method[a] (A)	(B)	Formula		Analysis (%) C	H	N
60	Me	H	Me	H	>300 EtOH	13(T)		$C_9H_{11}O_2N_3$	Calcd.	55.95	5.74	21.75
									Found	55.83	5.89	21.69
61	Me	Me	H	H	>300 EtOH	21(E)		$C_9H_{11}O_2N_3$	Calcd.	55.95	5.74	21.75
									Found	56.09	5.92	21.84
62	Me	Et	H	H	270—272 EtOH	30(E)		$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
									Found	57.68	6.55	20.36
63	Me	*n*-Bu	H	H	186—187 AcOEt	29(E)	41(T)	$C_{12}H_{17}O_2N_3$	Calcd.	61.25	7.28	17.86
									Found	61.49	7.35	17.83
64	Me	Me	Me	H	>300 EtOH	72(E)	72(E) 81(T)	$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
									Found	57.56	6.69	20.38

Compd. No.	R^1	R^5	R^6	R^7	mp (°C) Recryst. solvent	Yield (%) Method[a] (A)	(B)	Formula		Analysis (%) C	H	N
65	Me	Me	Me	Me	233—234 AcOEt		59(E)	$C_{11}H_{15}O_2N_3$	Calcd.	59.71	6.83	18.99
									Found	59.91	6.95	19.16
66	Me	Et	Me	H	287 AcOEt		68(E)	$C_{11}H_{15}O_2N_3$	Calcd.	59.71	6.83	18.99
									Found	59.70	6.95	19.02
67	Me	iso-Pr	Me	H	251—252 AcOEt		34(E)	$C_{12}H_{17}O_2N_3$	Calcd.	61.25	7.28	17.86
									Found	61.40	7.27	17.96
68	Me	*n*-Bu	Me	H	249 AcOEt		48(E)	$C_{13}H_{19}O_2N_3$	Calcd.	62.62	7.68	16.86
									Found	62.65	7.70	17.06
69	Me	iso-Bu	Me	H	271 AcOEt		62(E)	$C_{13}H_{19}O_2N_3$	Calcd.	62.62	7.68	16.86
									Found	62.79	7.82	16.98
70	Me	*n*-Am	Me	H	231 AcOEt		65(E)	$C_{14}H_{21}O_2N_3$	Calcd.	63.85	8.04	15.92
									Found	63.72	8.24	16.06
71	Me	Me	Et	H	268 EtOH–H_2O		72(E)	$C_{11}H_{15}O_2N_3$	Calcd.	59.71	6.83	18.99
									Found	59.86	6.97	19.02
72	Me	Et	*n*-Pr	H	217—218 AcOEt		76(E)	$C_{13}H_{19}O_2N_3$	Calcd.	62.62	7.68	16.86
									Found	62.76	7.76	17.04
73	Me	Me	Ph	H	285 EtOH		63(E)	$C_{15}H_{15}O_2N_3$	Calcd.	66.90	5.61	15.61
									Found	66.89	5.90	15.69
74	Me	Et	Ph	H	211 EtOH–H_2O		49(E)	$C_{16}H_{17}O_2N_3 \cdot H_2O$[b]	Calcd.	63.77	6.36	13.95
									Found	64.21	6.29	14.30
75	Me	*n*-Bu	Ph	H	200 EtOH–H_2O		42(E)	$C_{18}H_{21}O_2N_3$	Calcd.	69.43	6.80	13.50
									Found	69.39	6.90	13.47
76	Me	Ph	H	H	287 THF–ether	47(E)	54(T)	$C_{14}H_{13}O_2N_3$	Calcd.	65.87	5.13	16.46
									Found	65.81	5.34	16.31
77	Me	Ph	Ph	H	>300 EtOH		6(E)	$C_{20}H_{17}O_2N_3$	Calcd.	72.49	5.17	12.63
									Found	72.61	5.25	12.61
78	Me	$(CH_2)_3$		H	>300 EtOH–H_2O		78(E)	$C_{11}H_{13}O_2N_3$	Calcd.	60.26	5.98	19.15
									Found	60.18	5.76	19.33
79	Me	$(CH_2)_4$		H	>300 EtOH		86(E) 86(T)	$C_{12}H_{15}O_2N_3$	Calcd.	61.78	6.48	18.02
									Found	61.59	6.33	17.73
80	Ph	Me	Me	H	282 EtOH–H_2O		35(E) 95(T)	$C_{15}H_{15}O_2N_3$	Calcd.	66.90	5.61	15.61
									Found	66.64	5.53	65.67
81	Ph	Me	Me	Me	271 EtOH		65(T)	$C_{16}H_{17}O_2N_3$	Calcd.	67.82	6.05	14.83
									Found	67.86	6.08	14.70
82	Ph	Et	Me	H	218 EtOH–H_2O	43(T)	13(E)	$C_{16}H_{17}O_2N_3$	Calcd.	67.82	6.05	14.83
									Found	67.84	6.24	14.90
83	Ph	*n*-Bu	Me	H	214—215 EtOH–H_2O		42(E) 73(T)	$C_{18}H_{21}O_2N_3$	Calcd.	69.43	6.80	13.50
									Found	69.52	6.98	13.40
84	Ph	*n*-Bu	Me	Me	160 EtOH–H_2O		22(E)	$C_{19}H_{23}O_2N_3$	Calcd.	70.13	7.12	12.91
									Found	69.81	7.24	12.77
85	Ph	iso-Bu	Me	H	206 EtOH–H_2O		70(T)	$C_{18}H_{21}O_2N_3$	Calcd.	69.43	6.80	13.50
									Found	69.44	6.96	13.44
86	Ph	*n*-Am	Me	H	192 EtOH–H_2O		83(T)	$C_{19}H_{23}O_2N_3$	Calcd.	70.13	7.12	12.91
									Found	70.23	7.34	12.90
87	Ph	$(CH_2)_3$		H	>300 EtOH		94(T)	$C_{16}H_{15}O_2N_3$	Calcd.	68.31	5.38	14.94
									Found	67.73	5.42	14.93
88	Ph	$(CH_2)_4$		H	>300 EtOH		85(T)	$C_{17}H_{17}O_2N_3$	Calcd.	69.13	5.80	14.23
									Found	68.79	6.06	14.15
89	Me	CH_2-COOMe	Me	H	266 MeOH		53(T)	$C_{12}H_{15}O_4N_3$	Calcd.	54.33	5.70	15.84
									Found	54.41	5.95	16.10
90	Ph	CH_2-COOMe	Me	H	>300 MeOH		74(T)	$C_{17}H_{17}O_4N_3$	Calcd.	62.37	5.24	12.84
									Found	62.45	5.41	12.60
91	Me	CH_2-COOH	Me	H	284 H_2O		39	$C_{11}H_{13}O_4N_3$	Calcd.	52.58	5.22	16.73
									Found	52.31	5.33	16.59
92	Ph	CH_2-COOH	Me	H	242 EtOH–H_2O		92	$C_{16}H_{15}O_4N_3$	Calcd.	61.33	4.83	13.41
									Found	61.43	5.06	13.69

Ph=phenyl

a) reaction solvent: T, tetralin; E, ethylene glycol b) H_2O was confirmed by IR spectra.

Pharmacology

Diuretic activity (weight of urine for 3 hours in mice,[8] cardiac activity (chronotropic and inotropic),[9] CNS stimulating activity (spontaneous motor activity[10] and fighting activity[11]), and acute toxicity (LD_{50}) were tested concerning the resulting compounds. The results were given in Table V.

Table V. Diuretic, Cardiac, and CNS Stimulating Activities and Acute Toxicity of 7-Deazaxanthine Derivatives

Group	Compd. No.	Diuretic[a] activity		Cardiac[b] activities		CNS[c] stimulating activities		Acute toxicity[f] LD_{50} (mg/kg)
		100 mg/kg	200 mg/kg	Chronotropic	Inotropic	Spontaneous[d] motor activity	Fighting[e] activity	
A	**6**		2.4			##		168(119— 237)
	9	2.0	2.1	##	##	—	—	283(174— 461)
	14		1.2			—	—	476(338— 671)
	19		1.8					>800
	21		1.9				+	238(170— 336)
	23	1.3	2.7	##	##			200(134— 298)
	24		1.7				—	400(268— 596)
	26		1.4					>800
	64	2.3	3.2	+	+	##		400(245— 652)
	68	2.3	2.1			##	##	336(238— 474)
	73		1.5			+	##	>1600
	75		1.5	+	+		##	951(674—1341)
	80		1.1	—		—		1130
	83		1.2	—	—			>1600
	84		1.5					1130
	89		1.9					>1600
	90		0.7				+	>1600
	91		1.2				+	>1600
	92		0.8	+			##	>1600
B	**30**		2.6			+	##	336(238— 474)
	33	2.1	2.0	+	+	—		238(175— 231)
	40		1.5					>800
C	**94**		1.2					424(354— 508)
	95		0.9					692(633— 757)
	96		1.0					308(278— 343)
Caffeine		2.4	2.5	+	+	##	##	168(119— 237)
Theophylline		3.4	3.3	+		##	##	238(190— 336)
Methamphetamine						## (1 mg)	## (5 mg)	15

a) Weight of urine for 3 hours in mice (*p.o.*) compared with control.[9] *b*) The effect on isolated guinea pig heart perfused by the Langendorff's method.[9] *c*) 50 mg/kg in mice (*i.p.*) *d*) postexploratory activity by the Animex apparatus (A.B. Farad Co.)[10] *e*) followed the method of Tedeschi[11] *f*) in mice (*i.p.*)

As to caffeine-like activities, **6**, **9**, **23**, **30**, **64**, and **68** showed the same or more diuretic activity than that of caffeine, **9** and **23** were more activity than caffeine in cardiac activity, and **68** and **73** showed the most CNS stimulating activity. Compounds (**64**—**92**) having substituents at 5- and 6-positions generally showed low toxicity. Pharmacological activities of A and B groups were nearly parallel. Namely, a double bond between 5- and 6-positions

8) T. Mineshita, S. Matsumura, S. Kimoto, and O. Uno, *Pharmacometrics*, **4**, 33 (1970).
9) L. Ther, "Pharmakologische Methoden," Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1949, p. 170.
10) T.H. Svensson and G. Thieme, *Psychopharmacologia*, **14**, 157 (1969); *idem*, *J. Pharm. Pharmacol.*, **22**, 639 (1970).
11) R.E. Tedeschi, *J. Pharmacol. Exptl. Therap.*, **125**, 28 (1959); G. Chen, *Arch. int. Pharmacodyn.*, **142**, 30 (1963).

of compounds (A) had almost no effect on the pharmacological activities. In contrast to compounds of A and B groups, 2,4-dioxo-1,2,3,4,6,7-hexahydro-5H-cyclopenta[*d*]pyrimidines (C) did not show diuretic, cardiac, and CNS stimulating activities at all but weak analgetic activity like that of 1,3-disubstituted 5,6-dialkyluracils.[5,12] It indicates that the nitrogen atom at 7-position of compounds (A and B) plays an important role in showing caffeine-like pharmacological activities.

Experimental

1,3-Disubstituted 2,4-Dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (II) (5—20 in Table I)——In 15 ml of H_2O were dissolved 8.2 g of AcONa and 39.3 g of 30% chloroacetaldehyde. The mixture was gradually added to a suspended solution (temperature 70—75°) consisting of 0.1 mole of 1,3-disubstituted 6-aminouracils (I)[3] and 8.2 g of AcONa in 50—100 ml of H_2O. The mixture was stirred for a few minutes at 80°, and cooled on standing. The resulting precipitate was filtered, washed with H_2O, and recrystallized.

1,3-Disubstituted 7-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (III) (21—27 in Table I)——1,3-Disubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (II: **6**, **8**, **9**, **14**, **17**, **19**, or **20**) (0.01 mole) was dissolved in 10 ml of NaOH solution and the mixture was stirred for 1 hr with 1.5 g of Me_2SO_4 at 30—40°. The resulting crude crystals were filtered, washed with H_2O, and recrystallized.

1,3,7-Trisubstituted 2,4-Dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidines (IV) (28—42 in Table II)——A solution of 1,3,7-trisubstituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (III: **5**—**20**, or **26**) (0.01 mole) in EtOH (120 ml) was hydrogenated in an autoclave at 100—120° and 50—60 atm using Pd-C (0.5 g) as a catalyst. After 8—10 hr, the reaction solution was cooled to 80°, and activated carbon was added thereto. The catalyst was removed by filtration and washed well with EtOH. The filtrate and washings were collected and evaporated to dryness under reduced pressure. A small amount of acetone was added to the residue, the resulting crude crystals were filtered, washed with ether and recrystallized.

6-Hydrazino-3-methyl-1-phenyluracil (45)——To a solution of 6-chloro-3-methyl-1-phenyluracil[13] (30 g) in 50 ml of iso-PrOH was added 25 ml of 100% $NH_2NH_2 \cdot H_2O$, the mixture was refluxed for 30 min. After cooling, the precipitate was filtered, washed with H_2O, and recrystallized from MeOH to give 17.8 g of colorless crystals, mp 230—232°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_4$: C, 56.89; H, 5.21; N, 24.13. Found: C, 57.06; H, 5.28; N, 24.39.

3-Methyl-6-(1-methylhydrazino)-1-phenyluracil (46)——To a solution of 6-chloro-3-methyl-1-phenyluracil (4.7 g, 0.02 mole) in 10 ml of iso-PrOH was added 5 ml of methylhydrazine and the mixture was refluxed for 5 min. Solvent was evaporated *in vacuo* and the residue was treated with H_2O. The precipitate was filtered, washed with H_2O, and recrystallized from AcOEt to give 3.2 g (62%) of colorless prisms, mp 146°. *Anal.* Calcd. for $C_{12}H_{14}O_2N_4$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.77; H, 5.88; N, 22.98.

1-Substituted 6-Alkylenehydrazino-3-methyluracils (VI) (47—59 in Table III)——a) To 50 ml of EtOH was added 0.01 mole of 6-hydrazino-1,3-dimethyluracil (**43**)[14a], then 0.012 mole of aldehydes (MeCHO, EtCHO, PrCHO, AmCHO, $PhCH_2CHO$) or ketones ($AcCH_2COOEt$, $AcCH_2CH_2COOEt$) were added, and the mixture was heated under reflux for 0.5—1 hr. After cooling, the resulting precipitate was filtered. Or the reaction solution was evaporated *in vacuo*, ether was added to the residue, and resulting crystals were collected. The crude products were recrystallized from a suitable solvent to give hydrazones (VI: **47**—**50**, **53**, **56**, **58**).

b) Reaction of ketones (acetone, MeCOEt, MeCOPr, MeCOPh, N-methyl-4-piperidone) and 6-hydrazinouracils (V: **43**,[14a] **44**,[14b] **45**) were carried out in xylene in a similar manner as described above to give hydrazones (**51**, **52**, **54**, **55**, **57**, **59**).

1,5,6,7-Tetrasubstituted 3-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (VII) (60—90 in Table IV)——Method A: A solution of 1-substituted 6-alkylenehydrazino-3-methyluracils (VI: **47**—**55**) (0.01 mole) in 20 ml of tetraline (or ethylene glycol) was refluxed for 2—3 hr. After cooling, ether was added to the solution, the resulting precipitate was filtered to give crude products of **60**—**65**, **76**, **82**, and **89**.

Method B: To a solution of ketones (0.015 mole) in 20 ml of tetraline (or ethylene glycol) were added 0.01 mole of 6-hydrazinouracils (V: **43**—**46**[14]) and refluxed for 2—3 hr. After cooling, ether (or water) was added to the reaction solution, the resulting precipitate was filtered, and recrystallized to give **64**—**90**.

1-Substituted 5-Carboxymethyl-3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (91, 92 in Table IV)——1-Substituted 5-ethoxycarbonyl-3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]-pyrimidine (**89** or **90**) (0.01 mole) was dissolved in 10—30 ml of 5% NaOH solution with heating on a water

12) S. Senda, M. Honda, K. Maeno, and H. Fujimura, *Chem. Pharm. Bull.* (Tokyo), **6**, 490 (1958).
13) S. Senda, K. Hirota, and T. Asao, *Chem. Pharm. Bull.* (Tokyo), **22**, 189 (1974).
14) *a*) W. Pfleiderer and K.H. Schundehutte, *Ann. Chem.*, **612**, 158 (1958); *b*) H. Partenheimer, Ger. Patent 1186466 (1965) [*Chem. Abstr.*, 62, 13159 (1965)].

bath. After 5 min, the reaction solution was acidified with AcOH with cooling in ice water. The precipitate was filtered to give a crude product of **91** or **92**.

Hydrolysis of 5-Ethoxycarbonyl-1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (89) with Hydrochloric Acid——A solution of 1.8 g of **89** in 100 ml of 5% HCl was refluxed for 5 hr. After cooling, the resulting precipitate was filtered, washed with H_2O, and recrystallized from EtOH to give 1.0 g of 1,3,5,6-tetramethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**64**). This compound was identified by comparison of infrared spectra with an authentic sample obtained in the preparation of VII.

1,3,5,6-Tetramethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (93)——**64** (2.1 g, 0.01 mole) was hydrogenated in a similar manner as described in the preparation of IV. After the catalyst was removed by filtration of the hot reaction solution, on cooling to room temperature, 0.5 g of a starting material (**64**) was recovered by filtration. The filtrate was evaporated *in vacuo*, H_2O was added to the residue, the precipitate was filtered, and recrystallized from H_2O to give 0.3 g of **93**, mp 237°. *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.42; H, 7.40; N, 19.98.

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