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Fused Pyrimidines. V.[1] Synthesis of 2-Aminopyrimido[4,5-*e*]-1,3,4-thiadiazine and Some Related Compounds from 6-Thiosemicarbazidouracils[2]

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Oxidation of 1,3-dialkyl-6-(4-substituted-thiosemicarbazido)-uracils (II) with N-chlorosuccinimide in chloroform at room temperature furnished 5,7-dialkyl-2-substituted-amino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-diones (III) in good yields. Heating of III resulted in ring contraction to afford 3-substituted-aminopyrazolo[3,4-*d*]-pyrimidine-4,6(5H,7H)-diones (IV). Treatment of II with bromine gave 4,6-dialkyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-diones (IX) or N,N′-dialkyl-1,3,9,11-tetramethyl-dipyrimido[4,5-*e*: 4′,5′-*k*][1,7,3,4,9,10]dithiatetraazacyclododecine-2,4,6,10,12,14(1H,3H,9H,11H)-hexanone-6,14-diimines (VIII), depending on the reaction conditions employed. Compounds IX were also obtained either by treatment of 1,3-dialkyl-6-hydrazinouracils (I) with thionyl chloride or by treatment of III with bromine.

Keywords——pyrimido[4,5-*e*]-1,3,4-thiadiazine; 6-hydrazinouracil; 6-thiosemicarbazidouracil; pyrazolo[3,4-*d*]pyrimidine; 1,2,3-thiadiazolo[4,5-*d*]pyrimidine; dipyrimido[4,5-*e*: 4′,5′-*k*][1,7,3,4,9,10]dithiatetraazacyclododecine; N-chlorosuccinimide; bromine; ring closure; ring contraction

The preceding paper[1] reported that the treatment of 1,3-dialkyl-6-hydrazinouracils (I) with various isothiocyanates furnished 3-substituted-aminopyrazolo[3,4-*d*]pyrimidines *via* 1,3-dialkyl-6-substituted-thiosemicarbazidouracils (II). This paper deals with the synthesis of derivatives of pyrimido[4,5-*e*]-1,3,4-thiadiazine (III), a new ring system,[4] and of 1,2,3-thiadiazolo[4,5-*d*]pyrimidine (IX) from II.

Treatment of I with alkyl, aryl or acyl isothiocyanates afforded the corresponding 1,3-dialkyl-6-substituted-thiosemicarbazidouracils (II) in good yields (Table I). Oxidation of 1,3-diethyl-6-(4-ethylthiosemicarbazido)uracil (IIa) with N-chlorosuccinimide (NCS) in chloroform at room temperature afforded yellow-green crystals (IIIa) in 63% yield. Compound IIIa was assigned the structure 5,7-diethyl-2-ethylamino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-dione on the basis of its elemental analysis ($C_{11}H_{17}N_5O_2S$), mass spectrum (*m/e* 283, M^+) and nuclear magnetic resonance (NMR) spectrum, in which three N-ethyl groups were observed and a signal due to the proton at the 5-position of IIa was lost. Similarly, treatment of IIc—t with NCS afforded the corresponding IIIc—t in good yields (Table II). A compound having an amino group at the 2-position (IIIb, R^2=R^3=H) was prepared analogously from IIb, which was obtained by the reaction of 6-chloro-1,3-dimethyluracil[5] with thiosemicarbazide in methylcellosolve at 120° for 5 hr in 51% yield (Chart 1). N-Bromoacetamide and N-bromosuccinimide could also be used in this oxidation, but NCS gave the best results.

When IIIa—n were heated above their melting points, the yellow-green crystals changed to colorless needles and sulfur sublimed. The resulting needles were identified as 3-substi-

1) Part IV: T. Naka and Y. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **27**, 1328 (1979).
2) This work was presented at the 10th Congress of Heterocyclic Chemistry, Tsukuba, Japan, 1977; T. Naka and Y. Furukawa, *Heterocycle*, **9**, 101 (1978).
3) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
4) The pyrimido[4,5-*e*][1,2,4]thiadiazine ring system has already been reported; H.M. Gilow and J. Jacobus, *J. Org. Chem.*, **28**, 1994 (1963).
5) W. Pfleidere and K.H. Schündehütte, *Ann.*, **615**, 42 (1958).

Table I. 6-Substituted-thiosemicarbazidouracils (II)

Series	R1[a]	R2	R3	Yield (%)	mp, °C	Crystn.[b] Solvent	Formula[c]
a	Et	Et	H	87	200—202	A-C	$C_{11}H_{19}N_5O_2S$
b	Me	H	H	55	178—180	A-D	$C_7H_{11}N_5O_2S$
c	Me	Me	H	70	224—226	A-D	$C_8H_{13}N_5O_2S$
d	Me	Et	H	77	204—206	B-D	$C_9H_{15}N_5O_2S$
e	Me	iso-Bu	H	61	218—220	C	$C_{11}H_{19}N_5O_2S$
f	Me	Ph	H	53	210—212	A-D	$C_{13}H_{15}N_5O_2S$
g	Me	*p*-Cl-Ph	H	70	213—215	A-D	$C_{13}H_{14}ClN_5O_2S$
h	Et	Me	H	90	213—215	C	$C_{10}H_{17}N_5O_2S$
i	Et	iso-Bu	H	85	202—204	C	$C_{13}H_{23}N_5O_2S$
j	Et	Bzy	H	70	203—204	C	$C_{16}H_{21}N_5O_2S$
k	Et	Ac	H	69	202—204	B	$C_{11}H_{17}N_5O_3S$
l	Et	Bzo	H	89	135—137	B	$C_{16}H_{19}N_5O_3S$
m	*n*-Bu	Me	H	91	212—214	C	$C_{14}H_{25}N_5O_2S$
n	*n*-Bu	*p*-Cl-Ph	H	45	175—178	C	$C_{19}H_{26}ClN_5O_2S$
o	Me	All	H	88	193—195	A-D	$C_{10}H_{15}N_5O_2S$
p	Et	All	H	61	206—208	C	$C_{12}H_{19}N_5O_2S$
q	Me	Me	Me	71	217—219	C	$C_9H_{15}N_5O_2S$
r	Me	Et	Me	73	175—178	C	$C_{10}H_{17}N_5O_2S$
s	Et	Me	Me	70	175—177	C-D	$C_{11}H_{19}N_5O_2S$
t	Et	Et	Me	71	170—173	C	$C_{12}H_{21}N_5O_2S$

a) Me, Methyl; Et, ethyl; Bu, butyl; All, allyl; Ac, acetyl; Bzo, benzoyl; Ph, phenyl; *p*-Cl-Ph, *p*-chlorophenyl; Bzy, benzyl.
b) A, DMF; B, EtOH; C, MeOH; D, H_2O.
c) Satisfactory elemental analysis (C, H, N, S, Cl) data were obtained for all compounds.

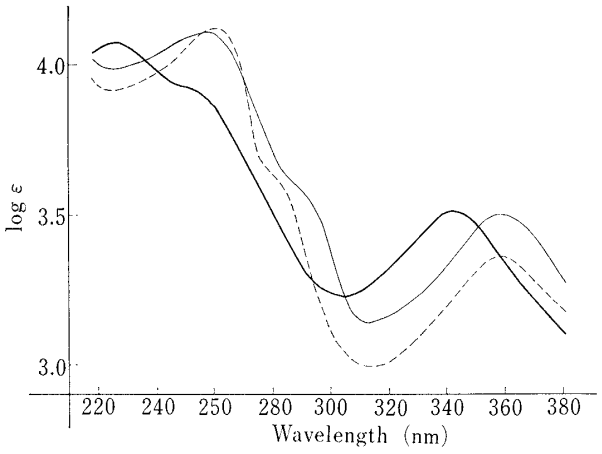


Fig. 1. UV Spectra of Pyrimido[4,5-*e*]-1,3,4-thiadiazine Derivatives (in MeOH)
——: IIIa, ------: IIIb, ——: IIIg.

tuted-aminopyrazolo[3,4-*d*]pyrimidine-4,6(5H,7H)-diones (IV) by comparing their melting points (shown in parentheses in Table II) and ultraviolet (UV) spectra with those of the authentic samples described in the preceding paper.[1] This ring contraction was also observed when IIIf was boiled in DMF for 1 hr. On the other hand, the 4-methyl derivatives (IIIq—t) were recovered unchanged under the same conditions; *i.e.*, the presence of a proton at the 4-position was necessary for this ring contraction. A possible mechanism of this reaction is presented in Chart 2.

Acetylation of IIIc with acetic anhydride in pyridine at room temperature for 2 hr afforded two products, VIc and Vc in 59 and 19% yields, respectively. Compound VIc was assigned the structure 4-acetyl-5,7-dimethyl-2-methylamino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-dione on the basis of its mass (*m/e* 283, M^+) and NMR (a singlet at δ 2.20 due to $>NCOCH_3$ and a doublet at δ 2.82 due to $-NHCH_3$) spectra. Compound Vc was assigned the structure 2-acetyl-5,7-dimethyl-3-methylaminopyrazolo[3,4-*d*]pyrimidine-5,7-(4H,6H)-dione on the basis of analysis and its failure to depress the melting point on admixture with the authentic sample mentioned previously.[1]

This reaction can be explained as shown in Chart 3; acetylation took place at the 3- or 4-position. The 3-acetyl derivative (VII) was particularly unstable to heat and changed to

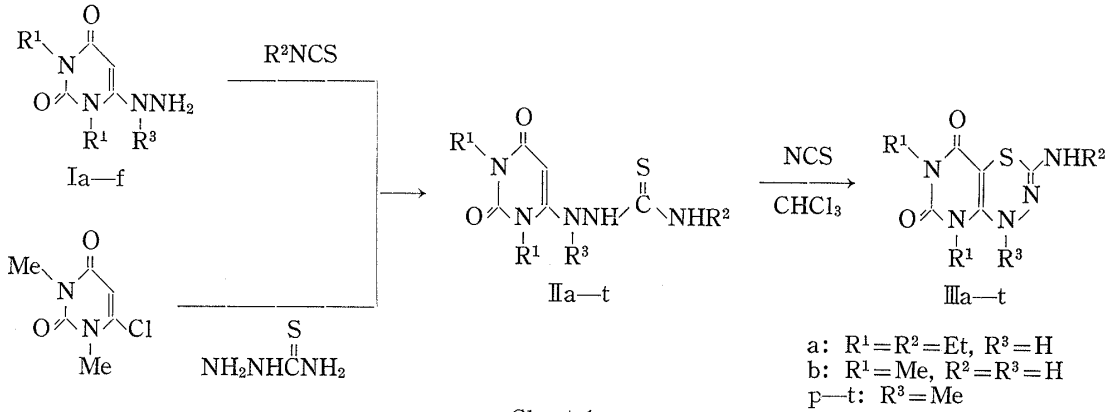


Chart 1

TABLE II. 3-Substituted-aminopyrimido[4,5-*e*]-1,3,4-thiadiazines (III)

Series	R¹[a]	R²	R³	(Method)[b] Yield (%)	mp, °C ( )[c]	Crystn.[b] Solvent	Formula	Analysis (%) Calcd. Found C	H	N	S
a	Et	Et	H	63[A]	190—200 (258—260)	C	$C_{11}H_{17}N_5O_2S$	46.68 (46.30	6.05 6.03	24.72 24.57	11.31 11.46)
b	Me	H	H	63[A] 60[B]	190—200 (>295, Sub)	A-D	$C_7H_9N_5O_2S$	36.99 (36.68	3.99 3.98	30.82 30.17	14.11 14.67)
c	Me	Me	H	52[A] 51[B]	220—230 (>300, Sub)	A-D	$C_8H_{11}N_5O_2S$	39.82 (39.70	4.60 4.71	29.03 29.30	13.29 13.51)
d	Me	Et	H	45[B]	195—200 (>300, Sub)	C	$C_9H_{13}N_5O_2S$	42.34 (42.72	5.13 4.93	27.43 27.30	12.56 12.59)
e	Me	iso-Bu	H	35[B]	180—185 (238—239)	C	$C_{11}H_{17}N_5O_2S$	46.62 (46.82	6.05 5.86	24.72 24.99	11.32 11.41)
f	Me	Ph	H	51[B]	155—157 (243—245)	C	$C_{13}H_{13}N_5O_2S$	51.46 (51.32	4.32 4.12	23.09 23.29	10.57 10.81)
g	Me	*p*-Cl-Ph	H	48[B]	230—240 (275—277)	A-D	$C_{13}H_{12}ClN_5O_2S$	46.22 (46.50	3.58 3.49	20.73 20.52	9.49 9.83)
h	Et	Me	H	67[A] 40[B]	180—190 (>280, Sub)	C	$C_{10}H_{15}N_5O_2S$	44.59 (44.29	5.61 5.63	26.01 25.90	11.91 11.96)
i	Et	iso-Bu	H	54[A]	145—147 (157—159)	C	$C_{13}H_{21}N_5O_2S$	46.68 (46.30	6.05 6.03	24.72 24.57	11.31 11.46)
j	Et	Bzy	H	53[A] 32[B]	143—146 (218—219)	A-D	$C_{16}H_{18}N_5O_2S$	55.63 (55.58	5.54 5.56	20.28 20.32	9.28 9.57)
k	Et	Ac	H	70[A]	220—230 (254—255)	A-D	$C_{11}H_{15}N_5O_3S$	44.44 (44.44	5.09 4.89	23.56 23.65	10.79 10.69)
l	Et	Bzo	H	50[A]	190—200 (262—264)	A-D	$C_{16}H_{16}N_5O_3S$	53.47 (53.23	4.77 4.75	19.49 19.70	8.92 8.92)
m	*n*-Bu	Me	H	60[A]	50—60 (260—265)	C	$C_{14}H_{23}N_5O_2S$	51.67 (51.53	7.12 7.01	21.52 21.29	9.85 9.61)
n	*n*-Bu	*p*-Cl-Ph	H	55[B]	158—160 (<300)	C	$C_{19}H_{24}ClN_5O_2S$	54.08 (53.79	5.73 5.48	16.60 16.51	7.60 7.68)
o	Me	All	H	40[B]	230—235	A-D	$C_{10}H_{13}N_5O_2S$	44.93 (45.11	4.90 5.09	26.20 25.96	11.99 11.77)
p	Et	All	H	51[A]	206—208	C	$C_{12}H_{17}N_5O_2S$	48.79 (48.43	5.80 5.82	23.71 23.70	10.86 10.74)
q	Me	Me	Me	61[B]	220—222	C-D	$C_9H_{13}N_5O_2S$	42.34 (42.26	5.13 5.06	27.43 27.78	12.56 12.96)
r	Me	Et	Me	61[B]	261—263	C-D	$C_{10}H_{15}N_5O_2S$	44.59 (44.62	5.61 5.46	26.01 26.17	11.91 11.96)
s	Et	Me	Me	75[A]	156—158	C-D	$C_{11}H_{17}N_5O_2S$	46.62 (46.65	6.48 6.12	24.72 24.84	11.32 11.25)
t	Et	Et	Me	70[A]	142—143	C	$C_{12}H_{19}N_5O_2S$	48.46 (48.17	6.44 6.19	23.55 23.40	10.78 10.67)

a) See Table I.
b) A, NCS treatment; B, NBS treatment.
c) Melting points of the corresponding pyrazolo[3,4-*d*]pyrimidine derivatives.
d) A, DMF; B, EtOH; C, MeOH; D, H_2O.

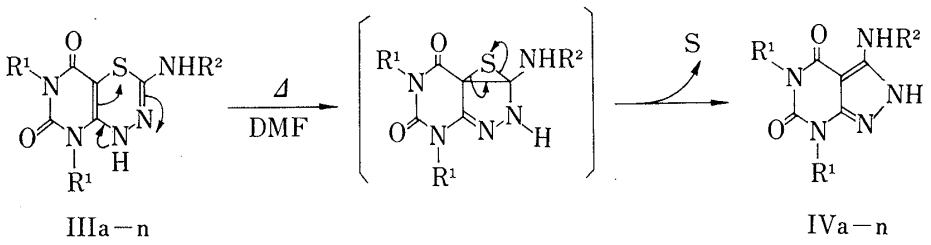


Chart 2

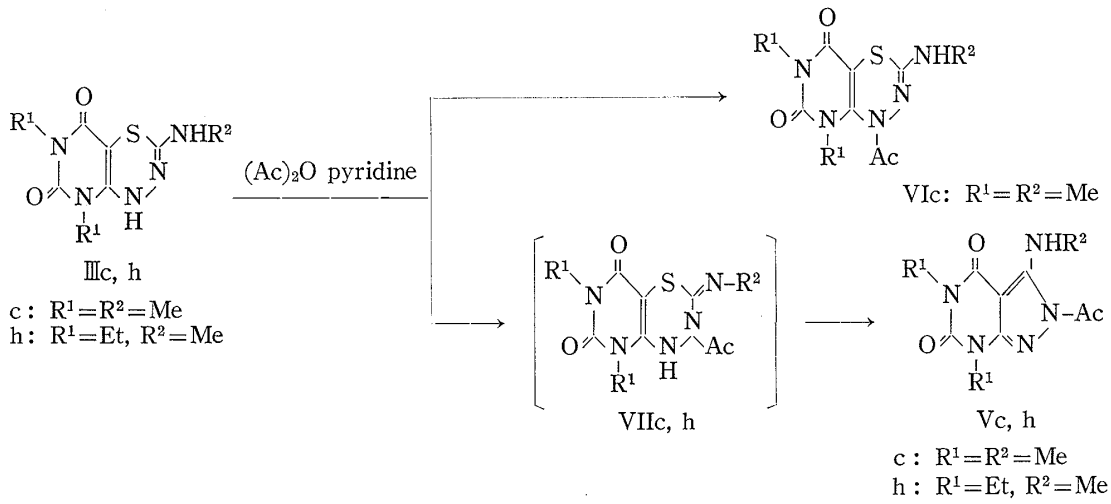


Chart 3

2-acetylpyrazolo[3,4-*d*]pyrimidine (V). In contrast, the 4-acetyl derivative (VI), which had no proton at the 4-position, was stable and could be isolated as such (Chart 3).

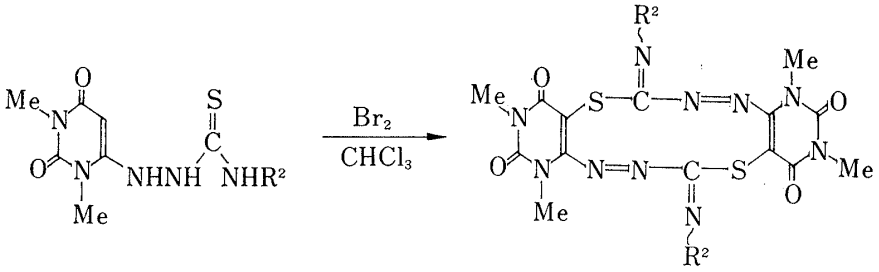
Acetylation of IIIh under the same conditions afforded 2-acetylpyrazolo[3,4-*d*]pyrimidine derivative (Vh) as a sole product, in contrast to the case of IIIc. These results indicate that nucleophilic attack at the 4-position was hindered more strongly by an N^5-ethyl group than by an N^5-methyl group.

Oxidation of II with NCS or NBS afforded III as described above, but oxidation with bromine gave quite different results. Namely, when bromine was added dropwise to a suspension of IId in chloroform and the mixture was allowed to react at room temperature for 1 hr, N,N′-diethyl-1,3,9,11-tetramethyldipyrimido[4,5-*e*; 4′,5′-*k*][1,7,3,4,9,10]dithiatetraazacyclododecine-2,4,6,10,12,14-(1H,3H,9H,11H)-hexanone-6,14-diimine (VIIId) was obtained in 35% yield by oxidative condensation of two molecules of IId (Chart 4). The structural assignment of VIIId was established from the spectral data: the NMR spectrum showed four $>NCH_3$ signals at δ 3.1—3.3 and two $=NCH_2CH_3$ signals at δ 1.0—1.2 and 3.8—4.0. The mass spectrum showed characteristic peaks at *m/e* 423 ($M^+-C_3H_5N_3$), 391 ($M^+-C_3H_5N_3S$) and 362 ($M^+-C_3H_5N_3S-C_2H_5$) along with a molecular ion peak *m/e* 506, which is consistent with the elemental analysis ($C_{18}H_{22}N_{10}O_4S_2$).

In contrast, when IId was added in portions to a solution of bromine in chloroform and the mixture was allowed to react at room temperature for 2 hr, another compound (IXa) was obtained in 52% yield. The structure of IXa was established to be 4,6-dimethyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione[6] on the basis of its NMR (two singlets at δ 3.43 and 3.95 due to two $>NCH_3$ groups) and mass (*m/e* 198, M^+) spectra and elemental analysis ($C_6H_6N_4O_2S$).

6) K. Senga, M. Ichiba, and S. Nishigaki, *Tetrahedron Lett.*, **1976**, 1129; *idem*, *J. Org. Chem.*, **43**, 1677 (1978); T. Naka and Y. Furukawa, Japan Kokai 52, 0105194. 3 Sep. 1977, April. 76/021512, 2 Feb. 1976.

Compound IXa was also obtained in good yield by the reaction of Ia with thionyl chloride[6] in chloroform at room temperature (Chart 5). The intermediate in the formation of IXa from IId was presumed to be IIId. In fact, oxidation of IIId with bromine in chloroform gave IXa in 60% yield and therefore, the mechanism of this ring contraction may be



IId, e

VIIId, e

d : R^2=Et
e : R^2=iso-Bu

Chart 4

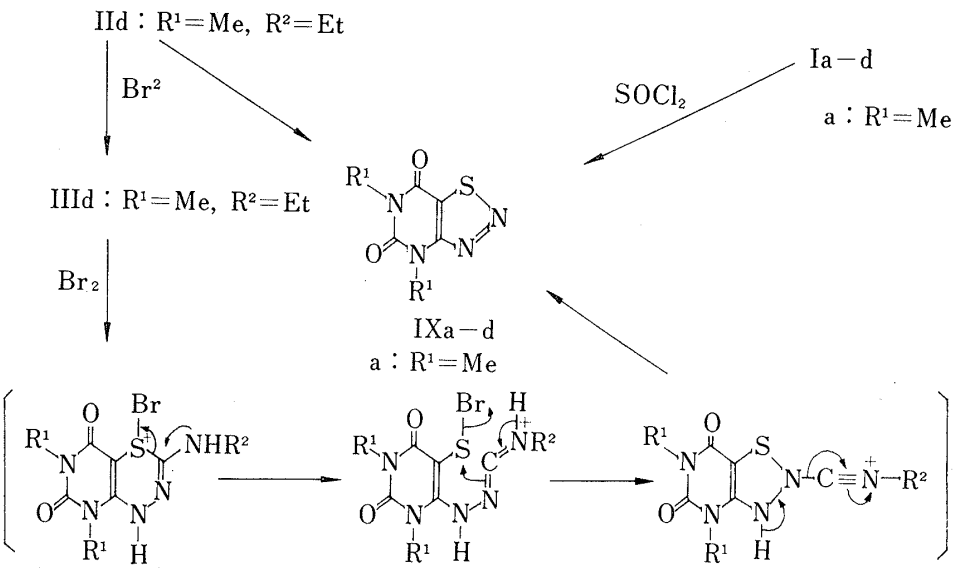


Chart 5

TABLE III. 1,2,3-Thiadiazolo[4,5-*d*]pyrimidine-4,6(5H,7H)-diones (IX)

Series	$R^{1a)}$	(Method)[b] Yield (%)	mp, °C	Crystn.[c] Solvent	Formula	Analysis (%) Calcd. (Found) C	H	N	S
a	Me	75[A] 52[B]	138—139	A	$C_6H_6N_4O_2S$	36.30 (36.30	3.09 3.05	28.50 28.23	16.32 16.16)
b	Et	83[A] 52[B]	65—66	A-B	$C_8H_{10}N_4O_2S$	42.46 (42.29	4.46 4.26	24.76 24.67	14.17 14.26)
c	*n*-Bu	82[A]	Oil	—	$C_{12}H_{18}N_4O_2S$	51.04 (50.62	6.43 6.56	19.84 19.52)	
d	C_6H_{11}	75[A]	140—142	A	$C_{16}H_{22}N_4O_2S$	57.11 (57.15	7.18 6.99	16.65 16.74	9.52 9.76)

a) See Table I; C_6H_{11}, cyclohexyl.
b) A, $SOCl_2$; B, Br_2.
c) A, MeOH: B, H_2O.

as depicted in Chart 5. 1,2,3-Thiadiazolo[4,5-*d*]pyrimidine derivatives were obtained analogously (Table III).

The synthesis of some derivatives of 1,3,4-thiadiazine[7] by the reaction of α-haloketone with thiosemicarbazide and the ring contraction of 1,3,4-thiadiazine to pyrazole by alkaline treatment have been reported.[8] We report here the synthesis of pyrimido[4,5-*e*]-1,3,4-thiadiazine (III), a new ring system, by a new oxidative cyclization[9] of II, the ring contraction of III to V by heating, and moreover, the oxidation of II with bromine to afford 1,2,3-thiadiazolo-[4,5-*d*]pyrimidine (IX) or VIII, depending on the reaction conditions used. Compound IX was also obtained either by treatment of I with thionyl chloride or of III with bromine. Most of the compounds obtained above were inhibitors of cyclic nucleotide phosphodiesterase.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. NMR spectra were recorded on a Hitachi R-24 spectrometer using tetramethylsilane as an internal standard. Ultraviolet, infrared and mass spectra were measured on Hitachi EPS-3T, Hitachi 215 (nujol mull) and Hitachi RMS-4 machines, respectively. Thin-layer chromatography was carried out on silica gel 60 F_{254} plates (Merck).

1,3-Dialkyl-6-hydrazinouracil (I)——1,3-Dimethyl-6-hydrazinouracil (Ia),[5] 1,3-diethyl-6-hydrazinouracil (Ib),[10] 1,3-di-*n*-butyl-6-hydrazinouracil (Ic)[1] and 1,3-dimethyl-6-(1-methylhydrazino)uracil (Ie)[11] were prepared by the reported procedures.

1,3-Dicyclohexyl-6-hydrazinouracil (Id)——Water (5 ml) was added dropwise to a suspension of 1,3-dicyclohexylbarbituric acid[12] (13 g) in $POCl_3$ (100 ml) with stirring, and the suspension was refluxed for 2 hr. The solution was evaporated to a syrup, which was poured onto ice-water and extracted with chloroform. The chloroform layer was washed with water and evaporated to a syrup, which was crystallized from hexane to give 6-chloro-1,3-dicyclohexyluracil as colorless crystals (10 g). mp 92—95°. A suspension of 1,3-dicyclohexyl-6-chlorouracil (10 g) in ethanol (20 ml) and hydrazine hydrate (100%, 20 ml) was heated at 80° for 2 hr. The solution was evaporated to dryness and the resulting powder was crystallized from 50% ethanol to give colorless crystals (6.7 g, 72%), mp 160—165°. NMR (d_6-DMSO) δ: 1.1—2.5 (20H, m, $-C_6H_{11}$), 3.47 (2H, s, H-5), 4.5 (2H, m, =N–N<u>H</u>$_2$), 4.4—4.7 (2H, m, >NC(H)<H>). *Anal.* Calcd. for $C_{16}H_{26}N_4O_2$ (306.40): C, 62.72; H, 8.55; N, 18.29. Found C, 62.49; H, 8.71; N, 18.39.

1,3-Diethyl-6-(1-methylhydrazino)uracil (If)——A solution of 6-chloro-1,3-diethyluracil[10] (5.0 g) and methylhydrazine (5.0 ml) in ethanol (50 ml) was refluxed for 30 min and evaporated down to yield a solid, which was washed with water to give colorless crystals (4.5 g, 85%), mp 117—118°. NMR (d_6-DMSO) δ: 1.0—1.4 (6H, m, >NCH$_2$C<u>H</u>$_3$), 3.6—4.1 (4H, m, >NC<u>H</u>$_2$CH$_3$), 2.89 (3H, s, –NC<u>H</u>$_3$NH$_2$), 4.56 (2H, s, –NCH$_3$-N<u>H</u>$_2$), 5.09 (1H, s, H-5). *Anal.* Calcd. for $C_9H_{16}N_4O_2$ (214.25): C, 50.45; H, 7.53; N, 26.15. Found: C, 50.68; H, 7.32; N, 26.38.

1,3-Dialkyl-6-(4-substituted-thiosemicarbazido)uracil (II)——A solution of 1,3-dialkyl-6-hydrazinouracil (30 mmol) and alkyl, acyl or aryl isothiocyanate (45 mmol) in DMF (50 ml) was stirred at 60—70° for 2 hr. The solution was evaporated to dryness and the residue was triturated with methanol to give crystals, which were recrystallized from an appropriate solvent to give colorless needles.

5,7-Diethyl-2-ethylamino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-dione (IIIa)——NCS (2.0 g, 15 mmol) was added to a suspension of IIa (4.0 g, 14 mmol) in chloroform (40 ml) in portions during 2 hr with stirring. After stirring for a further 1 hr, the yellow-green solution was evaporated to dryness. The resulting solid was dissolved in methanol (10 ml) and the solution was diluted with water to give crystals, which were recrystallized from methanol (30 ml) to give yellow prisms (2.5 g, 63%). UV λ_{max}^{MeOH} nm (log ε): 258 (4.11), 290 (3.59), 358 (3.50). λ_{min}^{MeOH} nm (log ε): 225 (3.99), 331 (3.14). MS *m/e*: 283 (M^+). NMR (d_6-DMSO) δ: 1.0—1.4 (9H, m, >NCH$_2$C<u>H</u>$_3$), 3.15 (2H, m, –NHC<u>H</u>$_2$CH$_3$), 3.8—4.1 (4H, m, >NC<u>H</u>$_2$CH$_3$), 6.62 (1H, t, –NHEt), 9.65 (1H, s, >NH).

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2-Acetylamino-5,7-diethyl-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-dione (IIIk)——NCS (2.0 g, 15 mmol) was added to a suspension of IIk (4.0 g, 13 mmol) in chloroform (50 ml) in portions during 2 hr with stirring. The crystals formed were collected by filtration and recrystallized from DMF–H_2O to give yellow needles (2.8 g, 70%). UV λ_{max}^{MeOH} nm (log ε): 252 (4.25), 280 (3.90), 370 (3.08). λ_{min}^{MeOH} nm (log ε): 224 (3.91), 274 (3.88), 314 (2.76). NMR (d_6-DMSO) δ: 1.0—1.3 (6H, m, $>NCH_2C\underline{H}_3$), 1.99 (3H, s, $-NHCOC\underline{H}_3$), 3.88 (4H, q, $>NC\underline{H}_2CH_3$), 9.97 (1H, s, $-N\underline{H}COCH_3$), 10.96 (1H, s, >NH).

5,7-Diethyl-4-methyl-2-methylamino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H, 7H)-dione (IIIs)——NBS (1.5 g, 8.4 mmol) was added to a solution of IIs (2.0 g, 6.7 mmol) in chloroform (15 ml) in portions during 1 hr with stirring. The solution was evaporated to give a syrup, which was chromatographed on silica gel (30 g) using chloroform as an eluent. After concentration of the main fraction, the resulting syrup was crystallized from methanol–H_2O to give pale yellow crystals (1.3 g, 75%). UV λ_{max}^{MeOH} nm (log ε): 226 (4.08), 251 (sh, 3.92), 342 (3.52). λ_{min}^{MeOH} nm (log ε): 305 (3.23). MS *m/e*: 283 (M^+). NMR (d_6-DMSO) δ: 1.0—1.4 (6H, m, $>NCH_2C\underline{H}_3$), 3.7—4.1 (4H, m, $>NC\underline{H}_2CH_3$), 2.73 (3H, d, $-NHCH_3$), 3.17 (3H, s, $>NCH_3$), 6.90 (1H, m, $-N\underline{H}CH_3$).

1,3-Dimethyl-6-thiosemicarbazidouracil (IIb)——A solution of 1,3-dimethyl-6-chlorouracil (3.0 g, 18 mmol) and thiosemicarbazide (3.0 g, 33 mmol) in methylcellosolve (15 ml) was heated at 130—135° for 5 hr. The solution was cooled to give colorless precipitates, which were recrystallized from DMF–H_2O to give colorless needles (2.0 g, 51%). UV λ_{max}^{MeOH} nm: 241, 268. λ_{min}^{MeOH} nm: 226, 257. NMR (d_6-DMSO) δ: 3.11 and 3.29 (3H each, s, $>NCH_3$), 4.69 (1H, s, H-5), 7.73 and 7.96 (1H each, br s, $-NH_2$), 8.97 (1H, s, $-N\underline{H}NHCS-$), 9.43 (1H, s, $-NHN\underline{H}CS-$).

2-Amino-5,7-dimethyl-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8-(5H,7H)-dione (IIIb)——NBS (2.0 g, 1.1 mmol) was added to a stirred suspension of IIb (2.0 g, 8.7 mmol) in chloroform (20 ml) in portions during 1 hr. After stirring for 2 hr, the insoluble matter was collected by filtration, washed with dilute ammonium hydroxide and crystallized from DMF–H_2O to give yellow-green needles (1.2 g, 60%). UV λ_{max}^{MeOH} nm (log ε): 250 (4.13), 281 (sh, 3.64), 358 (3.36). λ_{min}^{MeOH} nm (log ε): 223 (3.92), 315 (2.99). MS *m/e*: 227 (M^+). NMR (d_6-DMSO) δ: 3.30 and 3.46 (3H each, s, $>NCH_3$), 5.10 (2H, br s, $-NH_2$), 10.00 (1H, br s, >NH).

5,7-Dimethyl-3-phenylaminopyrazolo[3,4-*d*]pyrimidine-4,6-(5H,7H)-dione (IVf)——a) IIIf (200 mg) was heated gently on a free flame. The yellow-green crystals changed to colorless crystals and sulfur sublimed. The resulting crystals were recrystallized three times from ethanol to give colorless needles (150 mg, 84%). mp 243—245°. UV λ_{max}^{MeOH} nm: 220 (sh), 243 (sh), 256 (sh), 291. λ_{min}^{MeOH} nm: 268. NMR (d_6-DMSO) δ: 3.19 and 3.34 (3H each, s, $>NC\underline{H}_3$), 7.0—7.5 (5H, m, $-NHC_6\underline{H}_5$), 8.13 (1H, br s, >NH). *Anal.* Calcd. for $C_{13}H_{13}N_5O_2$ (271.27); C, 57.56; H, 4.83; N, 25.82. Found: C, 57.41; H, 4.96; N, 26.13.

b) A solution of IIIf (200 mg) in DMF (10 ml) was heated at 100° for 1 hr then evaporated to dryness. The residue was recrystallized twice from ethanol to give colorless needles (110 mg, 62%), mp 243—245°.

Acetylation of 5,7-Dimethyl-2-methylamino-4H-pyrimido[4,5-*e*]-1,3,4-thiadiazine-6,8(5H,7H)-dione (IIIc)——A solution of IIIc (800 mg) acetic anhydride (3 ml) and pyridine (5 ml) was heated at 50—60° for 3 hr and evaporated to dryness. The residue was crystallized from methanol to give Vc as colorless needles. The mother liquor was cooled to give crystals, which were recrystallized from methanol (80 ml) to give VIc as colorless needles. Vc: yield 150 mg (19%), mp 238—241°. UV λ_{max}^{MeOH} nm: 245, 261 (sh), 269 (sh), 312. λ_{min}^{MeOH} nm: 220, 258, 288. NMR (d_6-DMSO) δ: 2.50 (3H, s, $>NCOCH_3$), 3.13 and 3.30 (3H, each, s, $>NCH_3$), 3.45 (3H, d, $-NHC\underline{H}_3$), 8.55 (1H, m, $-N\underline{H}CH_3$). *Anal.* Calcd. for $C_{10}H_{13}N_5O_3$ (251.24): C, 47.80; H, 5.22; N, 27.88. Found: C, 47.63; H, 5.29; N, 27.98. VIc: yield 460 mg (59%); mp 273—275° (dec.). UV λ_{max}^{MeOH} nm (log ε): 222 (4.27), 312 (3.68). λ_{min}^{MeOH} nm (log ε): 283 (3.47). MS *m/e*: 283 (M^+), 251 (M^+-S). NMR (d_6-DMSO) δ: 2.20 (3H, s, $>NCOCH_3$), 2.82 (3H, d, $-NHC\underline{H}_3$), 3.20 (3H, s, $>NCH_3$), 3.24 (3H, s, $>NCH_3$), 7.76 (1H, q, $-N\underline{H}CH_3$). *Anal.* Calcd. for $C_{10}H_{13}N_5O_3S$ (283.31): C, 42.39; H, 4.63; N, 24.72; S, 11.32. Found: C, 42.44; H, 4.60; N, 24.57; S, 11.10.

N,N′-Diethyl-1,3,9,11-tetramethyldipyrimido[4,5-*e*: 4′,5′-*k*][1,7,3,4,9,10]dithiatetraazacyclododecine-2,4,6, 10,12,14(1H,3H,9H,11H)-hexanone-6,14-diimine (VIIId)——A solution of bromine (0.3 ml) in chloroform (1 ml) was added dropwise to a suspension of IId (300 mg) in chloroform (3 ml). The solution was stirred for 1 hr at room temperature, then neutralized with aqueous sodium bicarbonate and evaporated to dryness. The residue was dissolved in methanol and the insoluble material was removed by filtration. The filtrate was evaporated to a powder, which was recrystallized from methanol to give colorless needles (100 mg, 35%), mp 244—246°. UV λ_{max}^{MeOH} nm: 250 (sh), 326. λ_{min}^{MeOH} nm: 288. MS *m/e*: 506 (M^+), 423, 391, 362. NMR (d_6-DMSO) δ: 1.0—1.2 (6H, m, $=NCH_2C\underline{H}_3$), 3.1—3.3 (12H, m, $>NCH_3$), 3.8—4.0 (4H, m, $>NC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{18}H_{22}N_{10}O_4S_2$ (506.57): C, 42.68; H, 4.38; N, 27.65; S, 12.67. Found: C, 42.49; H, 4.38; N, 27.58; S, 12.37.

N,N′-Diisobutyl-1,3,9,11-tetramethyldipyrimido[4,5-e: 4′,5′-k][1,7,3,4,9,10]-dithiatetraazacyclododecine-2,4,6,10,12,14(1H,3H,9H,11H)-hexanone-6,14-diimine (VIIIe)——A solution of bromine (1.0 ml) in chloroform (5 ml) was added dropwise to a suspension of IIe (1.0 g) in chloroform (5 ml). After stirring at room temperature for 1 hr, the solution was worked up in the same way as for VIIId to give colorless crystals (0.3 g, 31%), mp 258—259°. UV λ_{max}^{MeOH} nm: 326. λ_{min}^{MeOH} nm: 288. MS *m/e*: 562 (M^+), 451, 419, 363. NMR (d_6-DMSO) δ: 0.9—1.1 (12H, m, $-CH\underline{Me}_2$), 1.4—1.8 (2H, m, $-CH_2C\underline{H}Me_2$), 2.8—3.1 (4H, m, $=NC\underline{H}_2CHMe_2$), 3.1—3.3 (12H,

m, $>NCH_3$). *Anal.* Calcd. for $C_{22}H_{30}N_{10}O_4S_2$ (562.67): C, 46.96; H, 5.37; N, 24.90; S, 11.40. Found: C, 46.94; H, 5.26; N, 24.92; S, 11.44.

4,6-Dimethyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (IXa)——a) IId (2.0 g) was added in portions to a stirred solution of bromine (1.5 ml) in chloroform (30 ml). After stirring at room temperature for 2 hr, the solution was evaporated to dryness and the residue recrystallized from methanol to give yellow needles (0.8 g, 52%). UV λ_{max}^{MeOH} nm: 215, 242 (sh), 330. λ_{min}^{MeOH} nm: 282. MS *m/e*: 198 (M^+). NMR (d_6-DMSO) δ: 3.43 and 3.95 (3H each, s, $>NCH_3$).

b) A solution of bromine (0.7 ml) in chloroform (5 ml) was added dropwise to a solution of IIId (1.0 g) in chloroform (10 ml). After stirring at room temperature for 3 hr, the solution was evaporated to give a syrup, which was crystallized from methanol to give needles (IXa) (0.5 g, 60%).

4,6-Diethyl-1,2,3-thiadiazolo[4,5-*d*]pyrimidine-5,7-(4H,6H)-dione (IXb)——Thionyl chloride (0.5 ml) was added dropwise to a solution of Ib (1.2 g) in chloroform (5 ml) during 1 hr with stirring. The solution was evaporated to give a syrup, which was chromatographed on silica gel (30 g) using chloroform as an eluent and the main fraction was evaporated down to give solids, which were crystallized from MeOH–H_2O to give pale brown needles (1.13 g, 80%). UV λ_{max}^{MeOH} nm (log ε): 217 (4.15), 240 (sh, 3.49), 331 (3.59). NMR (d_6-DMSO) δ: 1.0—1.3 (6H, m, $>NCH_2C\underline{H}_3$), 4.10 and 4.40 (2H each, d, $>NC\underline{H}_2CH_3$).

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