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Synthesis and Properties of [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine Derivatives Including Their Mesoionic Compounds. A New Class of Heterocycles[1]

Keitaro Senga,* Misuzu Ichiba, and Sadao Nishigaki

Pharmaceutical Institute, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan

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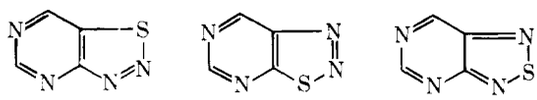
Treatment of 6-hydrazino-1,3-dimethyluracil (**1a**) with thionyl chloride gave 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**5a**), a new class of heterocycles. Reaction of 6-hydrazino-3-methyluracil (**8a**) with thionyl chloride afforded 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), which was subsequently converted to 6-methyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-dione (**14a**) by a novel 1,3-sulfur migration. Treatment of 3-methyl-6-(1-methylhydrazino)uracil (**8d**) with thionyl chloride provided the mesoionic compound, *anhydro*-3,6-dimethyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d**), via the 1,3-sulfur migration of 3,6-dimethyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10d**). Several other thiadiazolo[4,5-*d*]pyrimidines including their mesoionic compounds were also synthesized. Thiation of **5a** with phosphorus pentasulfide in pyridine yielded 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**17**). Nucleophilic displacement of **17** with hydrazines furnished the corresponding 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one 7(6*H*)-hydrazones (**18a–c**). The photolysis of **5a** in ethanol gave 1,3-dimethyl-5-mercaptouracil disulfide (**22**), while the thermolysis of **5a** in Dowtherm A yielded both 1,3,5,7-tetramethyl[1,4]dithiino[2,3-*d*;5,6-*e'*]dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (**26**) and 1,3,5,7-tetramethylthiopheno[2,3-*d*;4,5-*e'*]dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (**27**) probably via the thiirene intermediate **25**.

Although [1,2,3]thiadiazolo[5,4-*d*]pyrimidines (II)[2] and [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (III)[3] have been extensively studied, primarily as potential purine and pteridine antagonists, nothing has been reported on the isomeric [1,2,3]thiadiazolo[4,5-*d*]pyrimidines (I). The present paper



I II III

describes the synthesis and properties of derivatives of I, including their mesoionic compounds. The derivatives of type I are of interest from a chemical as well as a biological point of view. Thus, they may be considered analogues of various biologically important bicyclic fused pyrimidines, e.g., purines, pyrazolo[3,4-*d*]pyrimidines, *v*-triazolo[4,5-*d*]pyrimidines (by virtue of the fusion of the five-membered ring to the pyrimidine nucleus), pteridines, pyrimido[5,4-*e*]-*as*-triazines, and pyrimido[4,5-*e*]-*as*-triazines (by the isoelectronic relationship between a sulfur atom and an ethylenic group[4]). Moreover, they may also be regarded as cyclic analogues of 5-mercaptopyrimidines[5] and 6-azopyrimidines,[6] which have been known to exhibit interesting biological activities.

Treatment of 1,3-dialkyl-6-hydrazinouracils (**1a**[7] and **1b**[8]) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min afforded good yields of the corresponding 4,6-dialkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-diones (**5a** and **5b**), which were isolated by evaporation of the thionyl chloride and addition of water. The structures of these products were assigned by elemental analyses and spectral data. In particular, their UV spectra (see Table I) revealed the anticipated analogy with that of the known 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (**7**)[9] [λ_{max} (EtOH) 240 (log ϵ 3.98), 324 nm (3.56)].[4] Compounds **5a** and **5b** could also be obtained by similar treatment of 1,3-dialkyl-6-(1-methylhydrazino)uracils (**1c**[10] and **1d**) with thionyl chloride. When 6-hydrazino-1,3-dimethyl-2-thiouracil (**1e**) was used as a starting material, the product isolated was again **5a**. An analogous replacement of a sulfur by an oxygen has recently been reported on the reaction of 6-amino-1,3-diethyl-2-thiouracil with thionyl chloride–dimethylformamide mixture to give 5,7-diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.[11] The reaction of **1a** or **1b** with thionyl chloride presumably proceeds by the initial formation of the sulfinyl chloride intermediate (**2a** or **2b**), followed by cyclization to the thiadiazoline *S*-oxide (**3a** or **3b**), and subsequent dehydration via the Pummerer reaction intermediate (**4a** or **4b**). A similar mechanism for the conversion of **3** to **5** via **4** has been speculated in the reaction of 6-substituted amino-1,3-dimethyluracils with thionyl chloride, leading to 4,6-dimethylthiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones.[12] In the case of **1c** or **1d** with thionyl chloride, the analogously formed Pummerer reaction intermediate (**4c** or **4d**) would undergo demethylation by the acid hydrolysis of the methylthiadiazolium chloride intermediate (**6c** or **6d**) during the workup (Scheme I).

The reaction of 3-alkyl-6-hydrazinouracils (**8a**,[13] **8b**, and **8c**) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min also provided the corresponding 6-alkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**14a**, **14b**, and **14c**). However, these reactions appeared to involve a strikingly different and unexpected mechanism with that of the foregoing. Namely, careful treatment of **8a** with thionyl chloride at 0 °C for 30 min gave relatively stable 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]-pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), probably via the

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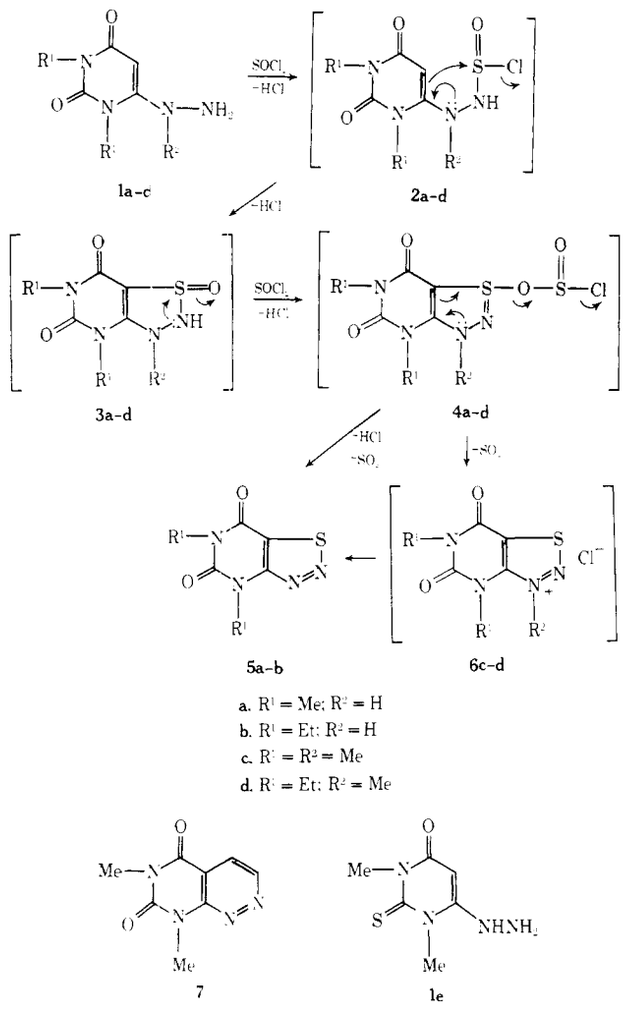
Table I. [1,2,3]Thiadiazolo[4,5-*d*]pyrimidines

Compd	Registry no.	Starting material	Registry no.	Yield, %	Mp,[a] °C	Formula[b]	NMR(Me$_2$SO-d_6), δ N-3	N-4	N-6	UV λ_{max} (EtOH), nm (log ε)	IR (Nujol), cm^{-1}
5a	60297-55-4	**1a**	40012-14-4	83	140–141	$C_6H_6N_4O_2S$		3.33 (s)	3.83 (s)	242 (3.81)	1715 (CO)
		1c	4318-53-0	78						327 (3.79)	
		1e	65150-59-6	63							
		14a		75							
5b	65150-55-2	**1b**	65150-60-9	92	81–82	$C_8H_{10}N_4O_2S$		1.25 (CH_3–, t)	1.40 (CH_3–, t)	240 (3.35)	1710 (CO)
		1d	65150-53-0	80				4.00 (–CH_2–, q)	4.08 (–CH_2–, q)	327 (3.37)	
14a	60297-58-7	**8a**	4318-55-2	82	235 dec	$C_5H_4N_4O_2S$		12.70 (br)[g]	3.26 (s)	250 (3.87)	1720 (CO)
		10a[c]	65150-61-0	52						320 (3.56)	3040–3200 (NH)
		10a[d]		90							
		14d		49							
14b	65150-57-4	**8b**	65150-54-1	47	142–144	$C_7H_8N_4O_2S$		11.33 (br)[g]	0.92 (CH_3–, t)	245 sh (3.46)	1720 (CO)
		14e		51					1.77 (–CH_2–, q)	275 (3.42)	3040–3200 (NH)
									4.20 (–CH_2–, q)	325 (3.44)	
14c	65150-58-5	**8c**	65150-56-3	72	179–181	$C_{11}H_8N_4O_2S$		9.63 (br)[g]	5.00 (–CH_2–, s)	230 sh (3.77)	1720 (CO)
		14f		35					7.30 (Ph, s)	260 (3.53)	3040–3200 (NH)
										398 (3.80)	
14d	60297-59-8	**8d**	42747-84-2	67	192–193	$C_6H_6N_4O_2S$	4.27 (s)		3.23 (s)	242 (5.22)	1690 (CO)
		10d	65150-64-3	71						300 (2.69)	
										405 (3.42)	
14e	65150-62-1	**8e**	65150-49-4	53	154–155	$C_8H_{10}N_4O_2S$	4.23 (s)		0.87 (CH_3–, t)	243 (3.68)	1680 (CO)
									1.53 (–CH_2–, q)	300 (2.27)	
									3.83 (–CH_2–, q)	410 (2.82)	
14f	65150-63-2	**8f**	52197-07-6	58	148–149	$C_{12}H_{11}N_4O_2S$	4.26 (s)		5.07 (–CH_2–, s)	245 (4.36)	1690 (CO)
									7.26 (Ph, s)	300 (2.69)	
										410 (3.59)	
14g	65150-52-9	**8g**	21236-98-6	90	294–295	$C_{11}H_8N_4O_2S$	7.66–8.33 (m)[e,f]		3.63 (s)[h]	225 (4.39)	1710 (CO)
										282 (4.42)	
17	65150-40-5	**5a**		82	159–160	$C_6H_6N_4OS_2$		3.73 (s)	3.83 (s)	250 (4.11)	1690 (CO)
										375 (4.03)	
18a	65150-42-7	**17**		85	229–230	$C_6H_8N_6OS$		3.31 (s)	3.66 (s)	245 sh (3.37)	1670 (CO)
									5.63 (s)[h]	325 (3.23)	3300 (NH)
18b	65150-43-8	**17**		84	135–136	$C_7H_{10}N_6OS$				243 sh (3.40)	1675 (CO)
										327 (3.26)	3220 (NH)
18c	65150-44-9	**17**		81	172–173	$C_{12}H_{12}N_6OS$				247 (3.74)	1690 (CO)
										325 (2.61)	3240 (NH)

[a] All compounds were recrystallized from EtOH. [b] All compounds were analyzed for C, H, and N within ±0.4%. [c] In the presence of thionyl chloride. [d] In the presence of EtOH. [e] Determined in CF_3COOD. [f] The chemical shift at position 2. [g] Exchangeable with D_2O. [h] The chemical shift of the extranuclear amino group.

sulfinyl chloride intermediate (**9a**), which upon refluxing in either thionyl chloride for 15 min or ethanol for a prolonged period resulted in the formation of **14a.** The structural assignment of **10a** was derived from its NMR and IR spectra: the presence of a singlet (δ 5.38) for position 4 and a sulfoxide absorption band (1090 cm^{-1}).[14] The formulation of **14a** was based on the close relationship of its UV spectrum to that of **5a** as well as its methylation to **5a** using methyl iodide in dimethylformamide containing potassium carbonate. The ring transformation of **10a** to **14a** involving a novel 1,3-sulfur migration can be best explained in terms of the initial ring opening of **10a** to the sulfinyl intermediate (**11a**), followed by intramolecular recyclization to the thiadiazolino[4,5-*d*]pyrimidine *S*-oxide (**12a**) (1,3-sulfur migration), and subsequent dehydration through the Pummerer reaction intermediate (**13a**). In the absence of thionyl chloride, **12a** would directly undergo dehydration to give **14a.** Attempts to isolate pure **10b** and **10c** in the reaction of **8b** or **8c** with thionyl chloride were unsuccessful, indicating that the stability of **10a** might arise from an electron-releasing character of the methyl group. The

Scheme I



isolation of **10a** is worthy of note as such a compound has rarely been isolated in the reaction of 2-hydrazinopyridine with thionyl chloride[15] (Scheme II).

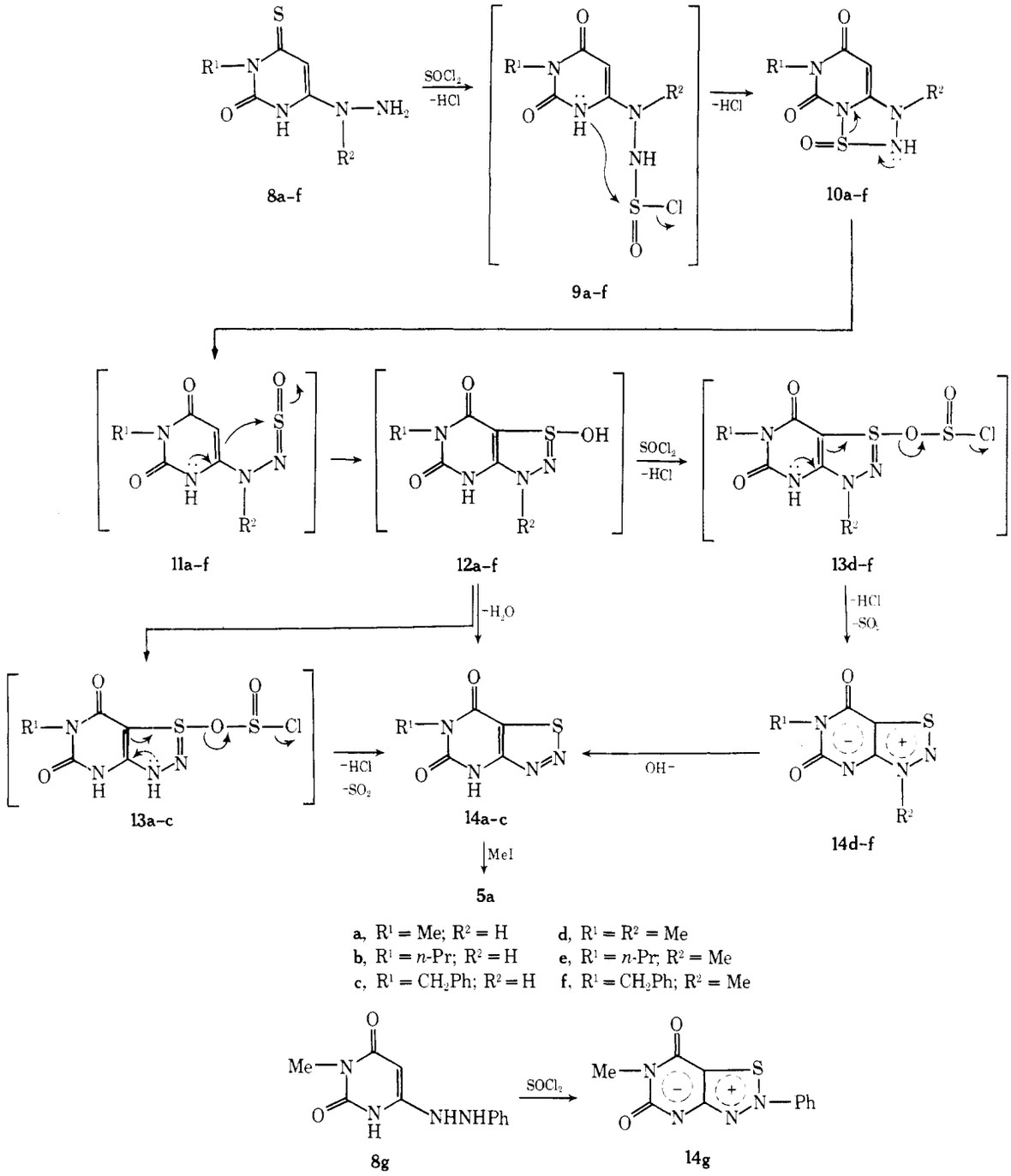
The reaction of hydrazinouracils with thionyl chloride described above could successfully be extended to the preparation of mesoionic [1,2,3]thiadiazolo[4,5-*d*]pyrimidines, a new class of mesoionic heterocycles. Namely, treatment of 3-methyl-6-(1-methylhydrazino)uracil (**8d**)[16] with thionyl chloride at 0 °C for 30 min gave 3,6-dimethyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10d**) [δ 5.32 (s, 1 H, C-4 H); 1100 cm^{-1} (SO)],[14] which upon refluxing in thionyl chloride for 15 min afforded the mesoionic compound, *anhydro*-3,6-dimethyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d**) in a good yield. Compound **14d** was also attained directly from **8d** by treatment with thionyl chloride at room temperature (an exothermic reaction). As depicted in Scheme II, the rearrangement of **10d** to **14d** accompanying 1,3-sulfur migration was envisioned as proceeding through the Pummerer reaction intermediate (**13d**). The thermal ring transformation observed on **10a** seems to be less favorable in the case of **10d,** since no reaction occurred even after refluxing **10d** in dioxane (bp 101 °C) for 1 h. In contrast with the reaction of **8d** with thionyl chloride giving **10d,** treatment of other 3-alkyl-6-(1-methylhydrazino)uracils (**8e** and **8f**[17]) with thionyl chloride directly gave the respective mesoionic compounds (**14e** and **14f**), and attempted isolation of the intermediates (**10e** and **10f**) was again unsuccessful. These findings are consistent with the observed instability of **10b** and **10c.** 3-Methyl-6-(2-phenylhydrazino)uracil (**8g**)[18] was also converted directly to *anhydro*-6-methyl-2-phenyl-5-hydroxy[1,2,3]thiadiazolo-[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14g**). The characterization of the mesoionic compounds prepared was established by analytical and spectral data as well as their smooth conversion to **14a, 14b,** and **14c** by the action of 0.5% sodium hydroxide in the cases of **14d, 14e,** and **14f.**

We next investigated the chemical properties of **5a.** Compound **5a** was extremely stable against acid hydrolysis. Thus, heating **5a** with concentrated hydrochloric acid in a sealed tube at 100 °C for 8 h resulted in the quantitative recovery of **5a.** Similar stability was also noted in the mesoionic compounds. For example, refluxing **14d** in 10% hydrochloric acid for 1 h did not give any hydrolyzed products. On the contrary, alkaline hydrolysis of **5a** with 0.6% potassium hydroxide gave the unexpected 1,3-dimethylbarbituric acid (**15**)[7] in 20% yield as the only isolatable product[19] (Scheme III). Reduction of **5a** with Raney nickel in ethanol caused the dethiation and nitrogen–nitrogen double bond cleavage to give a 60% yield of 6-amino-1,3-dimethyluracil (**16**).[20] Thiation of **5a** with excess phosphorus pentasulfide in pyridine furnished 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**17**) in a good yield. The actual site of thiation was decided by the fact that heating **17** with saturated ethanolic ammonia in a sealed tube yields the known 6-amino-1,3-dimethyl-4-thiouracil (1,3-dimethyl-6-thiocytosine) (**19**).[21] The sulfur atom at position 7 of **17** was found to react with hydrazines in a sealed tube to provide the corresponding 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one 7(6*H*)-hydrazones (**18a, 18b,** and **18c**). However, aniline did not give the expected product, presumably owing to its lower nucleophilicity than that of hydrazines.

In connection with recent interest in the possible involvement of thiirene intermediates in the photolysis and thermolyses of 1,2,3-thiadiazoles[22] and 1,2,3-benzothiadiazoles,[23] we also examined these reactions on **5a.** The irradiation of **5a** in ethanol by a high-pressure mercury lamp in a stream of nitrogen provided a 50% yield of symmetric 1,3-dimethyl-5-mercaptouracil disulfide (**22**). The disulfide **22** was readily characterized by the NMR spectrum and by its alternative synthesis consisting of the thermolysis of 1,3-dimethyl-5-mercaptouracil sulfide (**23**)[24] in Dowtherm A. A reasonable mechanism for the conversion of **5a** to **22** is that the initial formation of the diradical (**20a**) by the extrusion of nitrogen, followed by hydrogen abstraction from the solvent to give the thiyl radical (**21**), and subsequent dimerization. The thermolysis of **23** to **22** may also be explained by the participation of **21.** The structure of **22** was also supported by its thermal conversion to **23** in Dowtherm A (Scheme IV).

In contrast to the above results, the thermolysis of **5a** in Dowtherm A at 280 °C for 4 h surprisingly gave both 1,3,5,7-tetramethyl[1,4]dithiino[2,3-*d*;5,6-*e'*]dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (**26**) and 1,3,5,7-tetramethylthiopheno[2,3-*d*;4,5-*e'*]dipyrimidine-2,6,8,9-(1*H*,3*H*,5*H*,-7*H*)-tetrone (**27**) in 24 and 65% yield, respectively. Compound **27** was readily precipitated out from the reaction mixture and **26** was isolated by dilution of the filtrate with ethanol. When 5,7-dimethyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**24**),[25] an isomer of **5a,** was treated under the same conditions, **27** was again obtained in 84% yield.[26] The NMR data and elemental analyses of **26** and **27** supported the structures indicated; however, these data could not unequivocally exclude the possibility of the isomeric structures **29** for **26** and **30** or **31** for **27.** Rigorous structural proofs of **26** and **27** were accomplished by the following evidences. Heating **26** in Dowtherm A under similar conditions afforded **27,** indicating that **26** is a precursor of **27.** Reduction of **27** with Raney nickel furnished symmetric 5,5'-di(1,3-dimethyl)uracil (**28**), whose NMR spectrum (CF_3COOD) showed two singlets (δ 3.10 and 3.17) as four *N*-methyl groups and a singlet (δ 7.43)

Scheme II



as two protons at position 6 and 6′. The close proximity of the latter chemical shift to the reported value (CF_3COOD, δ 7.34)[27] for position 6 of 1,3-dimethyluracil supported the validity of the structure of **27**. Additional evidence for the assignment of **27** was derived from the comparison of its UV spectrum with that of recently reported 1,3,5,7-tetraethylthiopheno[2,3-*d*;4,5-*e*′]dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (**32**),[28] which could alternately be prepared by the thermolysis of **5b**. We suggest that the formation of **27** from either **5a** or **24** involves the intermediacy of thiirene (**25**). Thus, the thermolysis of **5a** or **24** could give the respective diradicals (**20a** and **20b**), both of which cyclize to **25**. Subsequent ring opening of **25** would provide both diradicals **20a** and **20b**, respectively. Reaction of either **20a** with **20b** or **25** with **20b** could yield **26**. Thus formed **26** can then undergo ring contraction to give **27**. The conversion of 1,4-dithiins to thiophenes has been well documented[29] (Scheme V).

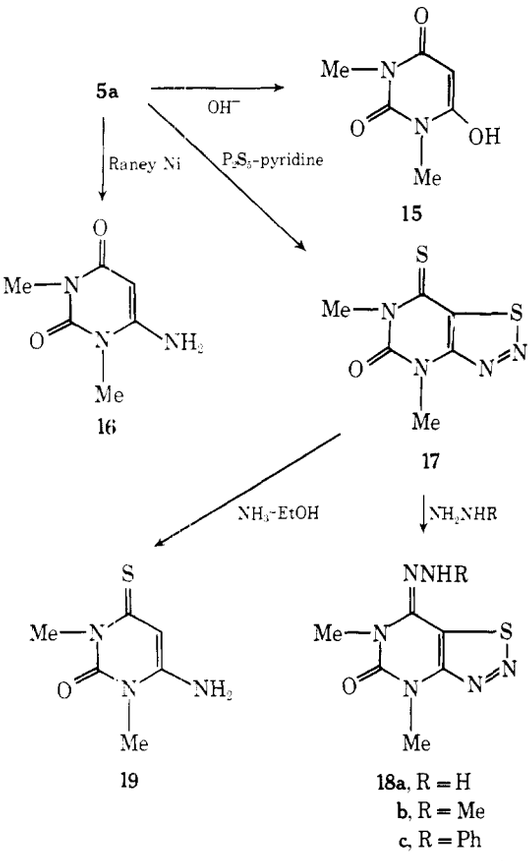
Experimental Section

Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd., spectrophotometer Model IR-E from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. UV spectra were recorded on a Hitachi 124 spectrophometer. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 75 eV. [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine derivatives prepared are summarized in Table I.

Preparation of 1,3-Dialkyl-6-hydrazinouracils (1a–e) and 3-Alkyl-6-hydrazinouracils (8a–g). Compounds **1a**,[7] **1b**,[8] **1c**,[10] **8a**,[13] **8d**,[16] **8f**,[17] and **8g**[18] were prepared according to the reported procedures, and other uracils were obtained as follows.

1,3-Diethyl-6-(1-methylhydrazino)uracil (1d) and 6-(1-Methylhydrazino)-3-*n*-propyluracil (8e). A mixture of 6-chloro-1,3-diethyluracil[7] (0.426 g, 0.002 mol) or 6-chloro-3-*n*-propyluracil[30] (1.0 g, 0.005 mol) and methylhydrazine (1 mL) in EtOH (10 mL) was stirred at room temperature for 3 h. The reaction mixture was evap-

Scheme III

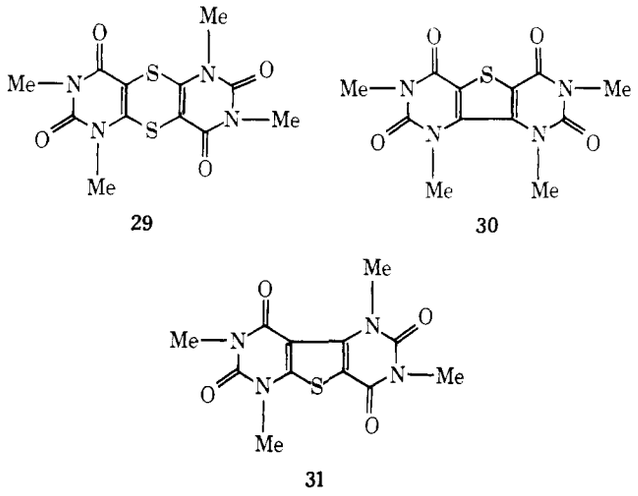


orated in vacuo and the residue was recrystallized from EtOH–H_2O to give the corresponding products.

Compound **1d** (0.26 g; 62%): mp 102–104 °C. Anal. Calcd for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 50.72; H, 7.59; N, 26.31.

Compound **8e** (0.86 g; 85%): mp 119–120 °C. Anal. Calcd for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.27. Found: C, 48.51; H, 7.05; N, 28.15.

6-Hydrazino-3-*n*-propyluracil (8b) and 3-Benzyl-6-hydrazinouracil (8c). A mixture of 6-chloro-3-*n*-propyluracil[13] (0.94 g, 0.005 mol) or 3-benzyl-6-chlorouracil[31] (0.6 g, 0.0025 mol) and 10% hydrazine hydrate (10 mL) was refluxed for 45 min. The reaction mixture



was evaporated in vacuo and the residue was covered with H_2O. The insoluble material was filtered and recrystallized from EtOH to give the corresponding products.

Compound **8b** (0.64 g; 62%): mp 242–243 °C. Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.43. Found: C, 45.33; H, 6.47; N, 30.48.

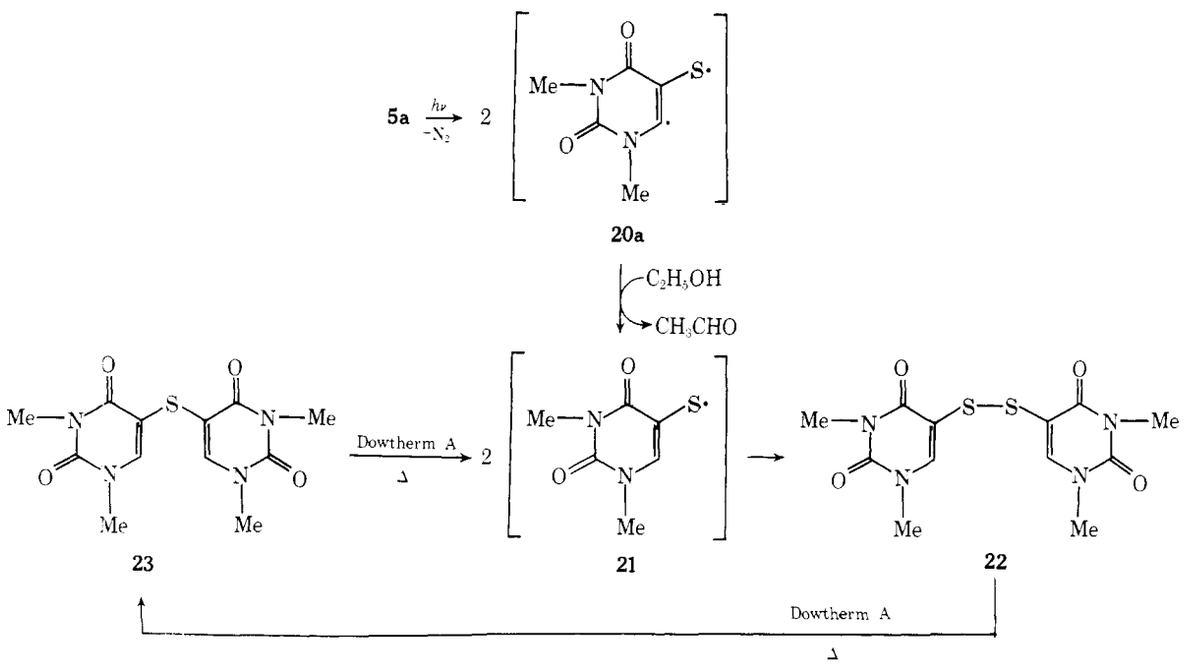
Compound **8c** (0.5 g; 90%): mp 212–213 °C. Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.13. Found: C, 56.83; H, 5.29; N, 24.34.

6-Hydrazino-1,3-dimethyl-2-thiouracil (1e). This compound was prepared by two steps starting with 1,3-dimethyl-2-thiobarbituric acid.[32] A mixture of 1,3-dimethyl-2-thiobarbituric acid (1.72 g, 0.01 mol) and $POCl_3$ (10 mL) containing H_2O (0.5 mL) was refluxed for 45 min. The excess $POCl_3$ was removed in vacuo and the residue (syrup) was poured onto ice–H_2O. The solution was extracted with $CHCl_3$ (three 30-mL portions) and dried (Na_2SO_4). The $CHCl_3$ extracts were evaporated in vacuo and the residue was recrystallized from EtOH to give 6-chloro-1,3-dimethyl-2-thiouracil (1 g; 53%): mp 189–191 °C. Anal. Calcd for $C_6H_7ClN_2OS$: C, 37.80; H, 3.71; N, 14.70. Found: C, 37.56; H, 3.77; N, 14.99.

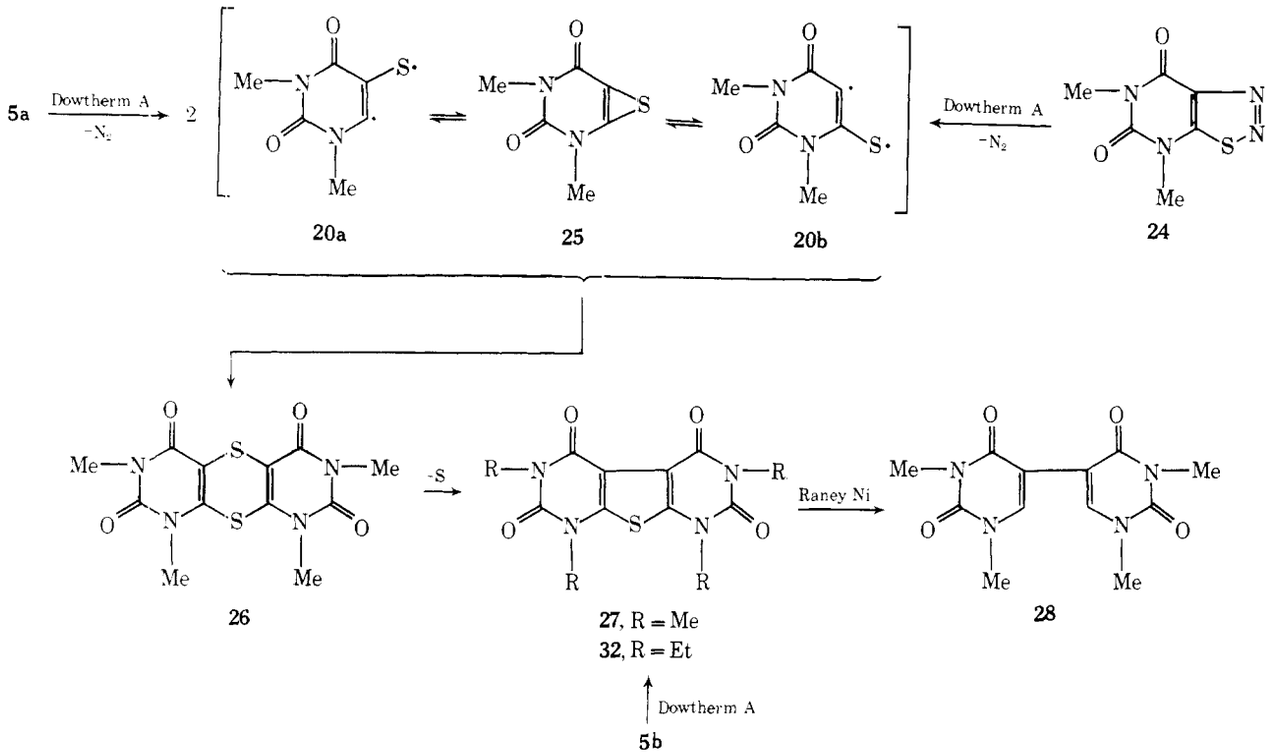
A mixture of the chlorouracil (0.38 g, 0.002 mol) and 10% hydrazine hydrate (5 mL) was treated as described in the preparation of **8b** and **8c** to give **1e** (0.21 g; 60%): mp 223–224 °C. Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.69; H, 5.42; N, 30.09. Found: C, 38.70; H, 5.31; N, 30.00.

4,6-Dialkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (5a–b). Method A. A mixture of the appropriate hydrazinouracils **1a–d** (0.01 mol) and thionyl chloride (20 mL) was stirred

Scheme IV



Scheme V



at room temperature (an exothermic reaction) for 30 min. The resulting solution was evaporated in vacuo and the residue was covered with chilled H_2O. The insoluble material was filtered and recrystallized to give the corresponding **5**.

In complete analogy with the above results, treatment of **1e** with thionyl chloride afforded **5a**.

Method B. A mixture of 6-methyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**14a**) (0.184 g, 0.001 mol), methyl iodide (0.426 g, 0.003 mol), and K_2CO_3 (0.414 g, 0.003 mol) in DMF (10 mL) was refluxed for 2 h. The reaction mixture was evaporated in vacuo and the residue was covered with H_2O. The insoluble solid was filtered and recrystallized to give **5a**.

6-Alkyl[1,2,3]thiadiazolo[4,5-d]pyrimidine-5,7(4*H*,6*H*)-diones (14a–c). Method A. A mixture of the appropriate hydrazinouracils **8a–c** (0.001 mol) with thionyl chloride (2 mL) was stirred at room temperature (an exothermic reaction) for 30 min. The reaction mixture was treated as described in method A of **5a–b** to give the corresponding **14**.

Method B. A suspension of 6-methyl[1,2,3,5]thiatriazolino[5,4-c]pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**) (0.2 g, 0.001 mol) and thionyl chloride (2 mL) was refluxed for 15 min. The reaction mixture was treated as described in method A of **5a–b** to give **14a**.

Method C. A mixture of **10a** (0.2 g, 0.001 mol) and EtOH (10 mL) was refluxed for 3 h. The reaction mixture was evaporated in vacuo and the residue was recrystallized to yield **14a**.

Method D. A suspension of the appropriate *anhydro*-6-alkyl-3-methyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d–e**) (0.001 mol) in 5% NaOH (5 mL) was heated at 95 °C for 10 min. The reaction mixture was neutralized with 5% HCl and extracted with $CHCl_3$ (three 10-mL portions). The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated in vacuo. Recrystallization of the residue afforded the respective **14a–c**.

6-Methyl[1,2,3,5]thiatriazolino[5,4-c]pyrimidine-5,7(6*H*)-dione 1-Oxides (10a and 10d). To ice-cooled (0 °C) thionyl chloride (5 mL) was added **8a** or **8d** (0.001 mol) over a period of 5 min with good stirring, and the mixture was maintained at the same temperature for 30 min. The reaction mixture was rapidly evaporated in vacuo at room temperature and the residue was covered with ice–H_2O. The separated solid was recrystallized to give the corresponding pure products.

Compound **10a:** recrystallized from MeOH (1.35 g; 67%); mp 197–198 °C; IR 1090 (SO), 1720 (CO), 3160 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 3.14 (s, 3 H, NCH_3), 5.38 (s, H, C-4 H), 12.50 (br, 2 H, N-2 H and N-3 H); MS *m/e* 202 (M^+); UV λ_{max} (EtOH) 260 (log ϵ 3.85), 400 nm (4.04). Anal. Calcd for $C_5H_6N_4O_3S$: C, 29.70; H, 2.97; N, 27.71. Found: C, 30.01; H, 3.01; N, 27.46.

Compound **10d:** recrystallized from EtOH (1.45 g; 67%); mp 202 °C; IR 1100 (SO), 1715 (CO), 3080 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 3.10 (s, 3 H, NCH_3), 4.00 (s, 3 H, NCH_3), 5.32 (s, 1 H, C-4 H), 12.00 (br, 1 H, NH); MS *m/e* 216 (M^+); UV λ_{max} (EtOH) 265 (log ϵ 4.25), 343 nm (4.24). Anal. Calcd for $C_6H_8N_4O_3S$: C, 33.32; H, 3.74; N, 25.92. Found: C, 33.61; H, 3.72; N, 25.96.

***anhydro*-6-Alkyl-3-methyl-5-hydroxy[1,2,3]thiadiazolo-[4,5-*d*]pyrimidinium-7(6*H*)-one Hydroxides (14d–f) and *anhydro*-6-Methyl-2-phenyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]-pyrimidinium-7(6*H*)-one Hydroxide (14g). Method A.** A mixture of the appropriate **8d–g** (0.001 mol) and thionyl chloride (1 mL) was stirred at room temperature (an exothermic reaction) for 30 min. The reaction mixture was evaporated in vacuo and the residue was dissolved in chilled H_2O (30 mL). The solution was extracted with $CHCl_3$ (three 20-mL portions) and the $CHCl_3$ extracts were dried (Na_2SO_4). Evaporation of the extracts in vacuo and the recrystallization of the residue afforded the corresponding products **14d–g.**

Method B. A mixture of **10d** (0.216 g, 0.001 mol) and thionyl chloride (2 mL) was refluxed for 15 min. The reaction mixture was treated as described in method A to give **14d.**

1,3-Dimethylbarbituric Acid (15). A suspension of **5a** (0.198 g, 0.001 mol) in 0.6% KOH (5 mL) was heated at 95 °C for 3 h. The reaction mixture was neutralized with AcOH and the precipitated solid was filtered. Recrystallization from EtOH gave **15** (0.03 g, 20%), mp 123–124 °C, identical with an authentic sample.[7]

6-Amino-1,3-dimethyluracil (16). A mixture of **5a** (0.198 g, 0.001 mol) and Raney Ni (NDHT-90, 0.5 g) in EtOH (20 mL) was refluxed for 1 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from EtOH–DMF to give **16** (0.09 g, 60%), mp >300 °C, identical with an authentic sample.[20]

4,6-Dimethyl[1,2,3]thiadiazolo[4,5-d]pyrimidin-5(4*H*)-one-7(6*H*)-thione (17). A mixture of **5a** (1.98 g, 0.01 mol) and P_2S_5 (4.44 g, 0.02 mol) in pyridine (60 mL) was refluxed for 3 h. The reaction mixture was evaporated in vacuo and the residue was covered with hot H_2O. After cooling, the precipitates were filtered and recrystallized to give **17.**

4,6-Dimethyl[1,2,3]thiadiazolo[4,5-d]pyrimidin-5(4*H*)-one 7(6*H*)-Hydrazones (18a–c). A mixture of **17** (0.214 g, 0.001 mol) and the appropriate hydrazines (1 mL) in EtOH (5 mL) was heated in a sealed tube at 100 °C for 3 h. The precipitated crystals were filtered and recrystallized to give the corresponding products **18a–c.**

6-Amino-1,3-dimethyl-4-thiouracil (1,3-Dimethyl-6-thiocytosine; 19). A suspension of **17** (0.214 g, 0.001 mol) in saturated ethanolic NH_3 (10 mL) was heated in a sealed tube at 100 °C for 2 h. The precipitated solid was filtered and recrystallized from EtOH to

give **19** (0.16 g; 94%), mp 267 °C dec, identical with an authentic sample.[21]

1,3-Dimethyl-5-mercaptouracil Disulfide (22). Method A. A solution of **5a** (0.198 g, 0.001 mol) in EtOH (400 mL) was irradiated with a 100-W high-pressure mercury lamp surrounded by a H_2O-cooled Pyrex filter at 30 °C for 2 h in a stream of nitrogen. The reaction mixture was evaporated in vacuo and the residue was recrystallized from EtOH to give **22** (0.086 g; 50%): mp 243–245 °C; IR 1710 cm^{-1} (CO); NMR (CF_3COOD) δ 3.23 (s, 6 H, two NCH_3), 3.33 (s, 6 H, two NCH_3), 8.17 (s, 2 H, two C-6 H); MS *m/e* 342 (M^+); UV λ_{max} (EtOH) 220 sh (log ϵ 3.93), 285 nm (4.01). Anal. Calcd for $C_{12}H_{14}O_4N_4S_2$: C, 42.09; H, 4.13; N, 16.36. Found: C, 42.20; H, 4.28; N, 16.30.

Method B. A mixture of 1,3-dimethyl-5-mercaptouracil sulfide (**23**)[24] (0.31 g, 0.001 mol) and Dowtherm A (1 mL) was heated at 280 °C for 2 h. The reaction mixture was diluted with *n*-hexane (10 mL) and the precipitated crystals were filtered. Recrystallization of the crude product from EtOH afforded **22** (0.08 g; 24%), identical with the material prepared by method A.

1,3-Dimethyl-5-mercaptouracil Sulfide (23). A mixture of **22** (0.103 g, 0.003 mol) and Dowtherm A (1 mL) was heated at 270 °C for 5 h. The reaction mixture was treated as described in method B of **22** to give **23** (0.03 g; 32%), mp 288 °C, identical with an authentic sample.[24]

1,3,5,7-Tetramethyl[1,4]dithiino[2,3-d;5,6-e']dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (26) and 1,3,5,7-Tetramethylthiopheno[2,3-d;4,5-e']dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (27). A mixture of **5a** (1.0 g, 0.005 mol) and Dowtherm A (2 mL) was heated at 280 °C for 4 h. After standing overnight at room temperature, the precipitated solid was filtered and recrystallized from DMF to give **27** (0.5 g; 65%): mp >300 °C; IR 1705 cm^{-1} (CO); NMR (CF_3COOD) δ 3.13 (s, 6 H, two NCH_3), 3.26 (s, 6 H, two NCH_3); MS *m/e* 308 (M^+); UV λ_{max} (EtOH) 245 (log ϵ 2.95), 304 nm (2.80). Anal. Calcd for $C_{12}H_{12}N_4O_4S$: C, 46.80; H, 3.97; N, 18.40. Found: C, 46.75; H, 3.90; N, 18.18.

The filtrate which removed **27** was diluted with EtOH (5 mL) and the precipitated crystals were filtered. The crude product was recrystallized from DMF–EtOH to give **26** (0.2 g; 24%): mp >300 °C; IR 1710 cm^{-1} (CO); NMR (CF_3COOD) δ 3.53 (s, 6 H, two NCH_3), 3.86 (s, 6 H, two NCH_3); MS *m/e* 340 (M^+); UV λ_{max} (EtOH) 230 (log ϵ 3.64), 280 (3.27), 310 nm (2.98). Anal. Calcd for $C_{12}H_{12}N_4O_4S_2$: C, 42.57; H, 3.24; N, 16.53. Found: C, 42.35; H, 3.53; N, 16.47.

Compound **27** was also prepared by the thermolysis of 5,7-dimethyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**24**) (0.8 g, 0.004 mol) in Dowtherm A (3 mL) at 290 °C for 3 h in 81% yield (0.41 g).

5,5-Di(1,3-dimethyl)uracil (28). A suspension of **27** (0.3 g, 0.001 mol) and Raney Ni (NDHT-90, 1 g) in EtOH (30 mL) was refluxed with stirring for 30 min. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from EtOH to give **28** (0.26 g, 95%): mp 286 °C; IR 1690 cm^{-1} (CO); NMR (CF_3COOD) δ 3.10 (s, 6 H, two NCH_3), 3.17 (s, 6 H, two NCH_3), 7.43 (s, 2 H, two C-6 H); MS *m/e* 278 (M^+); UV λ_{max} (EtOH) 238 sh (log ϵ 3.77), 294 nm (3.89). Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.78; H, 4.95; N, 19.76.

1,3,5,7-Tetraethylthiopheno[2,3-d;4,5-e']dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (32). A mixture of **5b** (0.45 g, 0.002 mol) and Dowtherm A (0.2 mL) was heated at 250 °C for 2 h. The reaction mixture was diluted with *n*-hexane (10 mL) and the precipitated crystals were filtered. Recrystallization from EtOAc afforded **32** (0.2 g; 55%): mp 204–205 °C (lit.[28] mp 204–205 °C); IR 1710 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.22 (t, 6 H, two CH_3–), 1.40 (t, 6 H, two CH_3–), 4.02 (two q, 8 H, four $-CH_2-$); MS *m/e* 364 (M^+); UV λ_{max} (EtOH) 245 (log ϵ 3.94), 304 nm (3.91). Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.72; H, 5.54; N, 15.38. Found: C, 52.75; H, 5.31; N, 15.33.

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Registry No.—**15,** 41949-07-9; **16,** 6642-31-5; **19,** 6506-84-9; **22,** 65150-45-0; **23,** 37737-50-1; **24,** 65150-48-3; **26,** 65150-46-1; **27,** 65150-47-2; **28,** 7033-42-3; **32,** 65150-50-7; 6-chloro-1,3-diethyluracil, 65150-41-6; 6-chloro-3-*n*-propyluracil, 50721-48-7; methylhydrazine, 60-34-4; 3-benzyl-6-chlorouracil, 5759-76-2; 1,3-dimethyl-2-thiobarbituric acid, 3158-63-2; 6-chloro-1,3-dimethyl-2-thiouracil, 65150-51-8; hydrazine, 302-01-2; phenylhydrazine, 100-63-0; 3-*n*-propylbarbituric acid, 5496-93-5.

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