Reaction of 6-Arylidenehydrazino-1,3-dimethyluracils with Thionyl Chloride Leading to Purine, Thiazolo[4,5-*d*]pyrimidine, Pyrimido[4,5-*e*][1,3,4]thiadiazine, Pyrazolo[3,4-*d*]pyrimidine, and [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine Derivatives

Misuzu Ichiba and Keitaro Senga*

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

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The reaction of 6-arylidenehydrazino-1,3-dimethyluracils with thionyl chloride in benzene afforded purine, thiazolo[4,5-*d*]pyrimidine, pyrimido[4,5-*e*][1,3,4]thiadiazine, pyrazolo[3,4-*d*]pyrimidine, and [1,2,3]thiadiazolo[4,5-*d*]pyrimidine derivatives, while the treatment of 6-(benzylidene-1'-methylhydrazino)-1,3-dimethyluracil with thionyl chloride in benzene gave 4-methylpyrimido[4,5-*e*][1,3,4]thiadiazine and 1-methylpyrazolo[3,4-*d*]pyrimidine derivatives. Plausible mechanisms for the formation of these fused pyrimidines are also described.

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Thionyl chloride, a bifunctional electrophile, is a useful reagent for the construction of a variety 5- or 6-membered heterocycles containing a sulfur. For example, the reactions of 6-aminouracils with this reagent have been reported to give isothiazolo[3,4-*d*]pyrimidines [1], thiazolo[4,5-*d*]pyrimidines [2], pyrimido[4,5-*c*][1,2,4]thiadiazines [3], and 5-thiaflavins [4,5], respectively. Previously, we have reported that the treatment of 6-hydrazinouracils with thionyl chloride affords the hitherto unknown heterocycle, [1,2,3]thiadiazolo[4,5-*d*]pyrimidines, including their mesoionic compounds [6]. In connection with these findings, we now wish to report the reaction of 6-arylidenehydrazino-1,3-dimethyluracils Ia-e [7] with thionyl chloride which resulted in the formation of some biologically intriguing fused pyrimidines, *i.e.*, purine, thiazolo[4,5-*d*]pyrimidine, pyrimido[4,5-*e*][1,3,4]thiadiazine, pyrazolo[3,4-*d*]-pyrimidine, and [1,2,3]thiadiazolo[4,5-*d*]pyrimidine derivatives. Additionally, we also describe the reaction of 6-(benzylidene-1'-methylhydrazino)-1,3-dimethyluracil (VII) [7] with thionyl chloride leading to 4-methylpyrimido-[4,5-*e*][1,3,4]thiadiazine and 1-methylpyrazolo[3,4-*d*]pyrimidine derivatives.

As a preliminary investigation, we first undertook brief reaction on Ia with 3 equivalents of thionyl chloride in dry benzene at 95° for 2 hours, and unexpectedly obtained the purine (IIIa, 2%) [8] and the thiazolo[4,5-*d*]pyrimidine (IVa, 13%) [2] along with the pyrazolo[3,4-*d*]pyrimidine (Va, 2%) [9]. Likewise, the treatment of other uracils Ib-e [7] with thionyl chloride under the same conditions gave the corresponding fused pyrimidines IIIb-e, IVb-e, and Vb-e in similar yields, respectively (Tables I and II). In general, the purines were readily precipitated out from the reaction mixture, while the other products were isolated by the fractional recrystallization of the filtrate from ethanol. The structures of these fused pyrimidines were confirmed by the analytical and spectral data as well as by comparison of their spectral data with those of authentic samples.

Since the isolation of purines and thiazolo[4,5-*d*]pyrimidines is of particular interest on the mechanistic ground as an abnormal type of Fisher's indole synthesis, the reaction was further carried out under several conditions in order to establish the mechanism for the formation of these fused pyrimidines. For example, stirring of Ia with 3 equivalents of thionyl chloride in benzene at room temperature for 30 minutes afforded the high melting point co-

Table I

Purines III, Thiazolo[4,5-*d*]pyrimidines IV and Pyrazolo[3,4-*d*]pyrimidines V

		Compounds					
		III [a] [b]		IV [c]		V [c] [d]	
	Ar	Mp (°C)	Yield (%)	Mp (°C)	Yield (%)	Mp (°C)	Yield (%)
a	C_6H_5	>300	2	242	13	242	2
b	4-Br-C_6H_4	>300	2	236	14	>300	2
c	4-Cl-C_6H_4	>300	4	291	23	>300	2
d	4-Me-C_6H_4	>300	2	196	21	>300	2
e	4-MeO-C_6H_4	>300	2	210	13	271	1

[a] All compounds were recrystallized from dimethylformamide. [b] All compounds were identical with the authentic samples [8]. [c] All compounds were recrystallized from ethanol. [d] All compounds were identical with the authentic samples [12].

lorless solid (>300°) as a major product and the purine IIIa (2%). The colorless solid, which exhibits carbonyl absorption bands at 1650 and 1705 cm^{-1} in the ir spectrum, was highly insoluble both in the protic and aprotic solvents, therefore, its purification and spectral (nmr, uv, and ms) measurements were found to be unsuccessful. However, the prolonged heating of this solid in dimethylformamide under reflux led to the exclusive formation of the pyrazolo[3,4-*d*]pyrimidine Va.

Table II

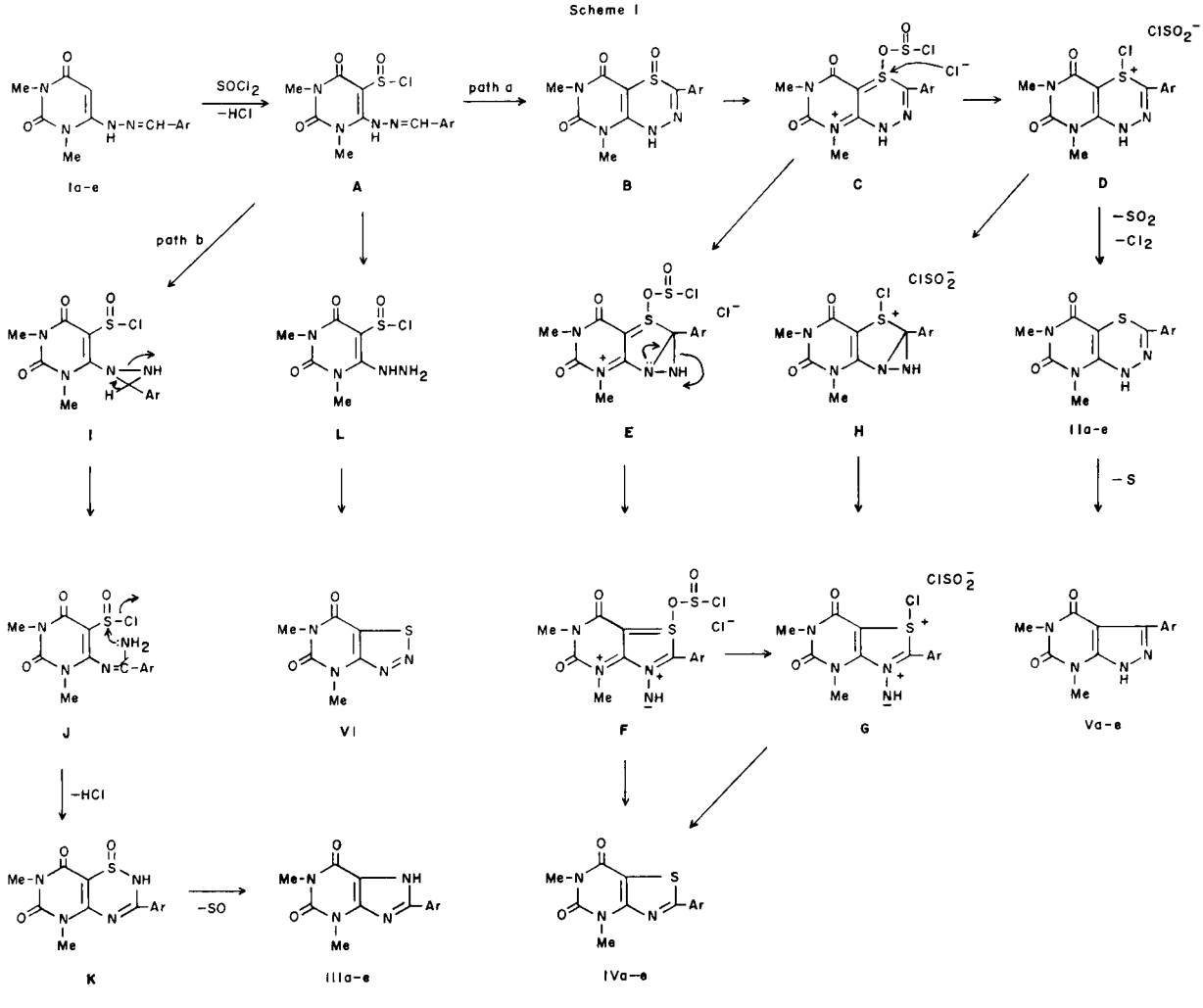
Thiazolo[4,5-*d*]pyrimidines IV

	Calcd. (%)				Found (%)		
	C	H	N	Formula	C	H	N
a	57.12	4.06	15.38	$C_{13}H_{11}N_3O_2S$	57.01	4.06	15.25
b	44.33	2.87	11.93	$C_{13}H_{10}BrN_3O_2S$	44.22	2.83	11.94
c	50.73	3.28	13.66	$C_{13}H_{10}ClN_3O_2S$	50.59	3.24	13.83
d	58.51	4.57	14.63	$C_{14}H_{13}N_3O_2S$	58.34	4.67	14.86
e	55.42	4.32	13.85	$C_{14}H_{13}N_3O_3S$	55.24	4.18	14.11

On the other hand, the treatment of Ia with 3 equivalents of thionyl chloride in dry benzene at 95° for 30 minutes yielded the pyrimido[4,5-*e*][1,3,4]thiadiazine (IIa, 2%) and [1,2,3]thiadiazolo[4,5-*d*]pyrimidine (VIa, 3%) [6] as additional new products along with IIIa (3%), IVa (13%), and Va (3%). These products were isolated by the multifractional recrystallization using ethanol. The characterization of IIa was based on the observation of a secondary amino absorption band (3250 cm^{-1}) in the ir spectrum as well as a strong M^+ ion and a remarkable M^+ -32 fragment ion due to the liberation of a sulfur in the mass spectrum. The structure of IIa was also supported by its successful thermal (250°, 5 minutes) desulfurization into the pyrazolo[3,4-*d*]pyrimidine Va (97%).

Further corroborating evidence could not be obtained for the formation of purines III and thiazolo[4,5-*d*]pyrimidines IV, however, the reaction of I with thionyl chloride leading to various fused pyrimidines would proceed by the

Scheme I



routes shown in the Scheme I. Namely, the electrophilic attack of thionyl chloride at the most electron rich 5-position of I would give the 5-sulfinyl chloride intermediate **A**. The **A** would then undergo cyclization by path a to the thiadiazine *S*-oxide **B** and subsequent deoxygenation *via* the *O*-sulfinyl chloride **C** and sulfenyl chloride **D** intermediates would yield the pyrimido[4,5-*e*][1,3,4]thiadiazine II. The formation of **C** is presumably accelerated by the electron donating methyl group on the pyrimidine nucleus rather than the hydrogen transfer in the thiadiazine moiety.

On the other hand, the intramolecular cyclization of **A** to the tricyclic intermediate **E** and subsequent ring contraction *via* the *O*-sulfinyl chloride **F** and sulfenyl chloride **G** intermediates would give the thiazolo[4,5-*d*]pyrimidine IV. As an alternative route, the intramolecular cyclization and ring contraction of **D** to IV *via* the intermediates **H** and **G** could not be ruled out.

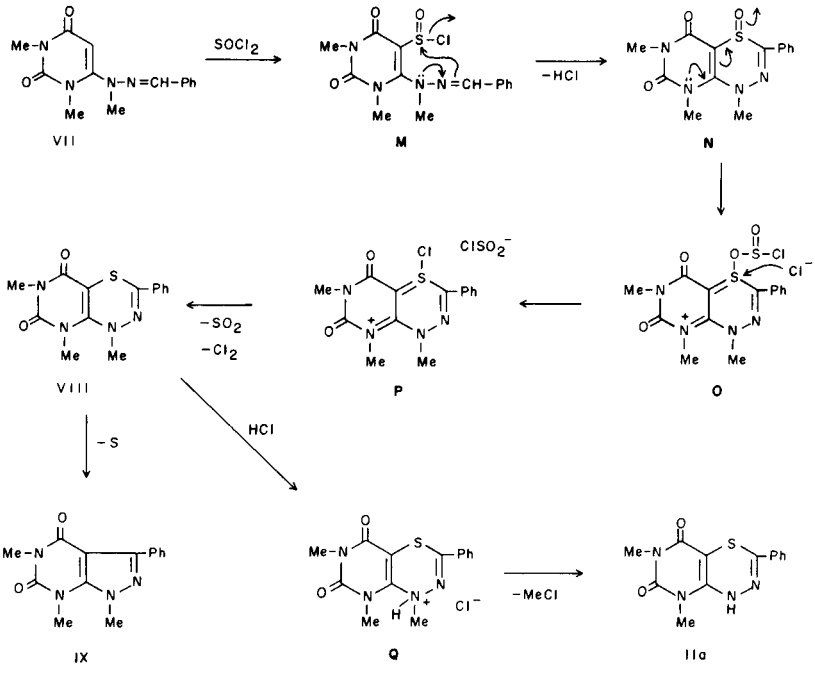
Furthermore, the formation of the purine III can be best explained by taking into account a diaziridine intermediate. Namely the intramolecular attack of the α-nitrogen atom of **A** at the electron deficient azomethine carbon would afford the diaziridinouracil I by the path b. Following *N-N* bond cleavage to the amidinouracil **J** and subsequent cyclization *via* the loss of sulfur monoxide of the pyrimidothiadiazine **K** would then yield III. The involvement of the diaziridine intermediate was supported by our recent findings [9] and the thermal ring contraction of **K** to III was substantiated by a precedent [3]. The formation of [1,2,3]thiadiazolo[4,5-*d*]pyrimidine VI would involve the simple hydrolysis of the azomethine function to the intermediate **L** and subsequent cyclization [6].

In connection with the above results, we also investigated the reaction of 6-(benzylidene-1′-methylhydrazino)-1,3-dimethyluracil VII with 3 equivalents of thionyl chloride in dry benzene at 40° for 6 hours, and obtained the 4-methylpyrimido[4,5-*d*][1,3,4]thiadiazine (VIII, 9%), the 1-methylpyrazolo[3,4-*d*]pyrimidine (IX, 45%) [10]. As shown in the Scheme II, the reaction of VII with thionyl chloride leading to VIII and IX would proceed through the intermediates **M**, **N**, **O**, and **P** by essentially similar mechanism described above. We have previously reported that the reaction of VII with thionyl chloride proceeds by the direct cyclization of **M** accompanying the loss of hydrogen chloride and sulfur monoxide to give IX, however, the successful isolation of VIII suggested the correction of our previous speculation [10]. The demethylation of VIII into IIa would involve the intermediate **Q** and the acid catalyzed demethylation of this type has been reported [11]. In contrast to the reaction of I with thionyl chloride, the reaction of VII with thionyl chloride did not afford any purine and thiazolo[4,5-*d*]pyrimidine since the benzylidene-1′-methylhydrazino group could not form the diaziridine intermediate.

EXPERIMENTAL

Melting points were taken on a Yanaco micro-hot-stage melting point apparatus and are uncorrected. The ir spectra were recorded on a Jasco A-100 spectrophotometer from samples mulled in Nujol. The nmr spectra were determined at 90 MHz with a Varian EM-390 spectrometer with tetramethylsilane as the internal standard. The uv spectra were performed on a Hitachi 124 spectrophotometer in ethanol. The molecular weights for all compounds were correctly analyzed by mass spectroscopy with a JEOL JMS D-300 spectrometer with a direct-inlet system at 70 eV.

Scheme II



Reaction of 6-Arylidenehydrazino-1,3-dimethyluracils Ia-e with Thionyl Chloride. A.

A mixture of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils Ia-e [7] (0.01 mole) and thionyl chloride (0.03 mole) in dry benzene (80 ml) was heated at 95° for 2 hours with stirring. After cooling, the precipitates were collected by filtration to give the corresponding purines IIIa-e. The filtrate was evaporated *in vacuo* at room temperature and the residue was covered with ethanol. The insoluble material was filtered and recrystallized from ethanol to yield the respective thiazolo[4,5-*d*]pyrimidines IVa-e. The filtrate was again evaporated *in vacuo* at room temperature and the residue was recrystallized to give the corresponding pyrazolo-[3,4-*d*]pyrimidines Va-e. The compounds IIIa-e and Va-e were identical with the authentic samples [8,12], respectively (Tables I and II).

B.

To a suspension of Ia (0.63 g, 0.0025 mole) in dry benzene (25 ml) was added dropwise thionyl chloride (0.89 g, 0.0075 mole) and the mixture was stirred at room temperature for 30 minutes. The precipitates were collected by filtration and washed with ethanol to give the purine IIIa (0.013 g, 2%), which was identical with the authentic sample [8]. The filtrate was evaporated to half the volume and the precipitates were filtered to give colorless solid (0.69 g), mp >300°; ir: 1650, 1705 cm^{-1} (CO). Refluxing of the colorless solid (0.50 g) in dimethylformamide (5 ml) for 1 hour, followed by evaporation of the reaction mixture and subsequent recrystallization gave the pyrazolo[3,4-*d*]pyrimidine Va (0.45 g), which was identical with the authentic sample [12].

C.

To a suspension of Ia (1.29 g, 0.005 mole) in dry benzene (40 ml) was added dropwise thionyl chloride (1.78 g, 0.015 mole) and the mixture was heated at 95° for 30 minutes with stirring. After cooling, the precipitates were collected by filtration, washed with ethanol and dried to give the purine IIIa (0.038 g, 3%), which was identical with the authentic sample [8]. The filtrate was recrystallized repeatedly from ethanol to afford the pyrimido[4,5-*e*][1,3,4]thiadiazine (IIa) (0.03 g, 2%), the thiazolo[4,5-*d*]pyrimidine (IVa) (0.18 g, 13%), the pyrazolo[3,4-*d*]pyrimidine (Va) (0.05 g, 3%), and the [1,2,3]thiadiazolo[4,5-*d*]pyrimidine (VI) (0.03 g, 0.3%). The compounds Va and VI were identical with authentic samples [12,6], respectively.

Compound IIa.

This compound had mp 210°; ir: 1640, 1705 (CO), 3250 cm^{-1} (NH); nmr (DMSO-d_6): δ 3.13 (s, 3H, N-Me), 3.36 (s, 3H, N-Me), 7.43-7.63 (m, 5H, Ph), 10.8 (s, 1H, NH, deuterium oxide exchangeable); ms: m/e 288 (M^+), 256 (M^+-32); uv (ethanol): λ max (log ε) 263 (4.48), 293 nm (4.06).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43. Found: C, 54.08; H, 4.20; N, 19.32.

5,7-Dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (Va).

The compound IIa (0.144 g, 0.0005 mole) was heated at 250° for 5 minutes. The reaction mixture was covered with ethanol and the insoluble material was collected by filtration. Recrystallization gave Va (0.12 g, 97%), which was identical with the authentic sample [9].

Reaction of 6-(Benzylidene-1'-methylhydrazino)-1,3-dimethyluracil (VII) with Thionyl Chloride.

A mixture of 6-(benzylidene-1'-methylhydrazino)-1,3-dimethyluracil (VII) [7] (0.52 g, 0.002 mole) with thionyl chloride (0.71 g, 0.006 mole) in dry benzene (10 ml) was stirred at 40° for 6 hours. After cooling, the precipitates were collected by filtration and recrystallized from ethanol to give the 1-methylpyrazolo[3,4-*d*]pyrimidine (IX) (0.24 g, 45%), which was identical with the authentic sample [10]. The filtrate was evaporated *in vacuo* at room temperature asnd the residue was covered with ethanol. The crystals which separated out were collected by filtration and recrystallized from ethanol to give the 4-methylpyrimido[4,5-*e*][1,3,4]thiadiazine (VIII) (0.05 g, 9%) and the pyrimido[4,5-*e*][1,3,4]thiadiazine (IIa) (0.06 g, 11%). The compound IIa was identical with the authentic sample obtained in the reaction of Ia with thionyl chloride.

Compound VIII.

This compound had mp 160°; ir: 1630, 1700 cm^{-1} (CO); ms: m/e 302 (M^+); uv (ethanol): λ max (log ε) 235 (4.14), 265 (4.12), 312 nm (3.46).

Anal. Calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.60; H, 4.68; N, 18.53. Found: C, 55.48; H, 4.39; N, 18.65.

1,5,7-Trimethylpyrazolo[3,4-*d*]pyrimidine-6,8(5*H*,7*H*)-dione (IX).

The compound VIII (0.03 g, 0.0001 mole) was heated at 250° for 5 minutes. After cooling, the reaction mixture was covered with ethanol and the insoluble material was filtered to give IX (0.026 g, 95%), which was identical with the authentic sample [10].

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