N-Bromosuccinimide in Heterocyclic Synthesis. Synthesis of Pyrazolo[3,4-*d*]pyrimidines, Pyrimido[5,4-*e*]-*as*-triazines, and Pyrimido[4,5-*c*]pyridazines from 6-Arylidenehydrazino-1,3-dimethyluracil Derivatives

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Reactions of 6-arylidenehydrazino-1,3-dimethyluracil derivatives with *N*-bromosuccinimide leading to pyrazolo[3,4-*d*]pyrimidines, pyrimido[5,4-*e*]-*as*-triazines, and pyrimido[4,5-*c*]pyridazines are described.

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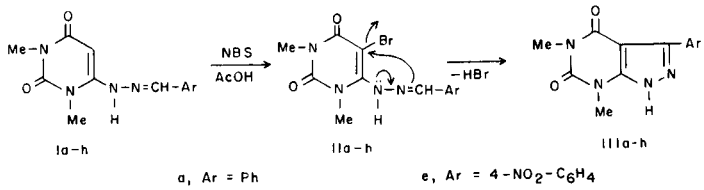
N-Bromosuccinimide (NBS) has been extensively employed as useful brominating and oxidizing agent in many classes of organic compounds [1], however, the versatility of this reagent for the construction of heterocyclic systems still remains to be studied. We have previously reported that the reaction of 6-amino-5-arylideneamino-1,3-dimethyluracils or 5-arylideneamino-1,3-dimethylbarbituric acids with NBS offers a convenient route to purines and oxazolo[5,4-*d*]pyrimidines, respectively [2]. In connection with these findings, we now report the reaction of 6-arylidenehydrazino-1,3-dimethyluracil derivatives with NBS leading to pyrazolo[3,4-*d*]pyrimidines, pyrimido[5,4-*e*]-*as*-triazines, and pyrimido[4,5-*c*]pyridazines. These heterocycles are of biological interest, since their structures are closely related to purine or pteridine.

Refluxing of 6-benzylidenehydrazino-1,3-dimethyluracil (Ia) [3] with an equimolar amount of NBS in acetic acid for 2 hours, followed by evaporation of the reaction mixture, and subsequent addition of ethanol caused the separation of 5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione (IIIa) in 66% yield. This reaction was equally applicable to other 6-arylidenehydrazino-1,3-dimethyluracils (Ib-h) to give the corresponding pyrazolopyrimidines (IIIb-h) in 63-81% yields (Table I).

As depicted in Scheme I, the reaction presumably proceeds through the initial formation of the 6-arylidenehydrazino-5-bromo-1,3-dimethyluracils (II) and subsequent cyclization accompanying dehydrobromination. The involvement of II was supported by the fact that the reaction of a uracil closely related to I with NBS leads to the formation of the corresponding 5-bromo derivative (*vide infra*).

Scheme I



a, Ar = Ph
b, Ar = 4-Br-C_6H_4
c, Ar = 4-Cl-C_6H_4
d, Ar = 3,4-Cl_2-C_6H_3
e, Ar = 4-NO_2-C_6H_4
f, Ar = 4-Me-C_6H_4
g, Ar = 4-MeO-C_6H_4
h, Ar = 3,4-CH_2O_2-C_6H_3

It should be noted that the pyrazolopyrimidines having an electron-releasing group on the phenyl group (*i.e.*, IIIa, f,g,h) were found to exist in two polymorphic forms. For example, the recrystallization of IIIa from ethanol and dimethylformamide (approximately 30:1) gave pale yellow fine needles which denoted as form I, while the recrystalli-

Table I

3-Aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

Compound Number	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
IIIa	256-257	ethanol-DMF [a]	66	60.93	4.72	21.87	$C_{13}H_{12}N_4O_2$	60.70	4.63	21.69 [a]
		DMF [b]						61.00	4.61	21.78 [b]
IIIb	>300	ethanol-DMF	67	46.58	3.31	16.72	$C_{13}H_{11}BrN_4O_2$	46.54	3.19	16.75
IIIc	>300	ethanol-DMF	77	53.70	3.82	19.27	$C_{13}H_{11}ClN_4O_2$	53.58	3.72	19.19
IIId	>300	DMF	67	48.01	3.11	17.23	$C_{13}H_{10}Cl_2N_4O_2$	48.36	3.27	17.60
IIIe	>300	DMF	63	51.83	3.68	23.25	$C_{13}H_{11}N_5O_4$	51.80	3.65	23.33
IIIf	>300	ethanol-DMF	81	62.21	5.22	20.73	$C_{14}H_{14}N_4O_2$	61.90	5.16	20.67
IIIg	271-272	ethanol-DMF	68	58.73	4.93	19.57	$C_{14}H_{14}N_4O_3$	58.51	4.98	19.35
IIIh	>300	ethanol-DMF	69	56.00	4.03	18.66	$C_{14}H_{12}N_4O_4$	56.00	3.98	18.40

[a] Form I. [b] Form II.

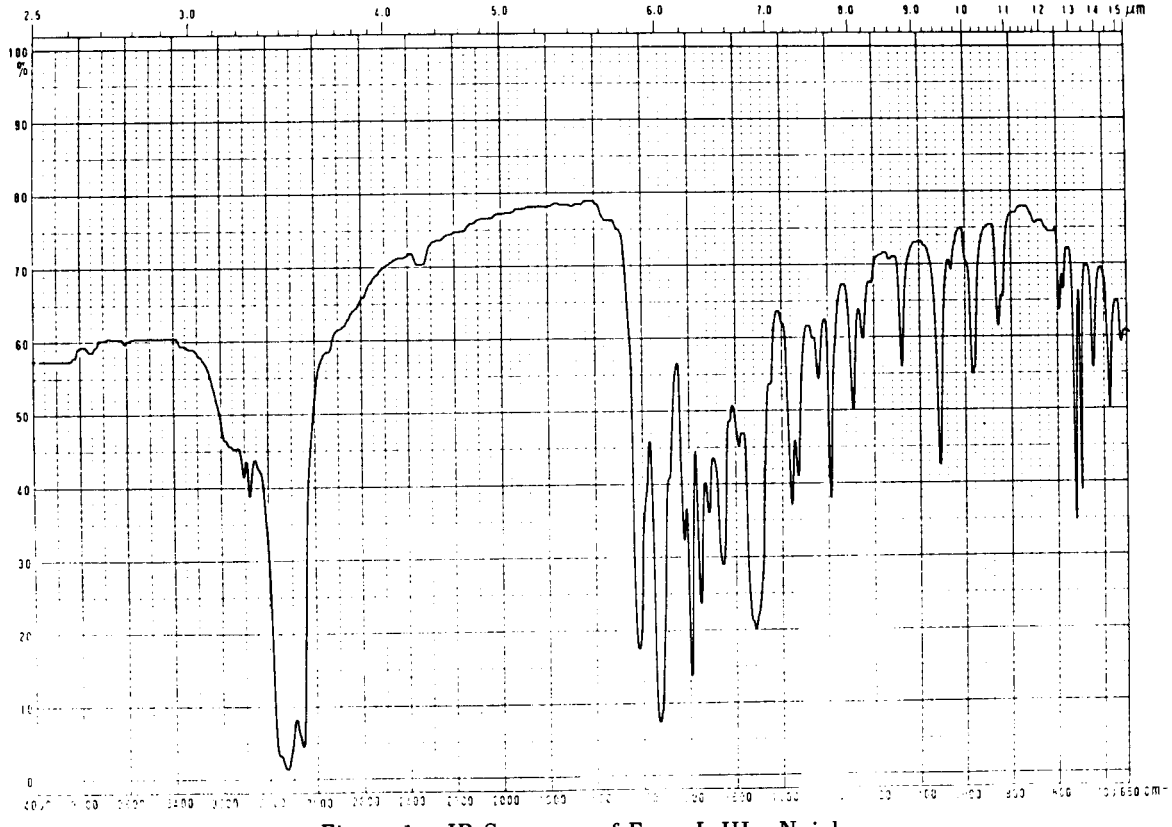


Figure 1. IR Spectrum of Form I, IIIa, Nujol.

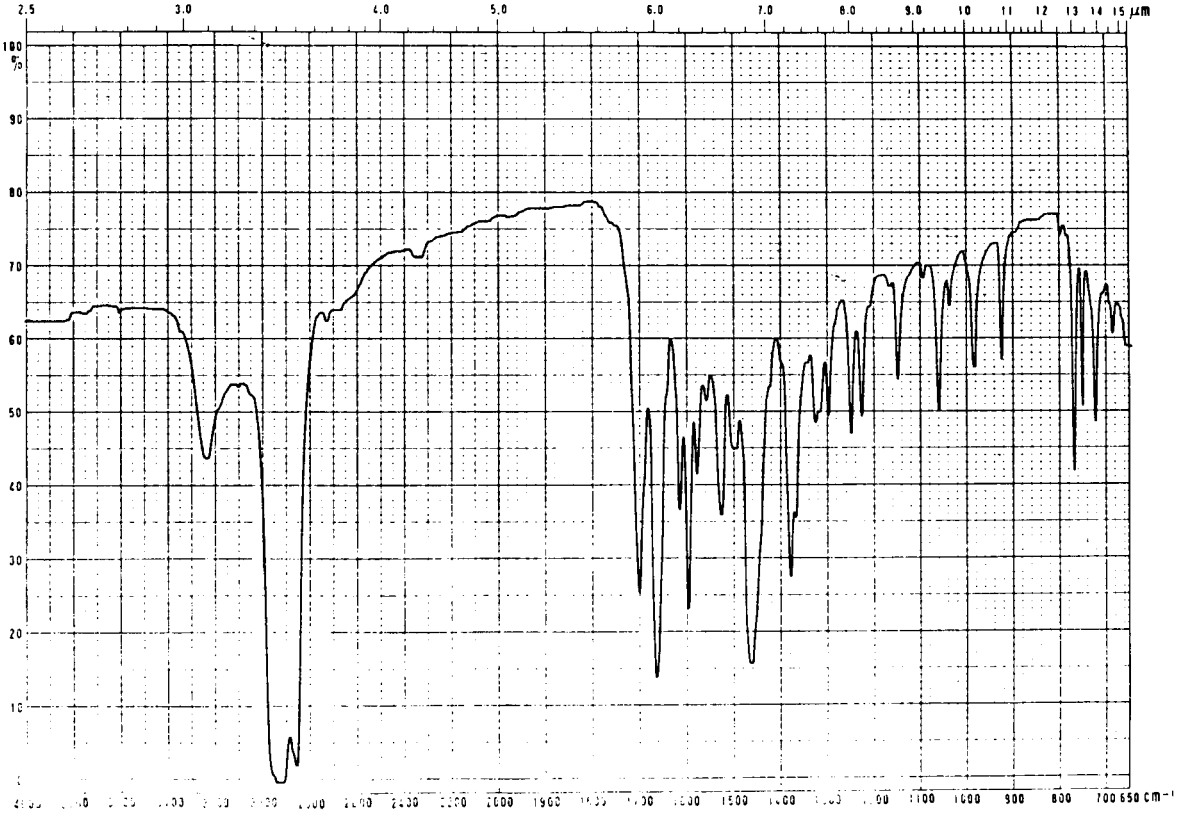


Figure 2. IR Spectrum of Form II, IIIa, Nujol.

zation of IIIa from dimethylformamide yielded the second polymorph, form II, as colorless fine needles. In general, the crude IIIa obtained by the dilution with ethanol exists in the crystal form I [4].

As shown in Figures 1 and 2, the significant differences were observed on the secondary amino absorption band in the range of 3000-3300 cm^{-1} in the ir spectra. Moreover, as shown in Figures 3 and 4, the dta (Differential Thermal Analysis) of form I exhibited two endothermic peaks, while the form II revealed a single endothermic peak. The small endothermic peak observed at 232° in form I may be attributed as the transition peak [5]. Since this peak is small, the melting point of form I exhibits essentially the same value with that of form II on determination by the naked eye. Although the X-ray diffraction technique should also be employed to establish the polymorphism, the ir and dta data strongly suggested the existence of two polymorphic forms. Compound IIIa has previously been reported and several melting points were recorded in the literature, however, the existence of polymorphic forms has been apparently overlooked [3,6]. In contrast to the above, the pyrazolopyrimidines having an electron-withdrawing substituent (*i.e.*, IIIb,c,d,e) predominantly exist in the form which classified as form II, and none of the crystals denoted as form I could be obtained.

The reaction of I with NBS was equally applicable to 6-(2′-arylidene-1′-methylhydrazino)-1,3-dimethyluracils (IVa-f) [3], however, somewhat different results were obtained. Namely, heating of IVa with an equimolar amount of NBS in acetic acid for 2 hours resulted in the formation of expected 1,5,7-trimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (VIa) [7] and unpredicted 6,8-dimethyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (Xa) [8] in 5 and 9% yields, respectively. Analogously, the other uracils IVb-e also react with NBS to give the corresponding pyrazolopyrimidines (VIb-e) and pyrimidotriazines (Xb-e) in 6-18 and 6-14% yields, respectively. Compounds VI and X were separated by careful fractional recrystallization. In contrast with IVa-e, treatment of 1,3-dimethyl-6-(1′-methyl-*p*-nitrobenzylidenehydrazino)uracil (IVf) with NBS afforded the corresponding pyrazolopyrimidine (VIf) in almost quantitative yield, and none of the pyrimidotriazine could be isolated (Table II and III). The preferential formation of VIf probably due to the strong electron-withdrawing nature of the *p*-nitro group. On the contrary to the pyrazolopyrimidines III, the 1-methylpyrazolopyrimidines VI did not exhibit the presence of any polymorphic forms. This indicates that the hydrogen atom on nuclear nitrogen of pyrazolopyrimidines III plays an important role for polymorphism.

As depicted in Scheme II, the reaction leading to pyrazolopyrimidines VI would involve the initial formation of the 5-bromo derivatives (V), followed by cyclization accompanying dehydrobromination. In fact, the intermediate Va could be isolated in 70% yield by treatment of IVa with NBS in boiling chloroform for 15 minutes, and refluxing of Va in acetic acid for 5 hours gave the pyrazolopyrimidine VIa and pyrimidotriazine Xa in 12% yields, respectively. On the other hand, the formation of pyrimidotriazines X would proceed through the condensation of V with 5-bromo-1,3-dimethyl-6-(1′-methylhydrazino)uracil (VII) (which would form by the acid hydrolysis of V) to give the

Table II

3-Aryl-1,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

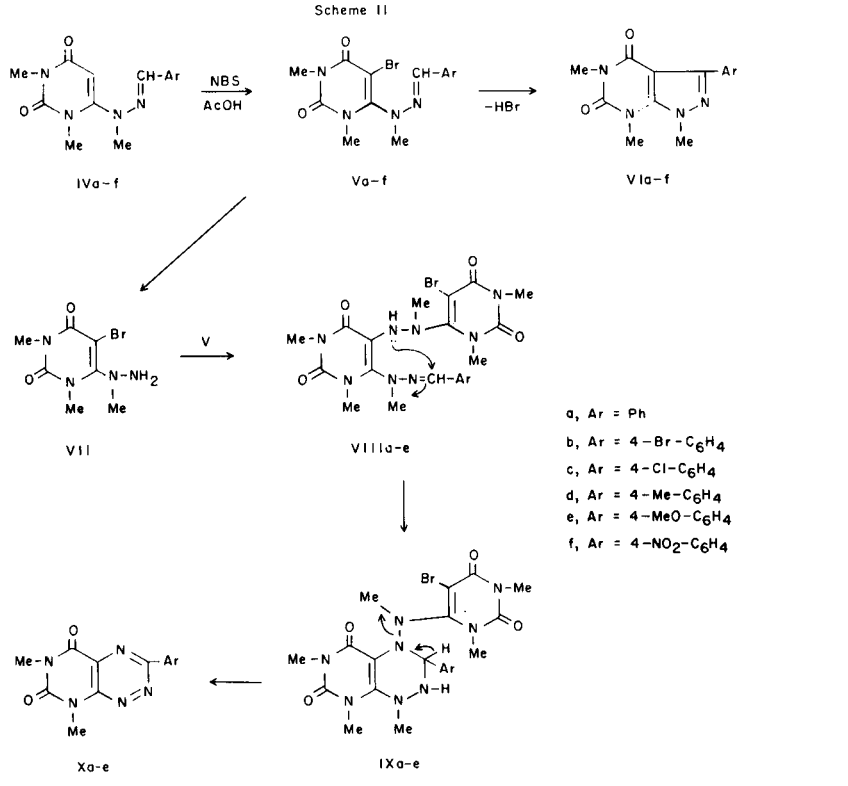
Compound Number	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
VIa	195-197	ethanol	5	62.21	5.22	20.73	$C_{14}H_{14}N_4O_2$	62.12	5.32	21.02
VIb	250-253	ethanol	6	48.15	3.76	16.05	$C_{14}H_{13}BrN_4O_2$	47.90	3.67	16.09
VIc	254-255	ethanol	8	55.17	4.31	18.39	$C_{14}H_{13}ClN_4O_2$	55.03	4.42	18.37
VId	238-240	ethanol	10	63.36	5.67	19.71	$C_{15}H_{16}N_4O_2$	63.35	5.62	19.86
VIe	213-214	ethanol	18	59.99	5.37	18.66	$C_{15}H_{16}N_4O_3$	59.86	5.31	18.72
VIf	263-266	ethanol	98	53.33	4.16	22.22	$C_{14}H_{13}N_5O_4$	53.20	4.54	21.82

Table III

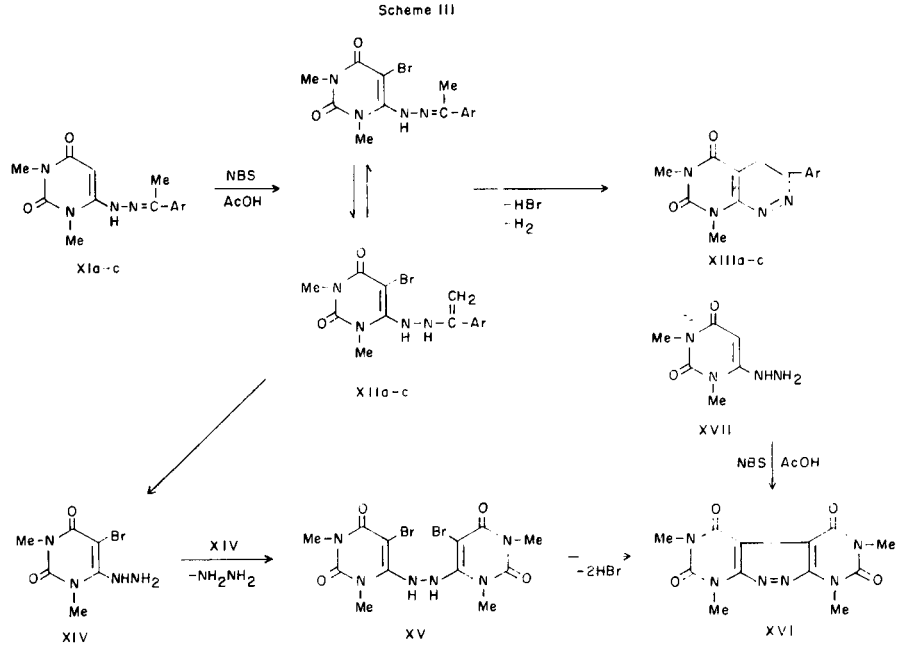
3-Aryl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-diones

Compound Number	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
Xa	268-269	ethanol	9	57.98	4.12	26.01	$C_{13}H_{11}N_5O_2$	57.88	4.03	26.34
Xb	>300	ethanol	6	44.84	2.90	20.10	$C_{13}H_{10}BrN_5O_2$	44.90	2.87	20.00
Xc	279-280	ethanol	4	51.40	3.33	23.06	$C_{13}H_{10}ClN_5O_2$	51.34	3.10	23.25
Xd	283-285	ethanol	14	59.35	4.63	24.72	$C_{14}H_{13}N_5O_2$	59.34	4.56	24.89
Xe	264-265	ethanol	10	56.18	4.38	23.40	$C_{14}H_{13}N_5O_3$	56.08	4.52	23.38

Scheme II



Scheme III



dimeric uracil intermediates (VIII). These would undergo further intramolecular cyclization accompanying the elimination of 5-bromo-1,3-dimethyl-6-methylaminouracil [9] and the acid catalyzed demethylation as well as aromatization *via* the pyrimido-tetrahydrotriazines (IX) to yield X.

The reactions of hydrazinouracils with NBS were further extended to the synthesis of pyrimido[4,5-*c*]pyridazines. Namely, treatment of 1,3-dimethyl-6-(α-methylarylidenehydrazino)uracils (XIa-c) [10] with an equimolar amount of NBS in acetic acid under reflux for 2 hours resulted in the formation of the corresponding 3-aryl-6,8-di-

Table IV

3-Aryl-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones

Compound Number	Mp (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
XIIIa	255-256	ethanol	22	62.68	4.51	20.89	$C_{14}H_{12}N_4O_2$	62.44	4.50	21.10
XIIIb	280-281	ethanol	20	55.54	3.67	18.51	$C_{14}H_{11}ClN_4O_2$	55.49	3.69	18.30
XIIIc	244-245	ethanol	20	60.39	4.73	18.78	$C_{15}H_{14}N_4O_3$	60.18	4.75	18.86

methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (XIIIa-c) [11] in approximately 20% yields (Table IV). As depicted in Scheme III, this reaction involves without doubt the intermediacy of the 5-bromo derivatives (XII), and whose cyclization with dehydrobromination and aromatization *via* the tautomeric forms then give pyrimidopyridazines XIII.

Along with the formation of pyrimidopyridazines XIII, a trace amount of 1,3,6,8-tetramethylpyridazino[3,4-*d*:6,5-*d'*]dipyrimidine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone (XVI) [12] was obtained as an insoluble material in the recrystallization of the crude reaction product from ethanol. The formation of XVI probably proceeds through the initial acid hydrolysis of XII to the 5-bromo-6-hydrazino-1,3-dimethyluracil (XIV), followed by the intermolecular condensation of XIV to the dimeric uracil intermediate (XV), and subsequent dehydrobromination. In fact, the compound XVI could be alternatively obtained by treatment of 6-hydrazino-1,3-dimethyluracil (XVII) with NBS in refluxing acetic acid for 2 hours in 8% yield.

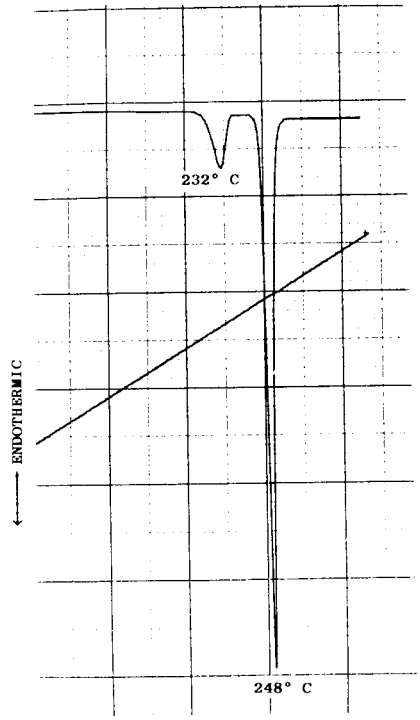


Figure 3. DTA of Form I, IIIa.

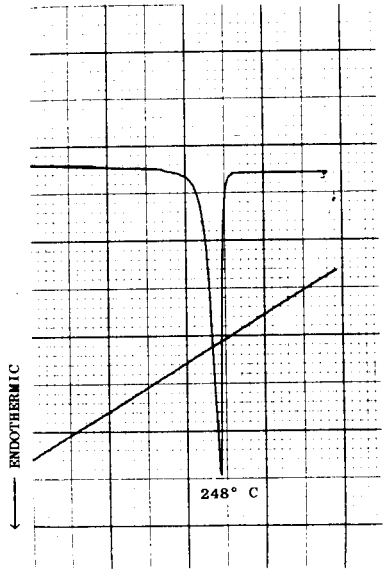


Figure 4. DTA of Form II, IIIa.

EXPERIMENTAL

The structures of all compounds were confirmed by the analytical and spectral data as well as by the comparison of the ir spectra with those of authentic samples. Melting points were taken on a YANACO micro-hot-stage melting point apparatus and are uncorrected. The ir spectra were determined in Nujol on a JASCO A-100 spectrophotometer and the nmr spectrum was determined at 100 MHz with a JEOL JNM-PS-100 spectrometer using tetramethylsilane as internal standard. The molecular weight determination was undertaken by mass spectroscopy with a JEOL D-300 spectrometer by a direct inlet system at 70 eV. The differential thermal analysis was done by using a ULVAC DT-1500 analyzer at the scanning speed of 5°/minute from the room temperature to 260° and very fine powder of aluminum oxide was used as the reference.

3-Aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (IIIa-h).

A mixture of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils (Ia-h) [3] (0.001 mole) and *N*-bromosuccinimide (NBS) (0.18 g, 0.001 mole) in acetic acid (10 ml) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was recrystallized to give the corresponding 3-aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (IIIa-h) (Table I).

Polymorphic Forms of Compound IIIa.

Recrystallization of the crude product from a mixture of ethanol and dimethylformamide (approximately 30:1) gave pale yellow fine needles, mp 256-257°, which denoted as form I (Figures 1 and 3).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.70; H, 4.63; N, 21.69.

Recrystallization of form I from dimethylformamide gave colorless fine needles, mp 256-257°, which denoted as form II (Figures 2 and 4).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 61.00; H, 4.61; N, 21.78.

3-Aryl-1,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (VIa-f) and 3-Aryl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-diones (Xa-e).

A mixture of the appropriate 1,3-dimethyl-6-(1'-methylarylidenehydrazino)uracils (IVa-f) [3] (0.0005 mole) and NBS (0.09 g, 0.0005 mole) in acetic acid (1 ml) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the fractional recrystallization from ethanol gave the corresponding 3-aryl-1,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (Va-f) and 3-aryl-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-diones (Xa-e). In the case of IVf, the product isolated in 98% yield was VIf (Table II and III).

5-Bromo-1,3-dimethyl-6-(1'-methylbenzylidenehydrazino)uracil (Va).

A mixture of IVa (0.136 g, 0.0005 mole) and NBS (0.09 g, 0.0005 mole) in chloroform (2 ml) was refluxed for 15 minutes. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized from ethanol to give 5-bromo-1,3-dimethyl-6-(1'-methylbenzylidenehydrazino)uracil (Va) (0.122 g, 70%), mp 117-120°; nmr (DMSO-d_6): δ 3.23 (3H, s, N-Me), 3.33 (3H, s, N-Me), 7.17-7.66 (5H, m, C_6H_5), 7.62 (1H, s, =CH-).

Anal. Calcd. for $C_{14}H_{15}BrN_4O_2$: C, 47.85; H, 4.31; N, 15.95. Found: C, 47.61; H, 4.34; N, 15.95.

Reaction of Compound Va in Acetic Acid.

A mixture of Va (1.05 g, 0.003 mole) and acetic acid (15 ml) was refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and ethanol was added to the residue. The insoluble material was filtered and recrystallized from ethanol to give Xa (0.09 g, 12%). The filtrate which removed Xa was evaporated *in vacuo* and the residue was recrystallized from ethanol to give VIa (0.095 g, 12%).

3-Aryl-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (XIIIa-c) and 1,3,6,8-Tetramethylpyridazino[3,4-*d*:6,5-*d'*]dipyrimidine-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-tetrone (XVI).

A mixture of the appropriate 1,3-dimethyl-6-α-methylarylidenehydrazinouracils (XIa-c) [10] (0.0005 mole) and NBS (0.09 g, 0.0005 mole) in acetic acid (1 ml) was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was filtered and recrystallized from ethanol to give the corresponding 3-aryl-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones (XIIIa-c) (Table IV).

In each case, a trace amount of 1,3,6,8-tetramethylpyridazino[3,4-*d*:6,5-*d'*]dipyrimidine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone (XVI) was obtained as an ethanol insoluble material during the recrystallization. Recrystallization of XVI from acetic acid gave pale yellow prisms, mp >300°.

Anal. Calcd. for $C_{12}H_{12}N_6O_4$: C, 47.37; H, 3.98; N, 27.62. Found: C, 47.35; H, 4.05; N, 27.61.

Alternative Synthesis of XVI.

A mixture of 6-hydrazino-1,3-dimethyluracil (XVII) (0.17 g, 0.001 mole) and NBS (0.18 g, 0.001 mole) in acetic acid was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* and the residue was covered with ethanol. The insoluble material was filtered and recrystallized from acetic acid to give XVI (0.025 g, 8%), mp >300°.

Acknowledgement.

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[3] F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 1484 (1975) [lit mp of IIIa is 242°].

[4] The crude products of IIIf,g and h also exist in the polymorphic form which classified as form I, respectively.

[5] Form I changes to form II by heating to 260° with the disappearance of the transition peak and consequently exhibits the same dta curve with that of form II.

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