Construction of Pyrimido[5,4-*e*]-*as*-triazine, Purine, *v*-Triazolo-[4,5-*d*]pyrimidine and Pyrazolo[3,4-*d*]pyrimidine Ring Systems from 5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils (1)

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Reaction of 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (II), prepared by the treatment of 6-arylidenehydrazino-1,3-dimethyluracils (I) with diazotized arylamines, with dimethylformamide dimethylacetal resulted in the formation of pyrimido[5,4-*e*]-*as*-triazine (V) system, while the thermolysis of II resulted in the formation of purine (X), *v*-triazolo[4,5-*d*]pyrimidine (XII), and pyrazolo[3,4-*d*]pyrimidine (XIV, XIX) systems in lieu of the expected V. Reasonable mechanisms have been proposed for the formation of the various ring systems in these reactions.

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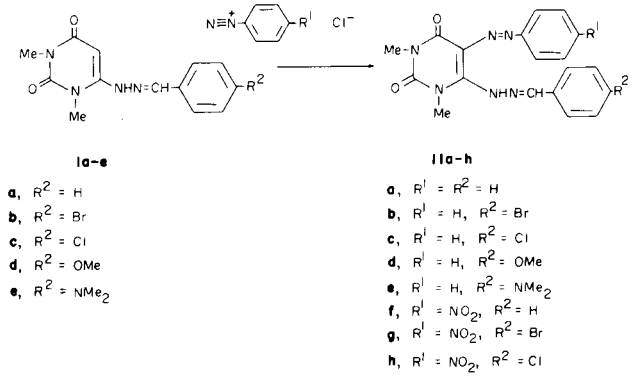
Recent studies have shown that 6-arylidenehydrazino-1,3-dimethyluracils served as useful starting materials for various biologically intriguing heterocycles, *i.e.*, pyrimido-[5,4-*e*]-*as*-triazine (2), pyrimido[4,5-*c*]pyridazine (3), and pyrazolo[3,4-*d*]pyrimidine (4). In connection with these findings and our interest in the synthetic potential of 5-arylazouracils as fused pyrimidines (5) prompted us to investigate the chemistry of 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (II). The present paper deals with the construction of pyrimido[5,4-*e*]-*as*-triazine system by the reaction of II with dimethylformamide dimethylacetal (DMFDMA) as well as purine, *v*-triazolo[4,5-*d*]pyrimidine, and pyrazolo[3,4-*d*]pyrimidine systems by the thermolysis of II.

Scheme I



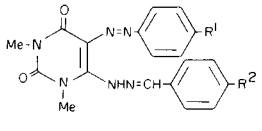
Construction of the Pyrimido[5,4-*e*]-*as*-triazine System.

The starting materials in this study, 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h), were readily prepared by reaction of the appropriate 6-arylidenehydrazino-1,3-dimethyluracils (Ia-e) (4b) with diazotized arylamines by the conventional method (6) in 30-56% yields (7) (Table I) (Scheme I).

Refluxing of IIa with excess DMFDMA at 150° for 5 hours, followed by concentration of the reaction mixture *in vacuo* and addition of ethanol, caused the separation of

Table I

5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h)



Compound Number (a)	Substituent R¹	Substituent R²	Mp (°C)	Yield (%)	Calcd. (%) C	Calcd. (%) H	Calcd. (%) N	Formula	Found (%) C	Found (%) H	Found (%) N
IIa	H	H	187-188	56	62.97	5.01	23.19	$C_{19}H_{18}N_6O_2$	62.89	4.98	23.45
IIb	H	Br	213-215	47	51.70	3.89	19.05	$C_{19}H_{17}BrN_6O_2$	51.70	3.83	19.17
IIc	H	Cl	200-202	56	57.50	4.33	21.18	$C_{19}H_{17}ClN_6O_2$	57.50	4.31	21.36
IId	H	OMe	144-145	31	61.21	5.14	21.42	$C_{20}H_{20}N_6O_3$	61.12	5.12	21.45
IIe	H	NMe_2	176-178	30	62.20	5.73	24.18	$C_{21}H_{23}N_7O_2$	62.21	5.69	24.34
IIf	NO_2	H	256-257	46	56.01	4.21	24.07	$C_{19}H_{17}N_7O_4$	55.91	4.21	24.06
IIg	NO_2	Br	235-236	42	46.92	3.32	20.16	$C_{19}H_{16}BrN_7O_4$	46.66	3.30	20.25
IIh	NO_2	Cl	223-225	34	51.64	3.66	22.19	$C_{19}H_{16}ClN_7O_4$	51.53	3.61	22.37

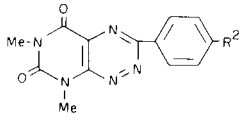
(a) All compounds were recrystallized from DMF.

6,8-dimethyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione (3-phenylfervenulin) (Va) (8) in 50% yield. Likewise, the treatment of other uracils IIb-e with DMFDMA afforded the corresponding 3-arylfervenulins (Vb-e) (8) in 20-60% yields.

The yields of Va-e were depending upon the nature of arylidenehydrazino group of the uracils IIa-e. Namely, the uracils with an electron-withdrawing arylidenehydrazino group gave better results than those with an electron-releasing group. Similar substituent effect was also observed on the arylazo group. Thus, treatment of the uracils (IIf-h), which possess a strong electron-withdrawing *p*-nitrophenylazo group, with DMFDMA caused pronounced improvement in the yields of Va-c (82-97%) (Table II).

Table II

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



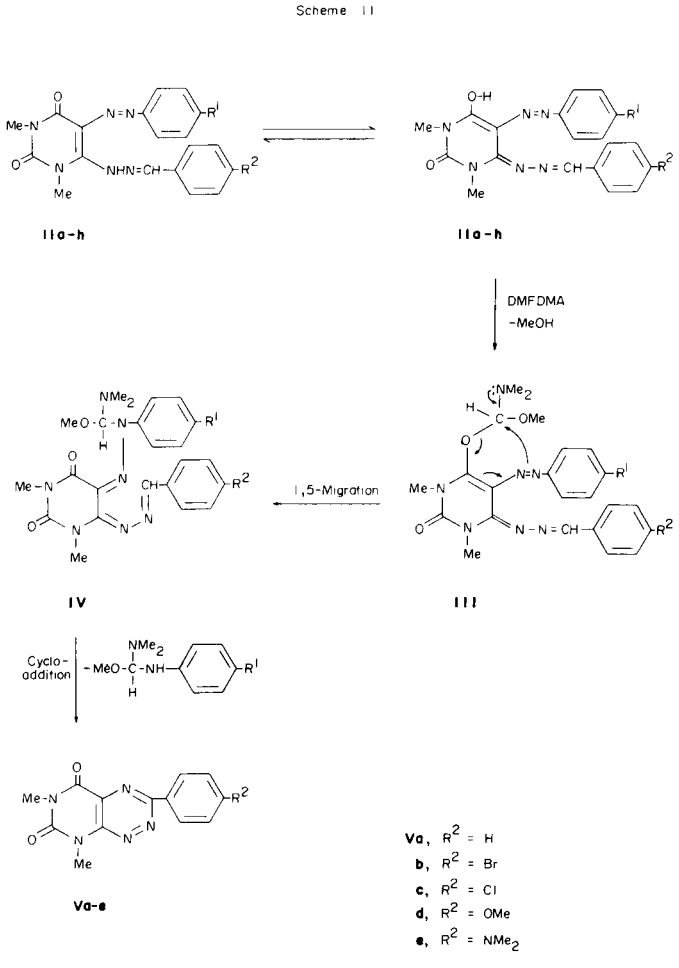
Compound Number (a)	Substituent R^2	Mp (°C)	Yield (%)
Va	H	273-275	50 (b), 88 (c),
Vb	Br	>300	60, 97 (d)
Vc	Cl	280-283	56, 82 (e)
Vd	OMe	263-264	26
Ve	NMe_2	>300	20

(a) All compounds were recrystallized from ethanol. (b) Yield from IIa. (c) Yield from IIf. (d) Yield from IIg. (e) Yield from IIh.

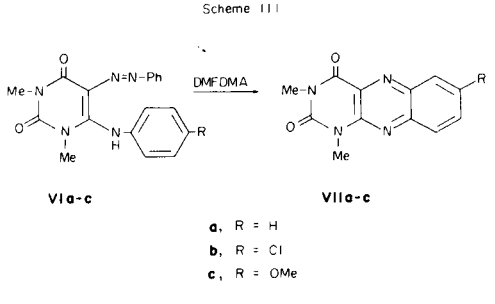
It should be noted that the reaction of IIa with dimethylformamide instead of DMFDMA under the same conditions resulted in the recovery of IIa. Moreover, the use of sodium ethoxide or aqueous sodium hydroxide found to be without effect. Therefore the reaction of the uracils IIa-h with DMFDMA leading to the pyrimidotriazines Va-e can be rationalized by assuming the initial formation of the intermediate (III) through the enol form of II, followed by 1,5-migration of the 1-methoxytrimethylamino group to give (IV), which possesses a triaza-1,3,5-hexatriene-type structure. This could undergo intramolecular cycloaddition and aromatization by loss of 1-arylamino-1-methoxytrimethylamine to give V as a final product. The C-O bond formation as exemplified by III has been speculated in the reaction of certain enols with DMFDMA (9) and the intramolecular cycloaddition of aza analog of hexatriene has ample precedents (10). To our knowledge, this is the first example in which 5-arylazopyrimidine was directly used as a nitrogen source for N-4 of the pyrimido[5,4-*e*]-*as*-triazine ring system (Scheme II).

In order to test the generality of DMFDMA as a cyclizing agent, we also examined the reaction with 6-arylamino-1,3-dimethyl-5-phenylazouracils (VIa-c) (5b) (11) and found to give 1,3-dimethylalloxazines (VIIa-c) (12) in 38-57% yields (Scheme III).

Scheme II



Scheme III



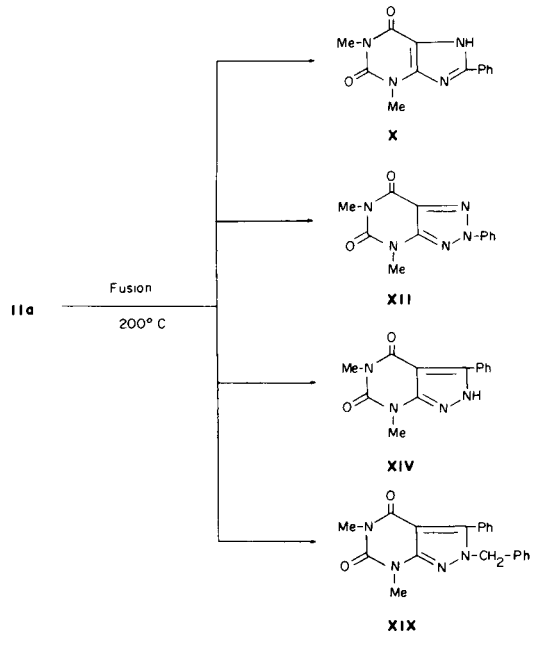
Construction of Purine, *v*-Triazolo[4,5-*d*]pyrimidine, and Pyrazolo[3,4-*d*]pyrimidine Systems.

Thermolysis of IIa at 200° (slightly higher than its melting point) for 3 hours, followed by dilution with acetone caused a separation of the unexpected 8-phenyltheophylline (X) (6) in 11% yield.

In order to clarify the mechanism for the formation of

the purine X as well as to identify other products, the filtrate which removed X was subjected to column chromatography and additional three products, *i.e.*, 4,6-dimethyl-2-phenyl-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XII) (13), 5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (XIV) (4b), 2-benzyl-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (XIX) (3) were isolated in 10, 11 and 7% yields, respectively (Scheme IV).

Scheme IV

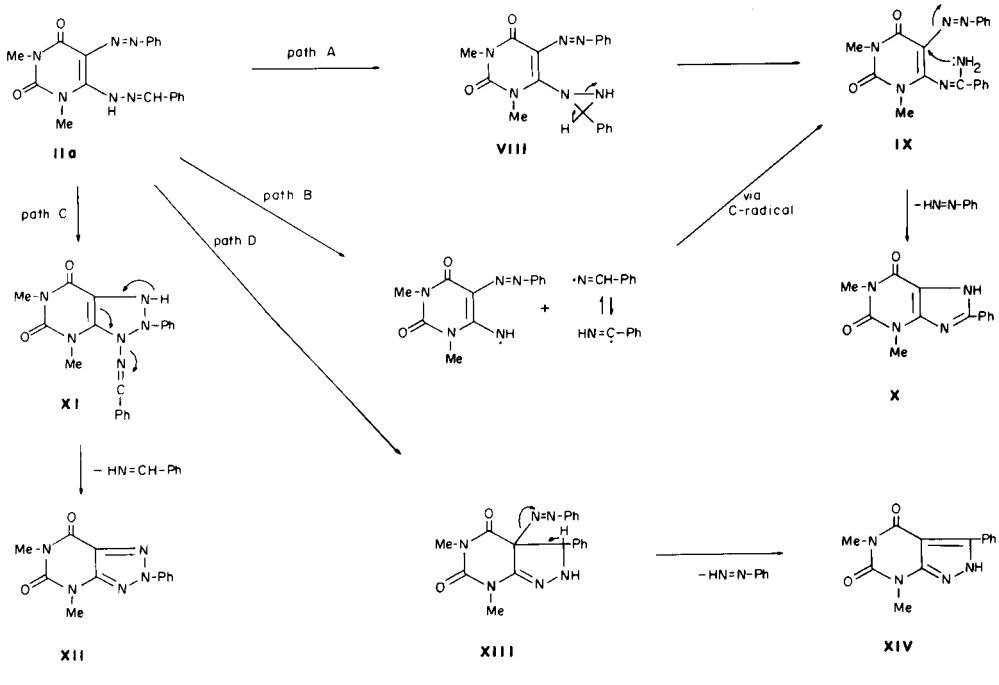


A reasonable mechanism for the construction of the purine X would involve the initial formation of the diaziridine intermediate VIII by the path A, followed by N-N bond cleavage of the diaziridine ring to the amidino intermediate IX, and subsequent cyclization by the loss of phenyldiimide. As an alternative route, however, the radical mechanism by the path B could not be ruled out (14). To the best of our knowledge, there seem to be no previous instances in which the β-nitrogen atom of the 6-hydrazino group served as a nitrogen source for N-7 of the purine ring system.

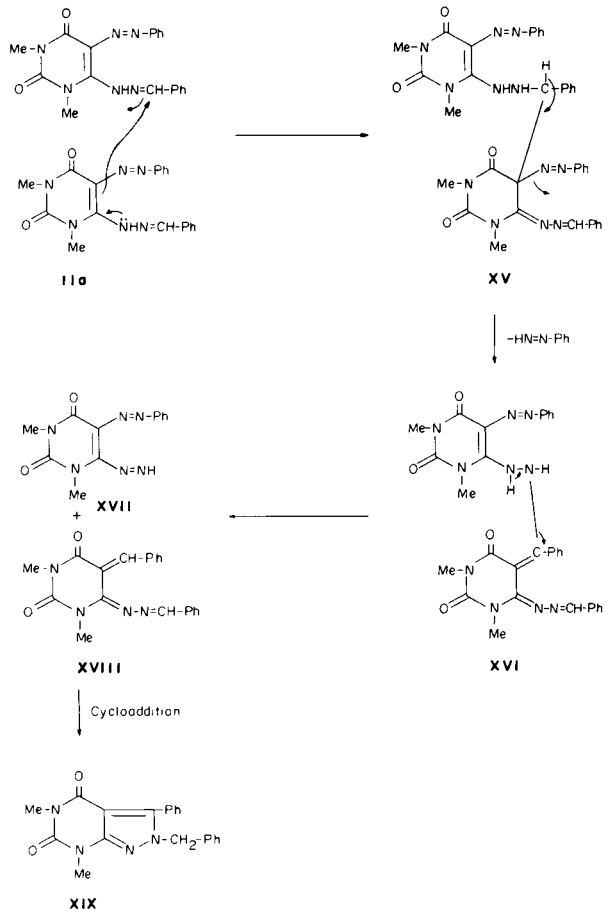
The transformation of the uracil IIa into the triazolopyrimidine XII probably proceeds through the intermediacy of XI by the path C and subsequent aromatization by the loss of benzylideneimine, while the conversion of the uracil IIa into the pyrazolopyrimidine XIV would proceed through the intermediacy of XIII by the path D, followed by cyclization accompanying the loss of phenyldiimide. The latter type of cyclization has been reported in the thermal conversion of 6-arylidenehydrazino-1,3-dimethyl-5-nitrouracils to 3-aryl-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (15) (Scheme V).

In contrast with the formation of X, XII, and XIV, the transformation of the uracil IIa into the other pyrazolopyrimidine XIX can be explained by assuming the intermolecular mechanism. Namely, the initial nucleophilic attack of the enamine activated 5 position of IIa on the anil carbon of another molecule of IIa would yield the adduct XV. Following the liberation of phenyldiimide to XVI and subsequent C-N bond cleavage could give both XVII and

Scheme V



Scheme VI



XVIII. Thus formed XVIII, possessing diazahexatriene type structure, would undergo intramolecular cyclization to give XIX. We have recently reported that XIX could be formed in the reaction of Ia with DMFDMA by the similar mechanism (3) (Scheme VI). It should be noted that the thermolysis of IIa did not afford the expected Va.

EXPERIMENTAL

All melting points were determined on a YANACO micro-hot-stage melting point apparatus and are uncorrected. Identity of compounds was confirmed by comparison of their ir spectra with those of authentic samples (Nujol mulls) with a JASCO A-100 spectrophotometer. The molecular weight for all compounds were collectively analyzed by mass spectroscopy with a JEOL D-300 spectrometer by a direct-inlet system at 70 eV.

5-Arylazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h) (Table I).

The appropriate arylamine (0.02 mole) was dissolved in 10% hydrochloric acid (60 ml) and sodium nitrite (0.02 mole) in water (10 ml) was added gradually under cooling with ice-water. On the other hand, the appropriate 6-arylidenehydrazino-1,3-dimethyluracil (Ia-e) (4b) (0.01 mole) was dissolved in 10% potassium hydroxide (60 ml). To this solution, the diazonium chloride solution was added dropwise with stirring at 0-5°. After stirring for 1 hour at the same temperature, the precipitates were filtered, washed with water, and then with ethanol to give the crude product. Recrystallization from dimethylformamide gave the corresponding 5-arylazo-6-arylidenehydrazino-1,3-dimethyluracils (IIa-h).

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

A mixture of the appropriate uracil (IIa-h) (0.0005 mole) and dimethylformamide dimethylacetal (DMFDMA) (2 ml) was heated at 150° for 5 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[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-diones (3-arylfervenulins) (Va-e), which were identical with authentic samples (8).

1,3-Dimethylalloxazines (VIIa-c).

A mixture of the appropriate 6-arylamino-1,3-dimethyl-5-phenylazouracil (VIa-c) (5b) (0.0005 mole) and DMFDMA (1 ml) was heated at 140° for 10 hours. After cooling, the reaction mixture was diluted with ethanol and the precipitates were filtered, washed with ethanol, and recrystallized from a mixture of dimethylformamide and ethanol to give the corresponding 1,3-dimethylalloxazines (VIIa-c), which were identical with authentic samples (12).

Compound VIIa.

This compound had mp 249-250° (57%).

Compound VIIb.

This compound had mp 268-269° (38%).

Compound VIIc.

This compound had mp 256° (43%).

Thermolysis of IIa.

The uracil IIa (0.005 mole) was fused at 200° (bath temperature) for 3 hours. The reaction mixture was triturated with boiling acetone and the insoluble material was filtered to give 8-phenyltheophylline (X).

The filtrate, from which the compound X has been removed is subjected to column chromatography through activated alumina (Wako Chemicals Co., Ltd.). Elution with benzene gave 5,7-dimethyl-2-phenyl-*v*-triazolo[4,5-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (XII). Further elution with a mixture of benzene and acetone (5:1) gave 2-benzyl-5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (XIX), and subsequent elution with methanol gave 5,7-dimethyl-3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (XIV). The compounds X, XII, XIV, and XIX were identical with authentic samples (6) (13) (4b) (3), respectively.

Compound X.

This compound had mp >300° (11%).

Compound XII.

This compound had mp 206-208° (10%).

Compound XIV.

This compound had mp 240-242° (11%).

Compound XIX.

This compound had mp 192-194° (7%).

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