Synthesis of 6-Aryl-1,3-dimethyl-6,7-dihydro-6-azalumazin-7-(6*H*)ones and their Conversion into 2-Aryl-1,2,4-triazine-3,5-(2*H*,4*H*)diones. A New Synthesis of 1-Aryl-6-azauracils

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Received May 23, 1980

Treatment of 6-amino-5-arylazo-1,3-dimethyluracils with urea or *N,N'*-carbonyldiimidazole gave the respective 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazin-7-(6*H*)ones, which were hydrolyzed with alkali to afford 2-aryl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids). Thermal decomposition of these carboxylic acids gave the corresponding 2-aryl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-aryl-6-azauracils). Methylation of the latter with methyl iodide gave the corresponding 2-aryl-4-methyl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-aryl-3-methyl-6-azauracils).

J. Heterocyclic Chem., **17**, 1365 (1980).

1,2,4-Triazine-3,5-(2*H*,4*H*)diones (6-azauracils) and its derivatives (I) are biologically interesting compounds, because of their demonstrated antitumor activity (2). However, the 6-azauracils possessing aryl substituents at the 1-position have not been widely investigated. The only known synthetic method for the prepartion of the 1-aryl-6-azauracils has involved the cyclization of arylhydrazones of 2-ketocarbonylurethane derivatives (3,4). We now wish to report a new synthetic approach to 1-aryl-6-azauracils which consists of the hydrolysis of 6-azalumazin-7-(6*H*)one derivatives followed by decarboxylation (5).

The starting materials, 6-amino-5-arylazo-1,3-dimethyluracils (Ia-j) were synthesized by the conventional diazo-coupling reaction toward 6-amino-1,3-dimethyluracil according to the reported procedure (6) (Table I).

SCHEME I

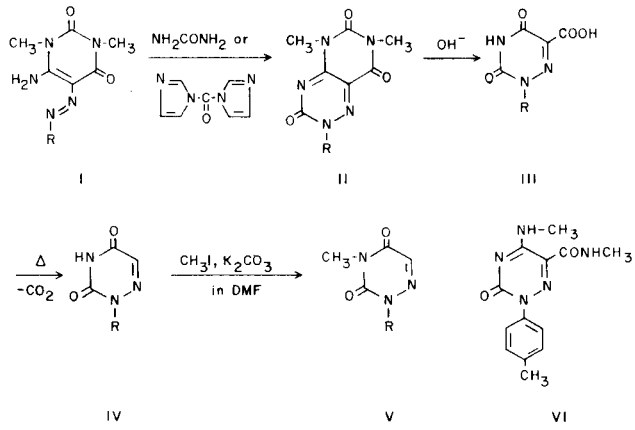
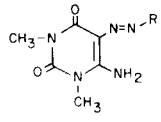


Table I

6-Amino-5-arylazo-1,3-dimethyluracils



Compound No.	R	Yield (%)	M.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia (6)	C_6H_5	90	254	yellow needles	$C_{12}H_{13}N_5O_2$	—	—	—	—	—	—
Ib	*m*-CH_3-C_6H_4	81	255	yellow prisms	$C_{13}H_{15}N_5O_2$	57.13	5.53	25.63	57.53	5.67	25.31
Ic	*p*-Cl-C_6H_4	82	269	yellow needles	$C_{12}H_{12}ClN_5O_2$	49.07	4.12	23.85	49.36	4.31	23.57
Id	*m*-Cl-C_6H_4	79	252	yellow prisms	$C_{12}H_{12}ClN_5O_2$	49.07	4.12	23.85	49.35	4.21	23.61
Ie	*p*-CH_3-C_6H_4	84	251	yellow needles	$C_{13}H_{15}N_5O_2$	57.13	5.53	25.63	57.37	5.23	25.31
If	3,4-$(CH_3)_2$-C_6H_3	87	282	yellow needles	$C_{14}H_{17}N_5O_2$	58.52	5.96	24.38	58.64	6.17	24.02
Ig	*p*-Br-C_6H_4	79	249	yellow needles	$C_{12}H_{12}BrN_5O_2$	42.62	3.58	20.71	42.94	3.71	20.41
Ih	*p*-F-C_6H_4	72	283	yellow prisms	$C_{12}H_{12}FN_5O_2$	51.98	4.36	25.26	51.69	4.38	24.88
Ii	*p*-CH_3O-C_6H_4	71	243	yellow prisms	$C_{13}H_{15}N_5O_3$	53.97	5.23	24.21	53.66	4.97	23.89
Ij	3,4-Cl_2-C_6H_3	76	274	yellow needles	$C_{12}H_{11}Cl_2N_5O_2$	43.92	3.38	21.34	44.20	3.35	21.48

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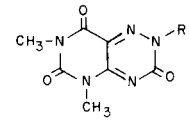
Table II

6-Aryl-1,3-dimethyl-6,7-dihydro-6-azalumazin-7-(6*H*)ones

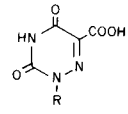


Compound No.	R	Method (a)	Yield (%)	M.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	C_6H_5	A	70	219	pale yellow needles	$C_{13}H_{11}N_5O_3$	54.73	3.89	24.55	54.65	3.74	24.17
IIb	m-CH_3-C_6H_4	A	61	227	pale yellow needles	$C_{14}H_{13}N_5O_3$	56.18	4.38	23.40	56.12	4.22	23.19
IIc	p-Cl-C_6H_4	A	54	233	colorless needles	$C_{13}H_{10}ClN_5O_3$	48.84	3.15	21.91	48.45	3.28	21.56
IId	m-Cl-C_6H_4	A	49	199	colorless needles	$C_{13}H_{10}ClN_5O_3$	48.84	3.15	21.91	48.49	3.04	21.51
IIe	p-CH_3-C_6H_4	A	62	195	pale yellow needles	$C_{14}H_{13}N_5O_3$	56.18	4.38	23.40	56.00	4.37	23.24
IIf	3,4-$(CH_3)_2$-C_6H_3	A	55	220	pale yellow needles	$C_{15}H_{15}N_5O_3$	57.50	4.83	22.34	57.85	5.02	21.95
IIg	p-Br-C_6H_4	B	91	258	pale yellow needles	$C_{13}H_{10}BrN_5O_3$	42.87	2.77	19.23	42.62	2.62	18.94
IIh	p-F-C_6H_4	B	93	227	pale yellow needles	$C_{13}H_{10}FN_5O_4$	51.49	3.32	23.10	51.68	3.50	23.34
IIi	p-CH_3O-C_6H_4	B	95	210	yellow needles	$C_{14}H_{13}N_5O_3$	55.33	4.16	22.22	53.14	4.23	22.01
IIj	3,4-Cl_2-C_6H_3	B	93	232	colorless needles	$C_{13}H_9Cl_2N_5O_3$	44.09	2.56	19.78	44.19	2.78	19.38

(a) A: Condensation of I with urea; B: condensation of I with *N,N'*-carbonyldiimidazole.

Table III

2-Aryl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic Acids (1-Aryl-6-azauracil-5-carboxylic Acids)



Compound No.	R	Yield (%)	M.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa (7)	C_6H_5	72	205	colorless needles	$C_{10}H_7N_3O_4$	51.51	3.03	18.02	51.24	3.26	18.38
IIIb	m-CH_3-C_6H_4	53	206	pale yellow prisms	$C_{11}H_9N_3O_4 \cdot C_2H_5OH$	53.24	5.16	14.33	53.46	4.98	14.00
IIIc (7)	p-Cl-C_6H_4	59	216	colorless prisms	$C_{10}H_6ClN_3O_4 \cdot H_2O$	42.05	2.82	14.71	41.94	2.55	15.01
IIId	m-Cl-C_6H_4	73	183	pale yellow prisms	$C_{10}H_6ClN_3O_4 \cdot H_2O$	42.05	2.82	14.71	42.36	2.63	14.48
IIIe (7)	p-CH_3-C_6H_4	54	200	colorless needles	$C_{11}H_9N_3O_4 \cdot H_2O$	49.81	4.18	15.84	49.55	4.35	15.57
IIIf	3,4-$(CH_3)_2$-C_6H_3	76	222	colorless needles	$C_{12}H_{11}N_3O_4 \cdot H_2O$	51.61	4.69	15.05	51.58	4.66	14.94
IIIg (7)	p-Br-C_6H_4	65	212	pale yellow needles	$C_{10}H_6BrN_3O_4 \cdot H_2O$	36.38	2.44	12.73	36.25	2.30	12.42
IIIh	p-F-C_6H_4	50	219	colorless prisms	$C_{10}H_6FN_3O_4 \cdot H_2O$	44.62	3.00	15.61	44.90	3.12	15.32
IIIi (7)	p-CH_3O-C_6H_4	63	212	pale yellow needles	$C_{11}H_9N_3O_5 \cdot H_2O$	46.98	3.94	14.94	47.26	4.41	14.61

Fusion of compounds I with excess urea (Method A) or *N,N'*-carbonyldimidazole (Method B) gave the respective 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazin-7-(6*H*)ones (IIa-j) (Table II).

The 6-azalumazin-7-ones (II) thus obtained were treated with 10% ethanolic potassium hydroxide under reflux to give the corresponding 2-aryl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids) (IIIa-i) (Table III). The structures of compounds III were established based on the satisfactory analytical and spectral data (they revealed only aromatic protons in the nmr). Furthermore, some of these carboxylic acids were identical with the authentic samples prepared by acid hydrolysis of 1-aryl-5-cyano-6-azauracils (7).

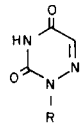
The mild hydrolysis of compound IIe with 2*N* sodium hydroxide at room temperature gave a 6-azacytosine derivative (VI) whose structure was confirmed by the nmr spectrometry. Further hydrolysis of VI with alkali gave compound IIIe.

Heating of the 6-azauracil-5-carboxylic acids (III) in diphenyl ether caused the decarboxylation to give rise to the respective 2-aryl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-aryl-6-azauracils) (IVa-h) (7) (Table IV). The structures of compounds IV were established by the analytical and spectral data, particularly by the presence of the characteristic 6-C proton signal at 7.8 ppm region in the nmr.

Methylation of compounds IV with methyl iodide and potassium carbonate in dimethylformamide gave the

Table IV

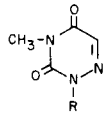
2-Aryl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-Aryl-6-azauracils)



Compound No.	R	Yield (%)	M.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa (7)	C_6H_5	61	215	colorless needles	$C_9H_7N_3O_2$	57.14	3.73	22.21	57.47	3.68	22.41
IVb (7)	*p*-Cl-C_6H_4	69	229	colorless needles	$C_9H_6ClN_3O_2$	48.34	2.70	18.79	48.74	2.98	18.45
IVc	*m*-Cl-C_6H_4	60	222	colorless prisms	$C_9H_6ClN_3O_2$	48.34	2.70	18.79	48.02	2.91	18.42
IVd (7)	*p*-CH_3-C_6H_4	59	212	colorless needles	$C_{10}H_9N_3O_2$	59.10	4.46	20.68	59.49	4.70	20.35
IVe	3,4-$(CH_3)_2$-C_6H_3	57	153	colorless needles	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.35	61.12	4.94	19.13
IVf (7)	*p*-Br-C_6H_4	72	250	colorless needles	$C_9H_6BrN_3O_2$	40.32	2.26	15.68	40.01	2.17	15.48
IVg	*p*-F-C_6H_4	55	200	colorless powder	$C_9H_6FN_3O_2$	52.18	2.91	20.29	52.36	3.03	20.13
IVh (7)	*p*-CH_3O-C_6H_4	70	236	colorless prisms	$C_{10}H_9N_3O_3$	54.79	4.14	19.17	54.57	4.02	19.27

Table V

2-Aryl-4-methyl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-Aryl-3-methyl-6-azauracils)



Compound No.	R	Yield (%)	M.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va	C_6H_5	72	93	colorless prisms	$C_{10}H_9N_3O_2$	59.10	4.46	20.68	59.12	4.43	20.99
Vb	*p*-Cl-C_6H_4	78	158	colorless prisms	$C_{10}H_8ClN_3O_2$	50.54	3.39	17.68	50.21	3.30	17.28
Vc	*m*-Cl-C_6H_4	75	159	colorless needles	$C_{10}H_8ClN_3O_2$	50.54	3.39	17.68	50.63	3.40	17.66
Vd	*p*-CH_3-C_6H_4	80	146	colorless needles	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.35	60.45	5.25	19.07
Ve	3,4-$(CH_3)_2$-C_6H_3	85	90	colorless needles	$C_{12}H_{13}N_3O_2$	62.32	5.67	18.17	61.98	5.52	18.08

desired 2-aryl-4-methyl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-aryl-3-methyl-6-azauracils) (Va-e) (Table V).

As indicated above, the readily accessible 6-azalumazine derivatives have been found to serve as convenient sources for various 1-aryl-6-azauracil derivatives.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Nmr spectra were determined with a JEOL-PMX 60 spectrometer (with tetramethylsilane as an internal standard). The identity of compounds was confirmed by comparison of infrared spectra (Nujol mulls) using a JASCO IR-A1 spectrometer.

6-Aryl-1,3-dimethyl-6,7-dihydro-6-azalumazin-7-(6*H*)ones. General Procedure. Method A (for IIa-f).

A mixture of a 6-amino-5-arylazo-1,3-dimethyluracil (I) (0.006 mole) and urea (0.06 mole) was fused under stirring at 220-240° for 2 hours. After cooling, the reaction mass was crushed in hot water and the crystals undissolved were collected by filtration. The crude product thus obtained was extracted by hot ethanol and the ethanol extracts were evaporated. The residue was washed with water, dried and recrystallized from ethanol to give the corresponding 6-azalumazine-7-one (II) (Table II).

Method B (for IIg-j).

A mixture of a 6-amino-5-arylazo-1,3-dimethyluracil (I) (0.003 mole) and *N,N'*-carbonyldiimidazole (0.006 mole) was fused under stirring at 125-140° for 2 hours. After cooling, the reaction mixture was crushed in ether or ethanol and the separated crystals were collected by filtration. Recrystallization from ethanol or methanol to give the corresponding 6-azalumazine-7-one (II) (Table II).

2-Aryl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic Acids (1-Aryl-6-azauracil-5-carboxylic Acids) (IIIa-i). General Procedure.

To 10% ethanolic sodium hydroxide (ethanol:water = 9:1) (10 ml.) was added a 6-azalumazin-7-one (II) (0.003 mole) and the mixture was refluxed for 1 hour. After cooling, the reaction mixture was neutralized with acetic acid to cause the separation of the sodium salt of a 2-aryl-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid, which was collected by filtration. The sodium salt was heated in concentrated hydrochloric acid to separate colorless crystals. After cooling, the separated crystals were filtered off, washed with water and recrystallized from water (for IIIa and c-i) or ethanol (for IIIb) to give the desired 6-carboxylic acid (III) (Table III).

2-Aryl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-Aryl-6-azauracils) (IVa-h). General Procedure.

The above carboxylic acid (III) (0.002 mole) was heated in diphenyl ether (1 ml.) at 200-220° for 1.5 hour under stirring. After cooling, the reaction mixture was diluted with ether (20 ml.) and allowed to stand overnight. The crystals which separated were filtered off, washed with ether and recrystallized from ethanol to give the corresponding 1-aryl-6-azauracil (IV) (Table IV).

2-Aryl-4-methyl-1,2,4-triazine-3,5-(2*H*,4*H*)diones (1-Aryl-3-methyl-6-azauracils) (Va-e). General Procedure.

A mixture of a 1-aryl-6-azauracil (IV) (0.002 mole), methyl iodide (0.006 mole) and potassium carbonate (0.005 mole) in dimethylformamide (5 ml.) was stirred at 120° for 2 hours. The reaction mixture was filtered and the filtrate was evaporated into dryness. The residue was treated with water to separate crystals which were filtered off, washed with water and recrystallized from ethanol giving the desired 3-methyl derivative (V) (Table V).

5-Methylamino-6-methylaminocarbonyl-2-(*p*-tolyl)-1,2,4-triazin-3-one (VI).

To 2*N* sodium hydroxide (50 ml.) was added compound IIe (1.5 g., 0.005 mole) and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was neutralized with acetic acid to give the precipitates which were filtered off, washed with water, dried and recrystallized from ethanol to give yellow needles (1.1 g., 77%), m.p. 262°; ms: m/e 273 (M^+); nmr (trifluoroacetic acid): δ ppm 3.09 (two N-CH_3), 2.49 (aromatic CH_3) and 7.33 (aromatic protons).

Anal. Calcd. for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.42; H, 5.62; N, 25.25.

Acknowledgement.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture. The authors are indebted to Misses Noriko Matsui and Hisako Tanaka for their technical assistance.

REFERENCES AND NOTES

(1) For example, J. Gut, in "Advances in Heterocyclic Chemistry", Vol. 1, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1963, p. 203.

(2) For example, C. A. Pasternak and R. E. Handschumachter, *J. Biol. Chem.*, **234**, 2992 (1959).

(3) M. A. Whitely and D. Yapp, *J. Chem. Soc.*, 521 (1927).

(4) J. Slouta, *Monatsh. Chem.*, **100**, 342 (1969).

(5) Preliminary report, F. Yoneda, M. Higuchi and Y. Nitta, *Heterocycles*, **9**, 1387 (1978).

(6) M. Ishidata, M. Sekiya, Y. Osaki and Y. Harada, *Yakugaku Zasshi*, **76**, 1107 (1956).

(7) J. Slouta, *Monatsh. Chem.*, **96**, 134 (1965).