Synthesis of some 5*H*-Imidazo[4,5-*e*]-*as*-triazin-6-(7*H*)ones (6-Azapurin-8-ones)

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Treatment of 1,3-dialkyl-7-azalumazine derivatives with alcoholic sodium hydroxide caused a benzylic acid type rearrangement followed by decarboxylation and oxidation by air to give the corresponding 5,7-dialkyl-5*H*-imidazo[4,5-*e*]-*as*-triazin-6-(7*H*)ones (7,9-dialkyl-6-azapurin-8-ones).

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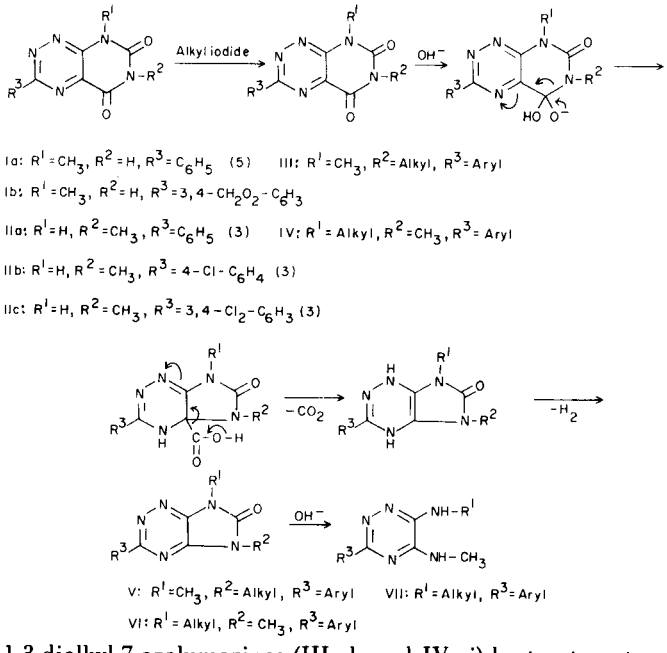
In previous papers (1-3), it was shown that the treatment of some 7-azapteridine derivatives with alcoholic sodium hydroxide caused a benzylic acid type rearrangement followed by decarboxylation and then aromatization to give the respective 6-azapurine derivatives. This was the first synthetic method for the preparation of 6-azapurine ring system. In the meantime, Kaji and co-workers (4) have reported the synthesis of 6-azapurine derivatives which consists of the cyclization of 5,6-diamino-*as*-triazine derivatives with one-carbon reagents.

In order to gain more information about properties of this ring system, we have prepared several new compounds of 5,7-disubstituted-5*H*-imidazo[4,5-*e*]-*as*-triazin-6-(7*H*)ones (7,9-disubstituted-6-azapurin-8-ones).

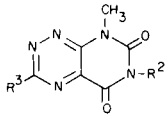
The requisite starting materials, 6-aryl-1-methyl-7-azalumazines [3-aryl-8-methylpyrimido[4,5-*e*]-*as*-triazine-5,7-(6*H*,8*H*)diones] (Ia and b) and 6-aryl-3-methyl-7-azalumazines [3-aryl-6-methylpyrimido[4,5-*e*]-*as*-triazine-5,7-(6*H*,8*H*)-diones] (IIa-c) were obtained by the condensation of 6-amino-1-methyl-5-nitrosouracil with benzaldehyde hydrazones in dimethylformamide (5) and by the dehydrative cyclization of 6-benzylidenehydrazino-5-nitroso-3-methyluracils with acetic anhydride (3) respectively. Compounds I and II gave the corresponding

Scheme



1,3-dialkyl-7-azalumazines (IIIa-h and IVa-i) by treatment with appropriate alkyl iodides in dimethylformamide in the presence of potassium carbonate (Tables I and II).

Table I



Compound No.	R^2	R^3	Yield (%)	M.p. (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	C_2H_5	C_6H_5	86	262	Yellow needles	$C_{14}H_{13}N_5O_2$	59.35	4.63	24.72	58.95	4.38	24.32
IIIb	*n*-C_3H_7	C_6H_5	82	201	Yellow needles	$C_{15}H_{15}N_5O_2$	60.59	5.09	23.56	60.91	5.38	23.29
IIIc	*iso*-C_3H_7	C_6H_5	78	261	Yellow needles	$C_{15}H_{15}N_5O_2$	60.59	5.09	23.56	60.32	5.39	23.21
IIId	*n*-C_4H_9	C_6H_5	79	177	Yellow needles	$C_{16}H_{17}N_5O_2$	61.72	5.50	22.50	62.02	5.27	22.56
IIIe	C_2H_5	3,4-CH_2O_2-C_6H_3	83	253	Yellow needles	$C_{15}H_{13}N_5O_4$	55.04	4.00	21.40	55.20	4.30	21.61
IIIf	*n*-C_3H_7	3,4-CH_2O_2-C_6H_3	81	251	Yellow needles	$C_{16}H_{15}N_5O_4$	56.30	4.43	20.52	55.99	4.24	20.72
IIIg	*iso*-C_3H_7	3,4-CH_2O_2-C_6H_3	84	208	Yellow needles	$C_{16}H_{15}N_5O_4$	56.30	4.43	20.52	56.01	4.52	20.20
IIIh	*n*-C_4H_9	3,4-CH_2O_2-C_6H_3	79	213	Yellow needles	$C_{17}H_{17}N_5O_4$	57.46	4.82	19.71	57.19	4.94	19.42

(a) All products were recrystallized from ethanol.

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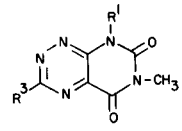
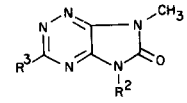
Table II



Compound No.	R^1	R^3	Yield (%)	M.p. (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	*n*-C_3H_7	C_6H_5	80	215	Yellow needles	$C_{15}H_{15}N_5O_2$	60.59	5.09	23.56	60.53	4.85	23.54
IVb	*iso*-C_3H_7	C_6H_5	78	190	Yellow needles	$C_{15}H_{15}N_5O_2$	60.59	5.09	23.56	60.67	5.24	23.39
IVc	*n*-C_4H_9	C_6H_5	75	181	Yellow needles	$C_{16}H_{17}N_5O_2$	61.72	5.50	22.50	61.66	5.31	22.44
IVd	*n*-C_3H_7	4-Cl-C_6H_4	91	205	Yellow needles	$C_{15}H_{14}ClN_5O_2$	54.30	4.25	21.11	54.62	4.17	20.83
IVe	*iso*-C_3H_7	4-Cl-C_6H_4	95	191	Yellow needles	$C_{15}H_{14}ClN_5O_2$	54.30	4.25	21.11	54.79	3.95	20.85
IVf	*n*-C_4H_9	4-Cl-C_6H_4	81	150	Yellow needles	$C_{16}H_{16}ClN_5O_2$	55.57	4.66	20.26	55.89	4.40	19.96
IVg	*n*-C_3H_7	3,4-Cl_2-C_6H_3	79	180	Yellow needles	$C_{15}H_{13}Cl_2N_5O_2$	49.19	3.58	19.13	49.07	3.29	19.35
IVh	*iso*-C_3H_7	3,4-Cl_2-C_6H_3	87	200	Yellow needles	$C_{15}H_{13}Cl_2N_5O_2$	49.19	3.58	19.13	48.90	3.42	18.88
IVi	*n*-C_4H_9	3,4-Cl_2-C_6H_3	90	135	Yellow prisms	$C_{16}H_{15}Cl_2N_5O_2$	50.54	3.98	18.42	50.52	3.69	18.12

(a) All products were recrystallized from ethanol.

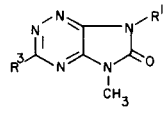
Table III



Compound No.	R^2	R^3	Yield (%)	M.p. (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va	C_2H_5	C_6H_5	73	174	Colorless needles	$C_{13}H_{13}N_5O$	61.16	5.13	27.44	60.96	5.43	27.14
Vb	*n*-C_3H_7	C_6H_5	68	161	Colorless prisms	$C_{14}H_{15}N_5O$	62.44	5.61	26.01	62.60	5.72	26.33
Vc	*iso*-C_3H_7	C_6H_5	55	188	Colorless needles	$C_{14}H_{15}N_5O$	62.44	5.61	26.01	62.18	5.72	25.73
Vd	*n*-C_4H_9	C_6H_5	52	141	Colorless needles	$C_{15}H_{17}N_5O$	63.58	6.05	24.72	63.78	6.38	24.46
Ve	C_2H_5	3,4-CH_2O_2-C_6H_3	81	235	Colorless needles	$C_{14}H_{13}N_5O_3$ ·H_2O	52.99	4.77	22.07	53.27	4.52	22.42
Vf	*n*-C_3H_7	3,4-CH_2O_2-C_6H_3	58	207	Colorless needles	$C_{15}H_{15}N_5O_3$	57.50	4.83	22.34	57.75	4.75	22.14
Vg	*iso*-C_3H_7	3,4-CH_2O_2-C_6H_3	63	238	Colorless powder	$C_{15}H_{15}N_5O_3$ ·2 H_2O	51.57	5.48	20.05	51.29	5.34	20.06
Vh	*n*-C_4H_9	3,4-CH_2O_2-C_6H_3	61	151	Colorless needles	$C_{16}H_{17}N_5O_3$ ·2 H_2O	52.88	5.83	19.28	53.09	5.60	19.28

(a) All products were recrystallized from ethanol.

Table IV

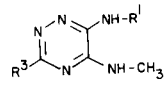


Compound No.	R^1	R^3	Yield (%)	M.p. (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIa	*n*-C_3H_7	4-Cl-C_6H_4	76	177	Colorless needles	$C_{14}H_{14}ClN_5O$	55.35	4.65	23.06	55.68	4.48	22.71
VIb	*n*-C_3H_7	3,4-Cl_2-C_6H_3	84	194	Colorless needles	$C_{14}H_{13}Cl_2N_5O$	49.72	3.87	20.71	49.61	3.85	20.38
VIc	*iso*-C_3H_7	3,4-Cl_2-C_6H_3	69	170	Colorless needles	$C_{14}H_{13}Cl_2N_5O$	49.72	3.87	20.71	49.28	3.54	20.35
VId	*n*-C_4H_9	3,4-Cl_2-C_6H_3	60	171	Colorless needles	$C_{15}H_{15}Cl_2N_5O$	51.15	4.29	19.89	50.92	4.31	19.77

(a) All products were recrystallized from ethanol.

Treatment of the 7-azalumazine derivatives (III and IV) thus obtained with 10% ethanolic sodium hydroxide for 1 hour under reflux, followed by acidification with acetic acid, resulted in the formation of the respective 5-alkyl-3-aryl-7-methyl-5*H*-imidazo[4,5-*e*]-*as*-triazin-6-(7*H*)ones (9-alkyl-2-aryl-7-methyl-6-azapurin-8-ones) (Va-h) and 7-alkyl-3-aryl-5-methyl-5*H*-imidazo[4,5-*e*]-*as*-triazin-6-(7*H*)-ones (7-alkyl-2-aryl-9-methyl-6-azapurin-8-ones) (VIa-d) (Tables III and IV), according to the benzylic acid type rearrangement depicted in the Scheme.

Table V



Compound No.	R^1	R^2	Yield (%)	M.p.(°C)	Ms m/e (M^+)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIa	n-C_3H_7	C_6H_5	65	215	243	$C_{13}H_{17}N_5$	64.17	7.04	28.79	64.03	6.89	28.84
VIIb	n-C_4H_9	C_6H_5	63	209	257	$C_{14}H_{19}N_5$	65.34	7.44	27.22	65.27	7.62	26.89
VIIc	n-C_3H_7	3,4-Cl_2-C_6H_3	54	258	311	$C_{13}H_{15}Cl_2N_5$	50.01	4.84	22.43	50.19	4.83	20.04

These 6-azapurine derivatives (V and VI) showed spectral characteristics typical of 7,9-dialkyl-6-azapurin-8-ones (absorption maxima at 310-, 280- and 250-nm regions) in ethanolic solution (3).

Next, by prolonged hydrolysis with 10% ethanolic sodium hydroxide, some 7-azalumazines (IVa,c and g) were converted into the corresponding 6-alkylamino-6-methylamino-*as*-triazine derivatives (VIIa-c) (Table V). The structures of compounds VII were ascertained by spectral data as well as elemental analyses.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-1A spectrophotometer.

6-(*p*-Chlorophenyl)-1-methyl-7-azalumazine (Ib).

A mixture of 6-amino-1-methyl-5-nitrosouracil (2.0 g., 0.012 mole), piperonal (2.5 g., 0.015 mole) and 100% hydrazine hydrate (0.8 g., 0.015 mole) in dimethylformamide (50 ml.) was refluxed for 5 hours. After cooling, the reaction mixture was evaporated *in vacuo*, the residue was diluted with ethanol and allowed to stand overnight. The crystals which separated were collected by filtration and recrystallized from ethanol to give yellow prisms (2.0 g., 55%), m.p. 320°.

Anal. Calcd. for $C_{13}H_{19}N_5O_4$: C, 52.18; H, 3.03; N, 23.41. Found: C, 51.90; H, 3.28; N, 23.10.

1,3-Dialkyl-7-azalumazine Derivatives (IIIa-h and IVa-i). General Procedure.

A mixture of 1-methyl- (I) or 3-methyl-7-azalumazine (II) (0.002 mole), an alkyl iodide (0.004 mole) and potassium carbonate (0.006 mole) in dimethylformamide (5 ml.) was heated at 120° for 2 hours under stirring. After cooling, the reaction mixture was diluted with water to precipitate crystals, which were filtered off and recrystallized from ethanol (Tables I and II).

Transformation of 7-Azalumazines (III and IV) into 6-Azapurin-8-ones (Va-h and VIa-d). General Procedure.

To 10% ethanolic sodium hydroxide (ethanol:water = 9:1) (10 ml.) was added a 7-azalumazine (0.003 mole) and the mixture was refluxed for 1 hour. After cooling, the reaction mixture was acidified with acetic acid and evaporated *in vacuo* into dryness. The residue was treated with water, the separated crystals were filtered off and recrystallized from ethanol to give a 6-azapurin-8-one (Tables III and IV).

6-Alkylamino-5-methylamino-*as*-triazines (VIIa-c). General Procedure.

To 10% ethanolic sodium hydroxide (ethanol:water = 9:1) (10 ml.) was added a 7-azalumazine (IV) (0.002 mole) and the mixture was refluxed for 6 hours. After cooling, the reaction mixture was neutralized with acetic acid to cause the separation of colorless crystals, which were collected by filtration, washed with water and recrystallized from ethanol to give colorless plates of a 6-alkylamino-5-methylamino-*as*-triazine (Table V).

insert Table V

REFERENCES AND NOTES

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(4) K. Kaji and M. Kawase, *ibid.*, **24**, 2274 (1976).

(5) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 2884 (1975).