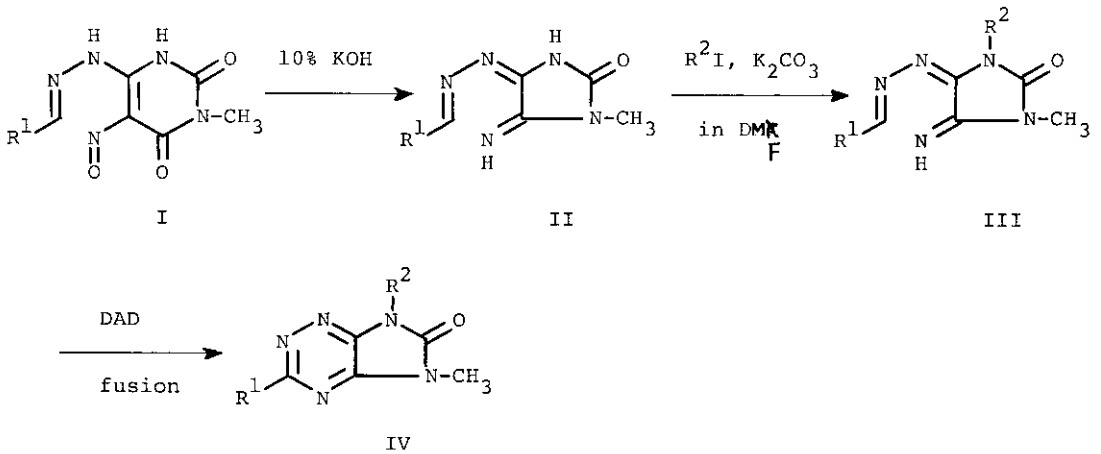
A NOVEL SYNTHESIS OF 6-AZAPURINES BY THE OXIDATIVE CYCLIZATION OF AZAHEXATRIENES WITH DIETHYL AZODICARBOXYLATE

Tetsuji Kametani
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Masatsugu Higuchi, Mitsuko Noguchi, Yuko Hashiguchi, and Fumio Yoneda
Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

Treatment of 6-benzylidenehydrazino-3-methyl-5-nitrosouracils with ethanolic potassium hydroxide caused a benzylic acid-type rearrangement accompanied with decarboxylation and dehydration to give 4,5-diimino-3-methylimidazolidin-2(1H)one 5-arylidenehydrazones. Alkylation of the latter with alkyl iodides gave the corresponding 1,3-dialkyl-4,5-diimino-imidazolidin-2(1H)one 5-arylidenehydrazones. Treatment of these azahexatriene-type imidazolidinones with diethyl azodicarboxylate gave the respective 3-aryl-5,7-dialkyl-5H-imidazo[4,5-e]-as-triazin-6(7H)ones (2-aryl-7,9-dialkyl-6-azapurine-8-ones) by the intramolecular cycloaddition through valence isomerization and then aromatization with diethyl azodicarboxylate.

The 6-azapurine (imidazo[4,5-e]-as-triazine) ring system is of interest from a chemical as well as a potential biological point of view. The known synthetic methods for the preparation of the 6-azapurine derivatives have involved the ring contraction of 7-azalumazine (pyrimido[4,5-e]-as-triazine) derivatives by a benzylic acid-type rearrangement[1-4] and the cyclization of 5,6-diamino-as-triazines with one-carbon reagents.[5] This paper describes a novel synthetic approach to the preparation of 6-azapurines consisting of the intermediate formation of an azahexatriene-type imidazolidinone which undergoes the oxidative cyclization with diethyl azodicarboxylate.

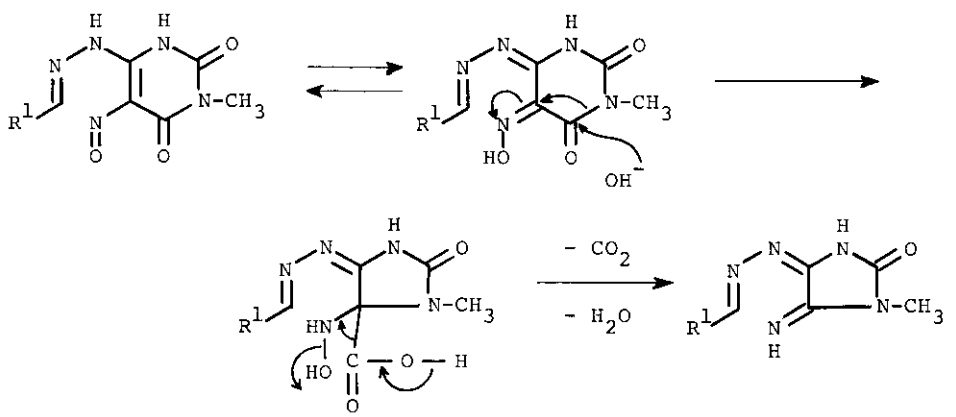
The requisite intermediates, 4,5-diimino-3-methylimidazolidin-2(1H)one 5-arylidenehydrazones (IIa-d) were prepared by the treatment of 6-benzylidene-hydrazino-3-methyl-5-nitrosouracils (Ia-d)[6] with 10% ethanolic potassium hydroxide. We suggest that these 4,5-diiminoimidazolidinone derivatives are formed from I by a benzylic acid-type rearrangement accompanied with decarboxylation and dehydration, as depicted in Scheme II. The analogous ring contraction were reported in the reactions of 6-amino-1,3-dimethyl-5-nitrosouracil[7] and 1,3-dimethyl-6-imino-5-phenoxyiminouracil[8] with aqueous sodium hydroxide. Such benzylic acid-type ring contractions have other precedents in pyrimidine chemistry.[9,10]



I II III IV

Scheme I

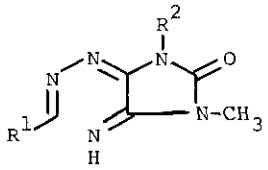
Compounds IIa-d gave the corresponding 1,3-dialkyl-4,5-diiminoimidazolidin-2(1H)one 5-arylidenehydrazones (IIIa-h) by treatment with appropriate alklyl iodides in dimethylformamide in the presence of potassium carbonate.



Scheme II

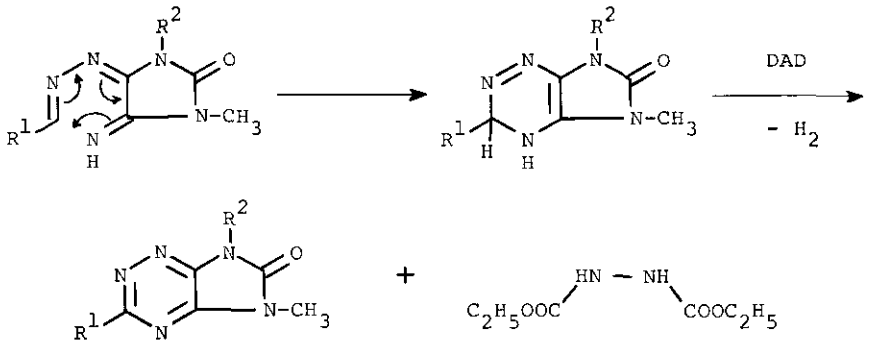
We have found that compounds III undergo smoothly the dehydrogenative cyclization with diethyl azodicarboxylate (DAD)[11] to give rise to the desired 6-azapurine derivatives. Thus, heating of compound IIIa with excess DAD for 1 hr, followed by dilution with ethanol, caused the separation of 5,7-dimethyl-3-phenyl-5H-imidazo[4,5-e]-as-triazin-6(7H)one (7,9-dimethyl-2-phenyl-6-azapurin-8-one) (IVa) in a high state of purity. Concentration of the filtrate gave diethyl hydrazodicarboxylate. Similarly, other 1,3-dialkyl-4,5-diiminoimidazolidinones (IIIb-h) gave the corresponding 6-azapurine derivatives (IVb-h) under the same conditions. Compounds IVa-h were identical in all respects with the authentic samples synthesized previously.[3]

Table I 4,5-Diiminoimidazolidin-2(1H)one 5-Arylidenehydrazones



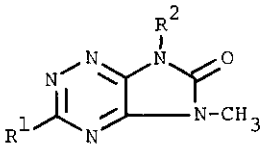
Compd. No.	R^1	R^2	Appearance	Yield (%)	mp (°C)	Formula	Analysis(%) Calcd. (Found) C	H	N
IIa	C_6H_5	H	colorless prisms	60	215	$C_{11}H_{11}N_5O$	57.63 (57.76	4.84 4.92	30.55 30.28)
IIb	4-Cl-C_6H_4	H	colorless prisms	82	232	$C_{11}H_{10}ClN_5O$	50.10 (50.33	3.82 3.88	26.56 26.74)
IIc	4-CH_3O-C_6H_4	H	yellow prisms	65	211	$C_{12}H_{13}N_5O_2$	55.59 (55.85	5.05 5.03	27.02 26.75)
IId	3,4-CH_2O_2-C_6H_3	H	yellow prisms	71	234	$C_{12}H_{11}N_5O_3$	52.74 (52.53	4.06 4.07	25.63 25.34)
IIIa	C_6H_5	CH_3	yellow needles	81	148	$C_{12}H_{13}N_5O$	59.25 (59.58	5.39 5.39	28.79 28.88)
IIIb	4-Cl-C_6H_4	CH_3	yellow needles	80	201	$C_{12}H_{12}ClN_5O$	51.90 (52.12	4.36 4.36	25.22 25.31)
IIIc	4-CH_3O-C_6H_4	CH_3	yellow needles	83	164	$C_{13}H_{15}N_5O_2$	57.13 (57.15	5.53 5.50	25.63 25.36)
IIId	3,4-CH_2O_2-C_6H_3	CH_3	yellow needles	85	217	$C_{13}H_{13}N_5O_3$	54.35 (53.95	4.56 4.38	24.38 24.13)
IIIe	C_6H_5	C_2H_5	yellow needles	93	114	$C_{13}H_{15}N_5O$	60.68 (60.89	5.88 5.86	27.22 26.91)
IIIf	4-Cl-C_6H_4	C_2H_5	yellow needles	90	125	$C_{13}H_{14}ClN_5O$	53.52 (53.90	4.84 4.92	24.01 23.75)
IIIg	4-CH_3O-C_6H_4	C_2H_5	yellow needles	91	140	$C_{14}H_{17}N_5O_2$	58.52 (58.74	5.96 5.96	24.38 24.26)
IIIh	3,4-CH_2O_2-C_6H_3	C_2H_5	yellow needles	94	133	$C_{14}H_{15}N_5O_3$	55.80 (55.76	5.02 4.92	23.25 23.15)

The reaction can be rationalized by assuming the intramolecular cycloaddition via valence isomerization accompanied with the aromatization with diethyl azodicarboxylate (Scheme III).



Scheme III

Table II Synthesis of 6-Azapurine Derivatives by Oxidative Cyclization of 4,5-Diiminoimidazolidinones with Diethyl Azodicarboxylate (DAD)



Compd. No.	R^1	R^2	Appearance	Yield (%)	mp[a] (°C)
IVa	C_6H_5	CH_3	colorless needles	85	203
IVb	4-Cl-C_6H_4	CH_3	colorless needles	72	251
IVc	4-CH_3O-C_6H_4	CH_3	colorless needles	91	255
IVd	3,4-CH_2O_2-C_6H_3	CH_3	colorless needles	87	330
IVe	C_6H_5	C_2H_5	colorless needles	87	190
IVf	4-Cl-C_6H_4	C_2H_5	colorless needles	74	225
IVg	4-CH_3O-C_6H_4	C_2H_5	colorless needles	90	243
IVh	3,4-CH_2O_2-C_6H_3	C_2H_5	colorless needles	88	218

a) All products were recrystallized from ethanol.

We consider this 6-azapurine synthesis as possessing considerable synthetic utility because of the good yields and the simplicity of procedure. Furthermore,

this reaction would establish an interesting precedent of the intramolecular cycloaddition of azahexatrienes[12] as well as the usefulness of DAD as an oxidant.[13]

EXPERIMENTAL

The melting points were determined 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-Al spectrometer.

4,5-Diimino-3-methylimidazolidin-2(1H)one 5-Arylidenehydrazones (IIa-d). General Procedure. ——— To 10% ethanolic potassium hydroxide (ethanol:water=1:3) was added a 6-benzylidenehydrazino-3-methyl-5-nitrosouracil (I) (0.005 mole) and the mixture was refluxed for 1 hr. 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 dried. Recrystallization from dimethylformamide gave colorless crystals of a 4,5-diimino-3-methyl-imidazolidin-2(1H)one 5-arylidenehydrazone (Table I).

1,3-Dialkyl-4,5-diiminoimidazolidin-2(1H)one 5-Arylidenehydrazones (IIIa-h). General Procedure. ——— A mixture of II (0.004 mole), an alkyl iodide (0.015 mole) and potassium carbonate (0.02 mole) in dimethylformamide (3 ml) was stirred at room temperature for 5 hr. The reaction mixture was diluted with water to precipitate crystals, which were collected by filtration, washed with water and recrystallized from ethanol (Table I).

Formation of 3-Aryl-5,7-dialkyl-5H-imidazo[4,5-e]-as-triazin-6(7H)ones (2-Aryl-7,9-dialkyl-6-azapurin-8-ones) (IVa-h) by Oxidative Cycloaddition of IIIa-h. General Procedure. ——— Heating of III (0.001 mole) with excess DAD (0.003 mole) under stirring at 175-180° for 1 hr, followed by dilution with ethanol, caused the separation of colorless crystals, which were collected by filtration and recrystallized from ethanol (Table II).

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