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NEW SYNTHESIS OF 1,3-DIMETHYL-7-HYDROXYPYRROLO[3,2-*d*]PYRIMIDINE-2,4(1*H*,3*H*)-DIONES (9-HYDROXY-9-DEAZATHEOPHYLLINES)

Fumio YONEDA,* Miyuki MOTOKURA, and Masaki OTAGIRI
Faculty of Pharmaceutical Sciences, Kumamoto University
Oe-honmachi, Kumamoto 862

Treatment of 5-nitro-1,3,6-trinitrouracil with aryl aldehydes in the presence of piperidine causes the condensation to the 5-nitro-6-styryluracil derivatives, followed by the intramolecular cyclization including piperidine-catalyzed oxidation-reduction to give rise to the corresponding 1,3-dimethyl-7-hydroxypyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9-hydroxy-9-deazatheophylline) derivatives in a single step. Some properties of these compounds are discussed.

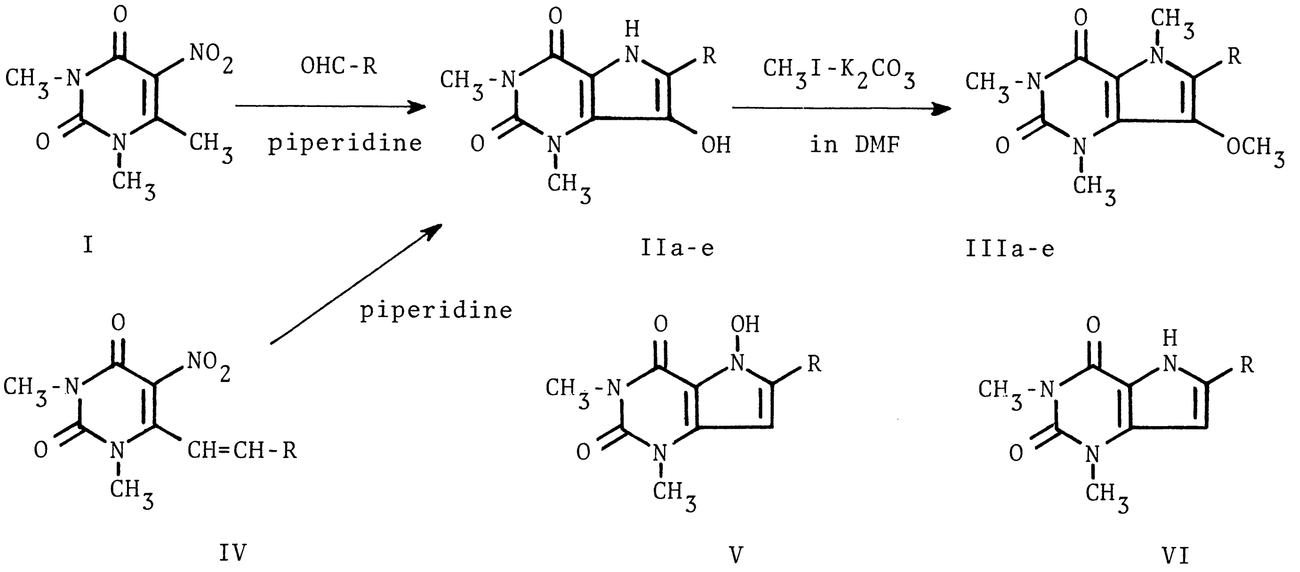
The pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) ring system has aroused considerable recent interest because of its close structural resemblance to purine as well as to other biological important heterocycles, *e.g.*, pyrrolo[2,3-*d*]pyrimidine, pyrazolo[4,5-*d*]pyrimidine, and indole.[1] We report here a new convenient synthesis of 7-hydroxypyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (referred to hereafter as 9-hydroxy-9-deazatheophyllines) which belong to an unexplored class of pyrrolo-[3,2-*d*]pyrimidines, except a contribution by Senda and coworkers.[2]

This synthesis consists of treatment of 5-nitro-1,3,6-trimethyluracil (I)[3] with aryl aldehydes in the presence of piperidine. For example, refluxing a mixture of I (0.5 g, 0.0025 mole), benzaldehyde (0.8 g, 0.0075 mole), and piperidine (0.32 g, 0.0037 g) in dimethylformamide (5 ml) for 2 hr, followed by evaporation of the reaction mixture *in vacuo* and recrystallization of the residue from ethanol gave 9-hydroxy-8-phenyl-9-deazatheophylline (IIa) (0.28 g, 42%) as yellow microcrystalline powder. Similarly, heating I with other aryl aldehydes in dimethylformamide in the presence of piperidine under the same conditions led to the formation of the respective 9-hydroxy-9-deazatheophyllines (IIb-e) (Table 1) in moderate yields.

The structures of IIa-e were assigned on the basis of elemental analyses, molecular weights as determined by mass spectrometry and the presence of a hydroxy proton at 8.3 ppm region (DMSO-d_6) as well as the absence of C-9 proton in the NMR. Furthermore, several kinds of reductions toward II did not work, with the starting materials being recovered. This fact excludes the possibility for II to possesses the 7-hydroxy-9-deazatheophylline-type structure (V). Finally, the structures of II were determined by X-ray analysis[4] of one of their dimethyl derivatives (III) (vide infra).

The treatment of 1,3-dimethyl-5-nitro-6-styryluracils (IV)[5,6] with piperidine in dimethylformamide under the same conditions gave also II, although in slightly lower yields (for example, 31% for IIa).

Therefore, we rationalize the conversion of I to II in terms of the initial formation of 5-nitro-6-styryluracils (IV). Intramolecular oxidation-reduction of IV catalyzed by piperidine would give the heterohexatriene-type 5-nitrosouracil intermediates (VII). Subsequent electrocyclization of VII to the 7,9-dihydroxy-9-deazatheophyllines and then the thermal deoxygenation would lead to the final products (II) (Scheme 2).



Scheme 1

Table 1. 9-Hydroxy-9-deazatheophyllines

Compound No.	R	Appearance	Mp (°C)[a)]	Yield (%)
IIa	C_6H_5	yellow powder	316	42
IIb	4-CH_3-C_6H_4	yellow powder	316	43
IIc	4-CH_3O-C_6H_4	yellow powder	221	47
IId	4-Cl-C_6H_4	yellow powder	333	52
IIe	4-F-C_6H_4	brown powder	207	52

a) All compounds were recrystallized from ethanol.

II did not show any proton signals in trifluoroacetic acid in the NMR, because of a radical formation in strong acids. In fact, II exhibited broad ESR signals at g=2.0033-2.0037 in trifluoroacetic acid under aerobic conditions (as well as under nitrogen) at room temperature as shown in Fig. 1.[7] Whether these ESR spectra observed are due to the cation radical or the neutral radical will have to await detailed ESR studies.

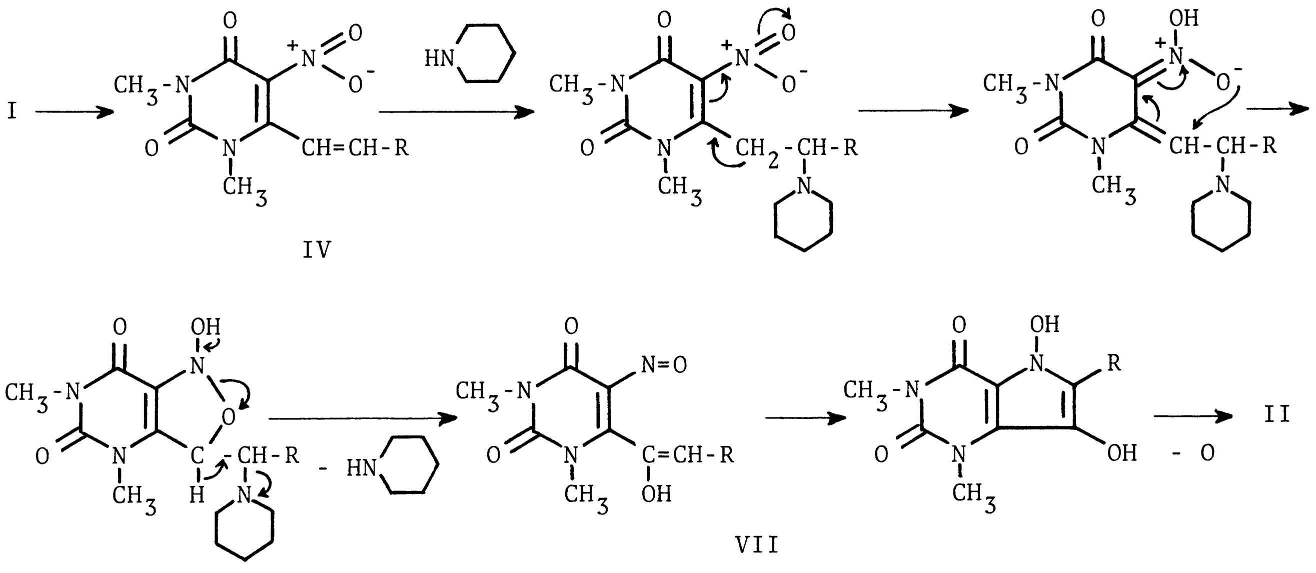
When II were treated with excess methyl iodide in dimethylformamide under reflux in the presence of potassium carbonate, the corresponding 9-methoxy-7-methyl-9-deazatheophyllines (IIIa-e) were obtained (Table 2). The structures of III were confirmed by satisfactory analytical data as well as their several spectra [III were stable in trifluoroacetic acid and exhibited characteristic proton signals of N_7-CH_3 and C_9-OCH_3 at 3.6 and 3.8 ppm regions in the NMR (trifluoroacetic acid)].

Table 2. 9-Methoxy-7-methyl-9-deazatheophyllines

Compound No.	R	Appearance	Mp (°C)[a)]	Yield (%)
IIIa	C_6H_5	pale yellow needles	175	78
IIIb	4-CH_3-C_6H_4	yellow needles	217	69
IIIc	4-CH_3O-C_6H_4	brown needles	224	62
IIId	4-Cl-C_6H_4	pale yellow needles	221	84
IIIe	4-F-C_6H_4	brown needles	191	42

a) All compounds were recrystallized from ethanol.

Senda and coworkers reported that the irradiation of 1,3-dimethyl-5-nitro-6-styryluracils (IV) in benzene gave 9-hydroxy-9-deazatheophyllines (II) as a by-product in low yields.[2] Furthermore, it is noted that the irradiation of IV in isopropanol gave 9-deazatheophyllines (VI)[2] and also the conventional reductions of IV gave the same products (VI).[5,6]



Scheme 2

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4) The result of X-ray analysis for compound IIId will be published in the full account of this paper.

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7) ESR spectra were measured at room temperature by a Varian E-4 X-band ESR spectrometer. It is evident from line width that there is a large spin density on the nitrogen or oxygen atoms.

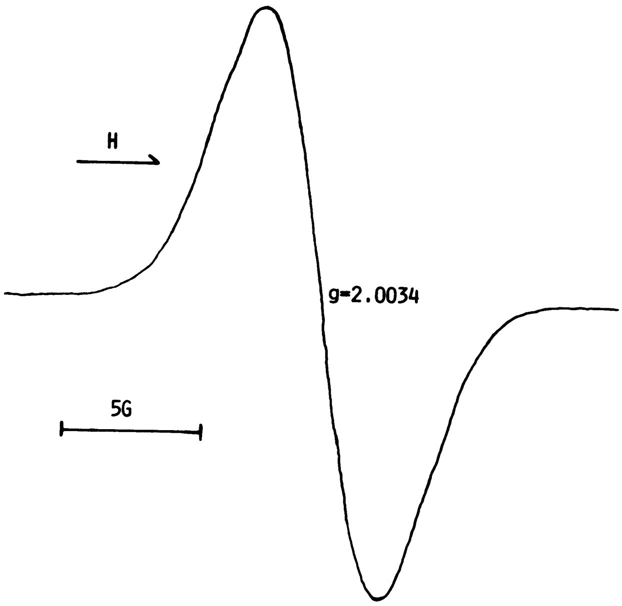

Fig. 1. ESR spectra of a radical formed from IIa in trifluoroacetic acid

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