A DICHOTOMY IN THE INTRAMOLECULAR CYCLOADDITION OF AZA ANALOGS OF HEXATRIENE. THERMOLYSIS AND PHOTOLYSIS OF 6-BENZYLIDENEAMINO-5-DIMETHYLAMINOMETHYLENEAMINO-1,3-DIMETHYLURACILS

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The 5-dimethylaminomethylene derivatives (II) resulting from the condensation of the 6-amino-5-benzylideneamino-1,3-dimethyluracils (I) with dimethylformamide diethylacetal underwent intramolecular cycloaddition by thermolysis in sulfolane to yield the respective 1,3-dimethyllumazine derivatives (III), while the photolysis of II in alcohol led to the formation of theophylline via another type of cycloaddition.

Recent investigations in this laboratory have established the novel synthetic method for preparation of heterocycles such as purines,[1] pteridines[3] and pyrazolo[3,4-d]pyrimidines[1,2] by intramolecular cycloaddition of aza analogs of hexatriene. This paper will describe the thermal and photolytic cyclization of 5-benzylideneamino-6-dimethylaminomethyleneamino-1,3-dimethyluracils (II)

as attractive candidates for the 2,5-diazahexatriene-type precursors, which eventually give the 6-substituted 1,3-dimethyllumazines (III) and theophylline (IV) respectively.

Table 1 5-Benzylideneamino-6-dimethylaminomethyleneamino-1,3-dimethyluracils

Compound No.	R	Mp (°C)	Yield (%)
IIa	C_6H_5	170	95
IIb	4-Cl-C_6H_4	185	93
IIc	4-CH_3O-C_6H_4	176	91
IId	3,4-CH_2O_2-C_6H_3	242	82

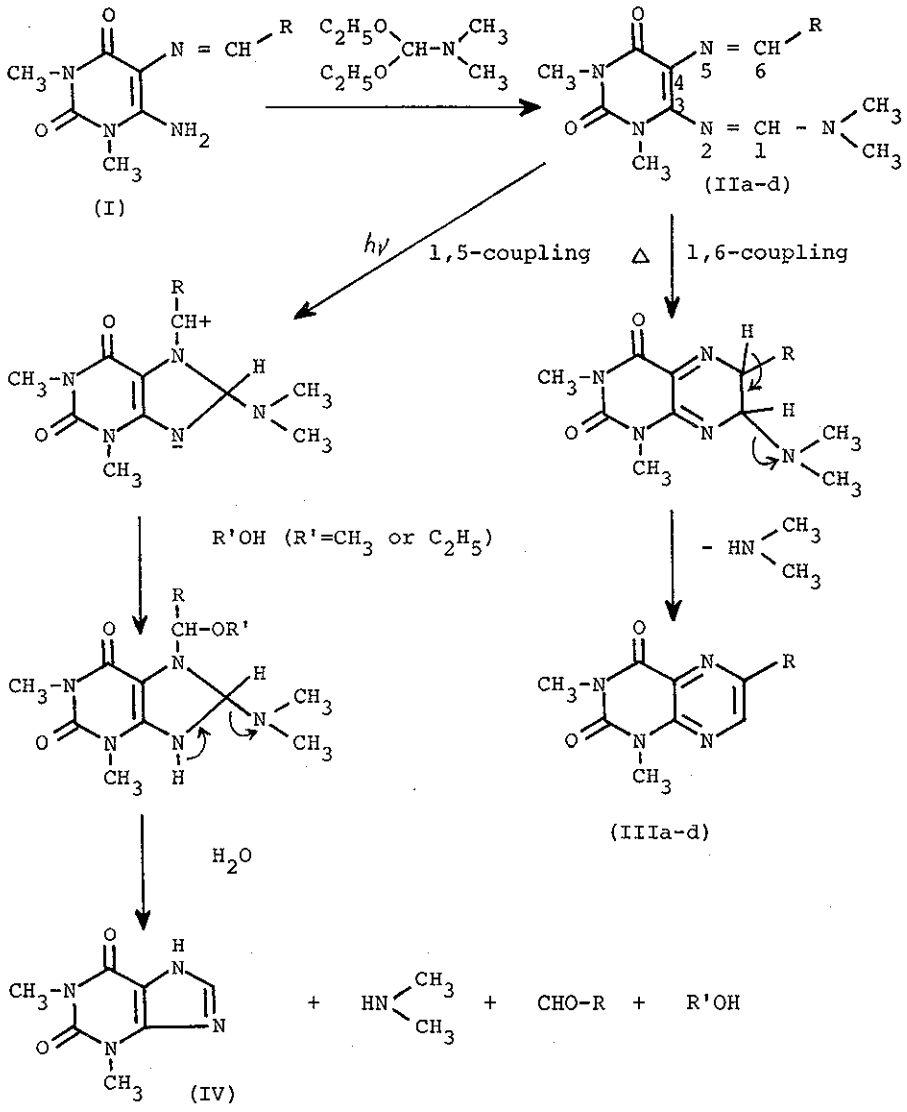
The key intermediates, compounds IIa-d, were prepared as follows. A mixture of 6-amino-5-benzylideneamino-1,3-dimethyluracils (I)[4] (0.005 mole) and dimethylformamide diethylacetal (0.015 mole) in ethanol (10 ml) was refluxed for 4 hr and allowed to stand overnight to precipitate IIa-d as yellow needles, which were filtered off and recrystallized from ethanol (see Table 1).

Table 2 Formation of 6-Substituted 1,3-Dimethyllumazines

Compound No.	R	Mp (°C)[a]	Yield (%)
IIIa	C_6H_5	257[3]	44
IIIb	4-Cl-C_6H_4	250[3]	43
IIIc	4-CH_3O-C_6H_4	222[3]	42
IIId	3,4-CH_2O_2-C_6H_3	250	39

It has been found that on thermolysis compounds II undergo the intramolecular cycloaddition followed by the aromatization by

a) These compounds were recrystallized from dimethylformamide.



elimination of dimethylamine to yield the respective 1,3-dimethyl-lumazines (III), as depicted in the above Scheme. The reaction

can be performed by heating compounds II (0.5 g) in sulfolane (5 ml) at 200° for 3 hr, followed by evaporation of the solvent and dilution with ethanol to precipitate the respective lumazines (IIIa-d) which were identical with authentic samples[3] (see Table 2).

The photolysis of compounds II was carried out as follows. A solution of compounds II (0.2 g) in ethanol or methanol (200 ml) in a Pyrex flask was exposed to the direct sunshine at ambient temperature for about 10 hr. The completion of the reaction could be judged by the bleaching of the initial yellow color of the solution. Removal of the solvent and recrystallization of the residue from ethanol gave theophylline (70-80%) along with a trace of the less soluble 1,3-dimethyllumazines (III). In the reaction mixture, dimethylamine and aryl aldehydes were detected. From these facts, the formation of theophylline can be explained by assuming the initial cyclization between the 1- and 5-positions of the 2,5-diazahexatriene-type precursors (II). Addition of solvent (alcohol) followed by elimination of dimethylamine and hydrolysis with adventitious water would lead to theophylline (IV) as depicted in the Scheme.

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