A DISPROPORTIONATION OF 6-AMINO-5-BENZYLIDENEAMINO-1,3-DIMETHYLURACILS IN FORMAMIDE. FORMATION OF 6,7-DIARYL-1,3-DIMETHYLLUMAZINES AND THEOPHYLLINE

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Heating of 6-amino-5-benzylideneamino-1,3-dimethyluracils in formamide led to the formation of the corresponding 6,7-diaryl-1,3-dimethyllumazines and theophylline.

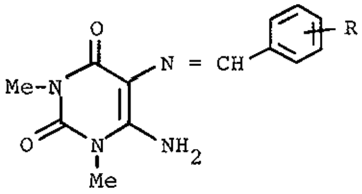
We describe here a new disproportionation of 6-amino-5-benzylideneamino-1,3-dimethyluracils in formamide, which leads eventually to the formation of the corresponding 6,7-diaryl-1,3-dimethyllumazines and theophylline.

Heating of 1 part of 6-amino-5-benzylideneamino-1,3-dimethyluracil (Ia)[1] in 10 parts of formamide at 180° for 4 hr, followed by dilution with ethanol caused the separation of a mixture of 1,3-dimethyl-6,7-diphenyllumazine (IIa)[2] and theophylline, together with a trace of 8-phenyltheophylline. Similarly, the treatment of other 6-amino-5-benzylideneamino-1,3-dimethyluracils (Ib-g), which were readily available by the condensation of 5,6-diamino-1,3-dimethyluracil with the respective aryl aldehydes in ethanol, in formamide under the same conditions gave the corresponding 6,7-diaryl-1,3-dimethyllumazines (IIb-g) and theophylline (see Table), sometimes with a trace of the corresponding 8-aryltheophyllines.

Table Formation of 6,7-Diaryl-1,3-dimethyllumazines and Theophilline by Heating of 6-Amino-5-benzylideneamino-1,3-dimethyluracils in Formamide

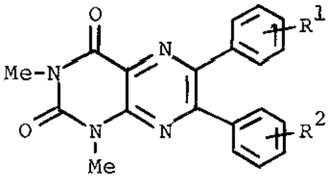
Starting material	Products				
	Lumazine[a]	M.p./°C	Yield/%	Theophylline/%	Total/%
(Ia)[1]	(IIa)[4]	232	25	39	64
(Ib)	(IIb)	191	16	37	53
(Ic)	(IIc)	210	18	48	66
(Id)	(IId)	189	28	42	70
(Ie)	(IIe)	125	20	47	67
(If)	(IIf)	274	21	48	69
(Ig)	(IIg)	255	8	36	44

a) These compounds were recrystallized from ethanol.



(I)

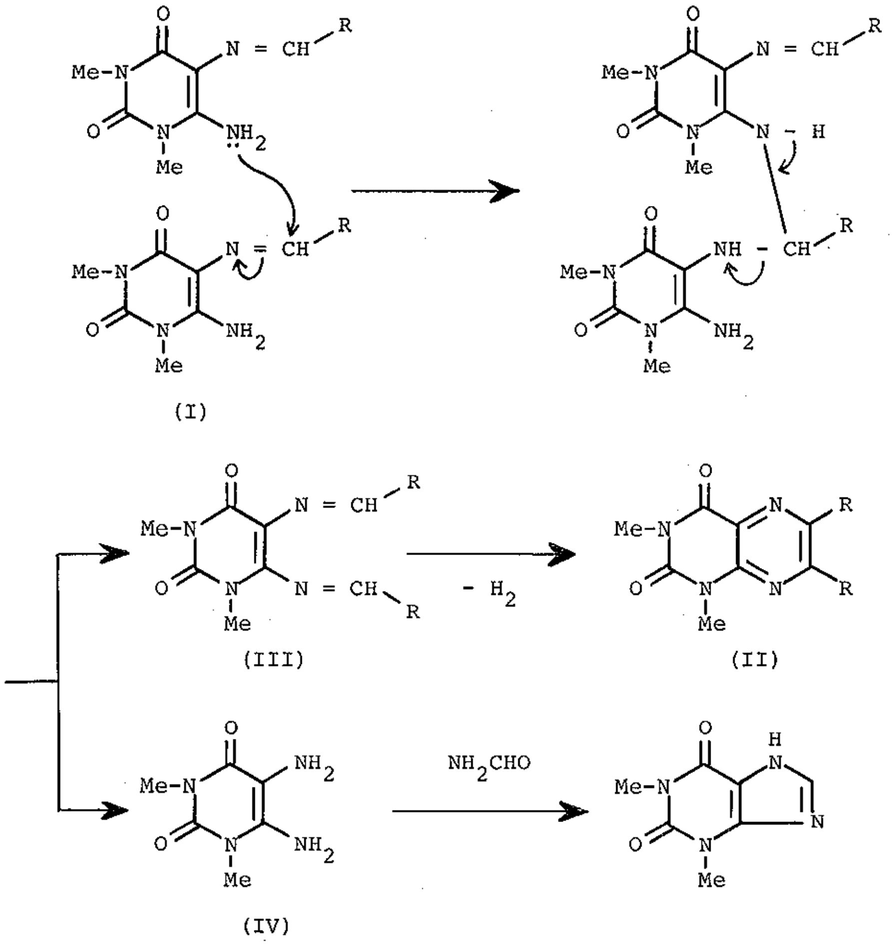
(a) R = H
(b) R = 4-Cl
(c) R = 3,4-Cl_2
(d) R = 4-OMe
(e) R = 3,4-$\mathrm{(OMe)}_2$
(f) R = 3,4-$\mathrm{O_2CH_2}$
(g) R = 4-NMe_2



(II)

(a) $R^1 = R^2$ = H
(b) $R^1 = R^2$ = 4-Cl
(c) $R^1 = R^2$ = 3,4-Cl_2
(d) $R^1 = R^2$ = 4-OMe
(e) $R^1 = R^2$ = 3,4-$\mathrm{(OMe)}_2$
(f) $R^1 = R^2$ = 3,4-$\mathrm{O_2CH_2}$
(g) $R^1 = R^2$ = 4-NMe_2
(h) R^1 = H, R^2 = 3,4-Cl_2
(i) R^1 = 3,4-Cl_2, R^2 = H

This reaction is best rationalized by assuming initial nucleophilic attack of the 6-amino group of (I) on the anil carbon of another molecule of (I). Subsequent nitrogen-carbon bond cleavage accompanying hydrogen transfer forms a mixture of 5,6-



Scheme

dibenzylideneamino-1,3-dimethyluracil (III) and 5,6-diamino-1,3-dimethyluracil (IV). The former could then be cyclized and dehydrogenated to give 6,7-diaryl-1,3-dimethyllumazine.[3] The latter should yield theophylline by the condensation with formamide (see Scheme).

The heating of a mixture of equimolar amounts of (Ia) and (Ic) in formamide under the same conditions gave, as major products, theophylline (49%) and the crossed products, 7-(3,4-dichlorophenyl)-1,3-dimethyl-6-phenyllumazine (IIh)[5] (m.p. 254°) (23%) and 6-(3,4-dichlorophenyl,-1,3-dimethyl-7-phenyllumazine (IIi)[5] (m.p. 156°) (14%), along with small amounts of (IIa) and (IIc).

REFERENCES AND NOTES

1. W. Traube and W. Nithak, Chem. Ber., 1906, **39**, 227.
2. R. B. Angier, J. Org. Chem., 1963, **28**, 1509.
3. It is known that the oxidative cyclization of 5,6-dibenzylideneamino-1,3-dimethyluracil gives 1,3-dimethyl-6,7-diphenyllumazine.[4]
4. W. Pfleiderer and H.-U. Blank, Angew. Chem., 1968, **80**, 534.
5. Compounds (IIh) and (IIi) were alternatively synthesized by fusion of (Ia) with 3,4-dichlorobenzaldehyde and by fusion of (Ic) with benzaldehyde, respectively, in accordance with Pfleiderer's procedure.[4]

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