OXIDATIVE CYCLIZATION OF 6-(N-ALKYLANILINO)-5-AMINOURACILS TO FLAVINS WITH DIETHYL AZODICARBOXYLATE OR NITROSOBENZENE

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Treatment of 6-(N-alkylanilino)-5-aminouracils with diethyl azodicarboxylate or nitrosobenzene in ethanol or acetic acid in the indirect sunshine gave the corresponding flavins. The reaction mechanism has been definitely shown by the isolation of the key intermediates, 6-(N-alkylanilino)-5-iminouracils.

We report a new synthesis of flavins in which diethyl azodicarboxylate (DAD) or nitrosobenzene acts as a useful reagent for the oxidative cyclization of 6-(N-alkylanilino)-5-aminouracils.

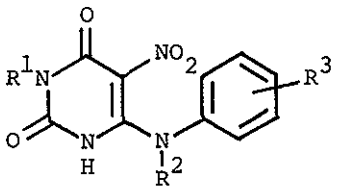
6-(N-Alkylanilino)-5-nitrouracils (Ia-l)[1], prepared by the condensation of 6-chloro-5-nitrouracil[2] and 6-chloro-3-methyl-5-nitrouracil[3] with N-alkylanilines, were hydrogenated in a mixture of ethanol and acetic acid (4:1) over palladium-charcoal to give the 6-(N-alkylanilino)-5-aminouracils (IIa-l) (see Table 1). To solutions of compounds IIa-l in ethanol or acetic acid was added a slight excess of equimolar amount of DAD and the mixtures were

allowed to stand in the indirect sunshine coming through a window for 4 to 6 hr to precipitate the respective flavins (IIIa-l)[4] (see Table 2).

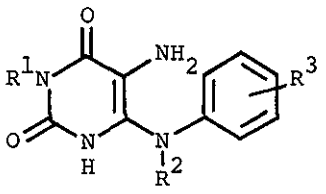
Table 1 Reduction of 6-(N-Alkylanilino)-5-nitrouracils to 6-(N-Alkylanilino)-5-aminouracils

Starting material	(Mp,°C)	R^1	R^2	R^3	Product	Mp(°C)	Yield(%)
Ia	(271)	H	Me	H	IIa	>360	75
Ib	(279)	H	Et	H	IIb	197	75
Ic	(276)	H	n-Pr	H	IIc	245	78
Id	(261)	H	n-Bu	H	IId	211	80
Ie	(273)	H	Et	3-Me	IIe	265	82
If	(263)	H	Et	4-Me	IIf	269	72
Ig[3]	(236)	Me	Me	H	IIg	164	70
Ih[3]	(234)	Me	Et	H	IIh	181	73
Ii	(178)	Me	n-Pr	H	IIi	171	75
Ij[3]	(157)	Me	n-Bu	H	IIj	118	82
Ik	(222)	Me	Et	3-Me	IIk	149	83
Il	(182)	Me	Et	4-Me	IIl	191	80

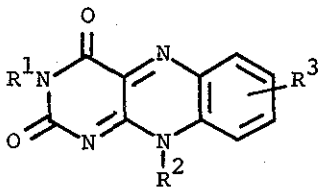
Stirring of IIh with DAD in ethanol or tetrahydrofuran at room temperature for 2 hr in the dark, followed by dilution with ether, precipitated an unstable adduct, 5-(1,2-bisethoxycarbonylhydrazino)-amino-6-(N-ethylanilino)uracil (IV) as colorless needles, mp 140°, in 85% yield. Heating of compound IV in ethanol at 60° for 10 min in the dark, followed by dilution with ether, caused the separation of 6-(N-ethylanilino)-5-imino-3-methyluracil (Vh) as yellow needles, mp 155°, in 80% yield. Concentration of the filtrate gave diethyl hydrazodicarboxylate in almost quantitative yield. The reaction of



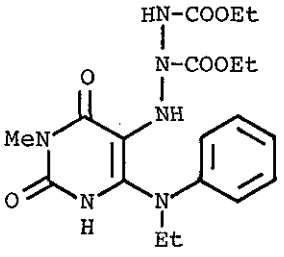
Ia-1



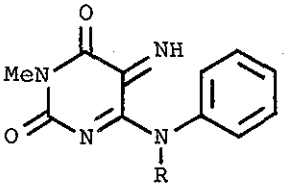
IIa-1



IIIa-1



IV



Vg R = Me

Vh R = Et

IIg with DAD in ethanol at room temperature in the dark directly 5-imino-6-(N-methylanilino)-3-methyluracil (Vg) as yellow needles, mp 145°, in 85% yield, without the isolation of the adduct of IV-type. The structures of the 5-imino compounds (V) were derived on the basis of the ir (presence of a sharp NH= absorption at 3180 cm^{-1}) and nmr spectra, and molecular weight determination by mass spectroscopy. An ethanolic solution of V was allowed to stand at room temperature in a bright room with the indirect sunshine for several hr to separate IIIg and IIIh via intramolecular cyclization followed by air oxidation.

The oxidative cyclization of II with excess nitrosobenzene in ethanol under the same conditions gave also the corresponding flavins in slightly lower yields than by the DAD oxidation (see

Table 2). Treatment of IIg with nitrosobenzene in ethanol at room temperature for 3 hr in the dark gave the same 5-imino intermediate (Vg) in 80% yield. Use of 30% hydrogen peroxide and nitric acid was also effective for the oxidative cyclization, however the yields were much lower.

Table 2 Flavin Formation by the Oxidative Cyclization of 6-(N-Alkylanilino)-5-aminouracils with DAD or Nitrosobenzene

Product	R^1	R^2	R^3	Solvent	Yield (%) With DAD	Yield (%) With Nitroso-benzene	Mp (°C)
IIIa[4]	H	Me	H	AcOH	85		>360
IIIb[4]	H	Et	H	AcOH	82		347
IIIc[4]	H	n-Pr	H	AcOH	79		349
IIId[4]	H	n-Bu	H	AcOH	77		335
IIIe	H	Et	8-Me	AcOH	74		363
IIIf	H	Et	7-Me	AcOH	69		>360
IIIg[4]	Me	Me	H	EtOH	92	84	334
IIIh[4]	Me	Et	H	EtOH	90	80	299
IIIi[4]	Me	n-Pr	H	EtOH	85	78	332
IIIj[4]	Me	n-Bu	H	EtOH	87	76	315
IIIk	Me	Et	8-Me	EtOH	87	75	314
IIIl	Me	Et	7-Me	EtOH	82	70	276

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