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A NOVEL RING EXPANSION OF PYRIMIDINES TO 1,3,5-TRIAZEPINES

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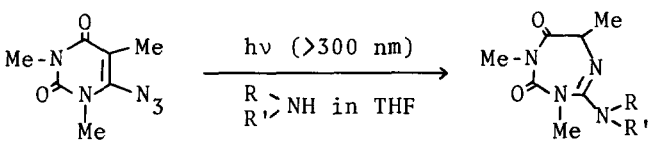
We recently reported that the irradiation of 6-azido-1,3-dimethyluracil in the presence of various amines gave 6-alkylamino-5-amino-1,3-dimethyluracils, lumazines, and fervenulins in one step[1]. In connection with this work, photolysis of 5-substituted 6-azidouracils, such as 6-azido-1,3-dimethylthymine (I) and 6-azido-5-cyano-1,3-dimethyluracil (II), in the presence of alkylamines or alcohols has been investigated. This communication describes the first example of ring transformation of pyrimidines to 1,3,5-triazepines[2].



I III

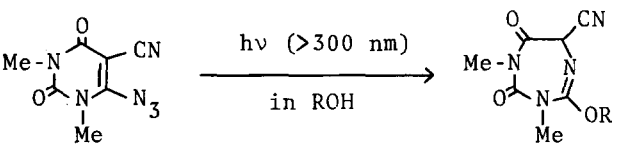
As a most illustrative example, a solution of I (0.015 mole) and methylamine (0.045 mole) in tetrahydrofuran (THF) was irradiated[3] under nitrogen at room temperature for 3 h. After evaporation of THF in vacuo, the residue was treated with ether to give 7H-2-methylamino-3,5,7-trimethyl-1,3,5-triazepin-4,6(3H,5H)-dione(IIIa, R=Me, R'=H), mp 171-172.5°C, in 40 % yield. The structure of IIIa was confirmed on the basis of elemental analysis and the following spectral data; NMR($CDCl_3$)δ 1.43 (3H, d, C_7-CH_3, J=6Hz), 2.78 (3H, d, NH-CH_3, J=4Hz, collapsing with D_2O to singlet), 3.10 and 3.23 (each 3H, each s, each N-CH_3), 3.93 (1H, q, C_7-H, J=6Hz), 4.05 (1H, b, NH, vanishing with D_2O); IR

(KBr) 3225 cm^{-1} (NH). The ultraviolet spectrum of IIIa shows only end absorption, implying that IIIa has a nonresonant structure. Similar irradiation of I (0.015 mole) and various alkylamines (0.045 mole) in THF gave the corresponding 2-alkylamino-1,3,5-triazepines (IIIb-f).[4] (Table 1)

Table 1 Photochemical formation of 2-alkylamino-1,3,5-triazepines (III)

Alkylamine	Product	R	R'	Mp, °C	Yield, %
methylamine	a	Me	H	171-172.5	40
ethylamine	b	Et	H	151-152.5	41
isopropylamine	c	i-Pr	H	150-152	30
dimethylamine	d	Me	Me	218-220 (picrate)	57
diethylamine	e	Et	Et	202-205 (picrate)	37
piperidine	f	—$(CH_2)_5$—		187-189 (picrate)	25

Analogous ring expansion leading to triazepine was observed when 6-azido-5-cyano-1,3-dimethyluracil (II) was irradiated without alkylamines in methanol.[5] Evaporation of the solvent gave only 7H-7-cyano-3,5-dimethyl-2-methoxy-1,3,5-triazepin-4,6(3H,5H)-dione(IVa, R=Me), mp 169-170°C, in 75 % yield; NMR(DMSO-d_6)δ 3.80 (3H, s, OCH_3), 5.81 (1H, s, C_7-H); IR(KBr) 2240 cm^{-1} (C≡N).



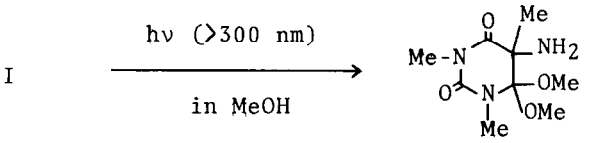
II IV

Table 2 Photochemical formation of 2-alkoxy-1,3,5,-triazepines (IV)

Alcohol	Product	R	Mp, °C	Yield, %
methanol	a	Me	169-170	75
ethanol	b	Et	109-110	63
isopropanol	c	i-Pr	121-122	53

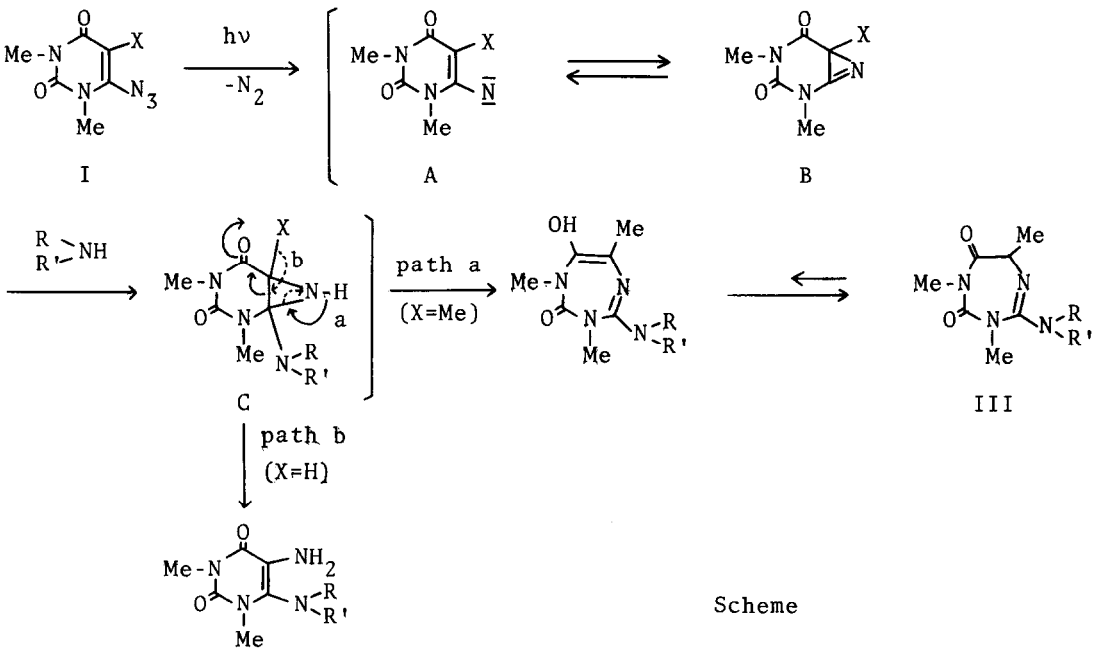
Similar photolysis of II in ethanol or isopropanol afforded the corresponding 2-alkoxy-1,3,5-triazepines (IVb, c). (Table 2)

We have also investigated the photolysis of I in methanol. The product thus obtained was not the expected triazepine but 5-amino-6,6-dimethoxy-1,3,5-trimethyl-5,6-dihydrouracil (V) (43 % yield).[6]



V

To the best of our knowledge, the ring expansion of uracils to seven-membered heterocycles has not been previously described, although the ring transformations to the other heterocycles, e.g. imidazole[7], pyrazole[8], isocytosine[9], have been reported. We propose the following plausible mechanism for this reaction (see Scheme). Photochemically inisiated loss of nitrogen from I gives a nitrene (A) which is in equilibrium with an azirine (B). Nucleophilic addition



Scheme

of the amine to (B) affords an azirine (C) which follows by scission of the C5-C6 bond giving III (path a, X=Me). This behavior is of interest, compared with that of 6-azido-1,3-dimethyluracil (path b, X=H) as discussed previously.[1)]

References and Notes

1) S. Senda, K. Hirota, M. Suzuki, T. Asao, and K. Maruhashi, J. Chem. Soc., Chem. Commun., 731 (1976); S. Senda, K. Hirota, T. Asao, and K. Maruhashi, J. Am. Chem. Soc., 99, 7358 (1977).

2) Scriven, et al. described that 6-azido-1,3-dimethyluracil had certain structural features which would appear to prevent ring expansion, in the recent literature; S.E. Carroll, B. Nay, E.F.V. Scriven, H. Suschitzky, and D.R. Thomas, Tetrahedron Letters, 3175 (1977).

3) Irradiation was carried out in a flask equipped with a Pyrex-jacketed immersion lamp. The light source was a Riko-UVL 100 W high-pressure mercury arc lamp.

4) All new compounds gave satisfactory elemental analyses and spectral properties consistent with the assigned structure.

5) When II was irradiated in the presence of alkylamine, a nucleophilic substitution product, 6-alkylamino-5-cyano-1,3-dimethyluracil was obtained in good yield.

6) The structure of V was confirmed by the following data; mp 91-95°C; NMR ($CDCl_3$)δ 1.23 (3H, s, 5-CH_3), 1.82 (2H, b, NH_2, vanishing with D_2O), 3.20 (6H, s, 2 x OCH_3), 3.17 and 3.67 (each 3H, each s, each NCH_3); IR(KBr) 3330 and 3400 cm^{-1} (NH_2).

7) B.A. Otter, E.A. Falco, and J.J. Fox, J. Org. Chem., 34, 2636 (1969), and references cited therein; S. Senda, K. Hirota, and K. Banno, Tetrahedron Letters, 3087 (1974).

8) For a review of ring transformations of pyrimidines, see H.C. van der Plas, "Ring Transformations of Heterocycles", Vol.2, Academic Press, New York, 1973, pp. 120.

9) K. Hirota, K.A. Watanabe, and J.J. Fox, J. Heterocycl. Chem., 14, 537 (1977).