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PHOTOADDITION OF ALCOHOLS TO METHYLTHIO-4-PYRIMIDINONES

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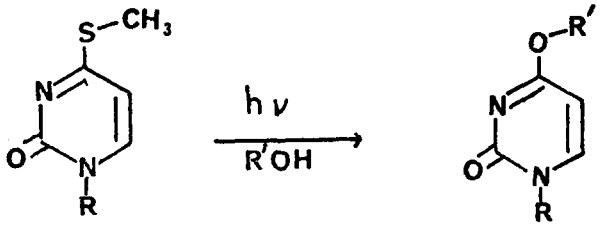
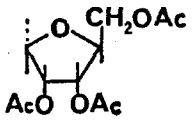
Uracil[1] and 5-fluorouracil[2] are the only known pyrimidinone derivatives which react efficiently with water or methanol in the presence of light (photoaddition). In the case of cytosine[3] and thymine[4] photohydrates have also been detected. In contrast, 4-thiouracil and 2-thiouracil which possess a thiocarbonyl chromophore are completly unreactive towards water photoaddition[5].

Our recent observation on the irradiation of 4-benzylthio-1-methylpyrimidinone in methanol leading to a 5, 6-dihydro-6-methoxy-1-methylpyrimidinone[6] suggested that a 4-alkylthiopyrimidinone could undergo solvent photoaddition. We were thus prompted to investigate the photochemistry of the 4-methylthiopyrimidinones 1 and 2 in alcoholic solution.



1 R = CH_3

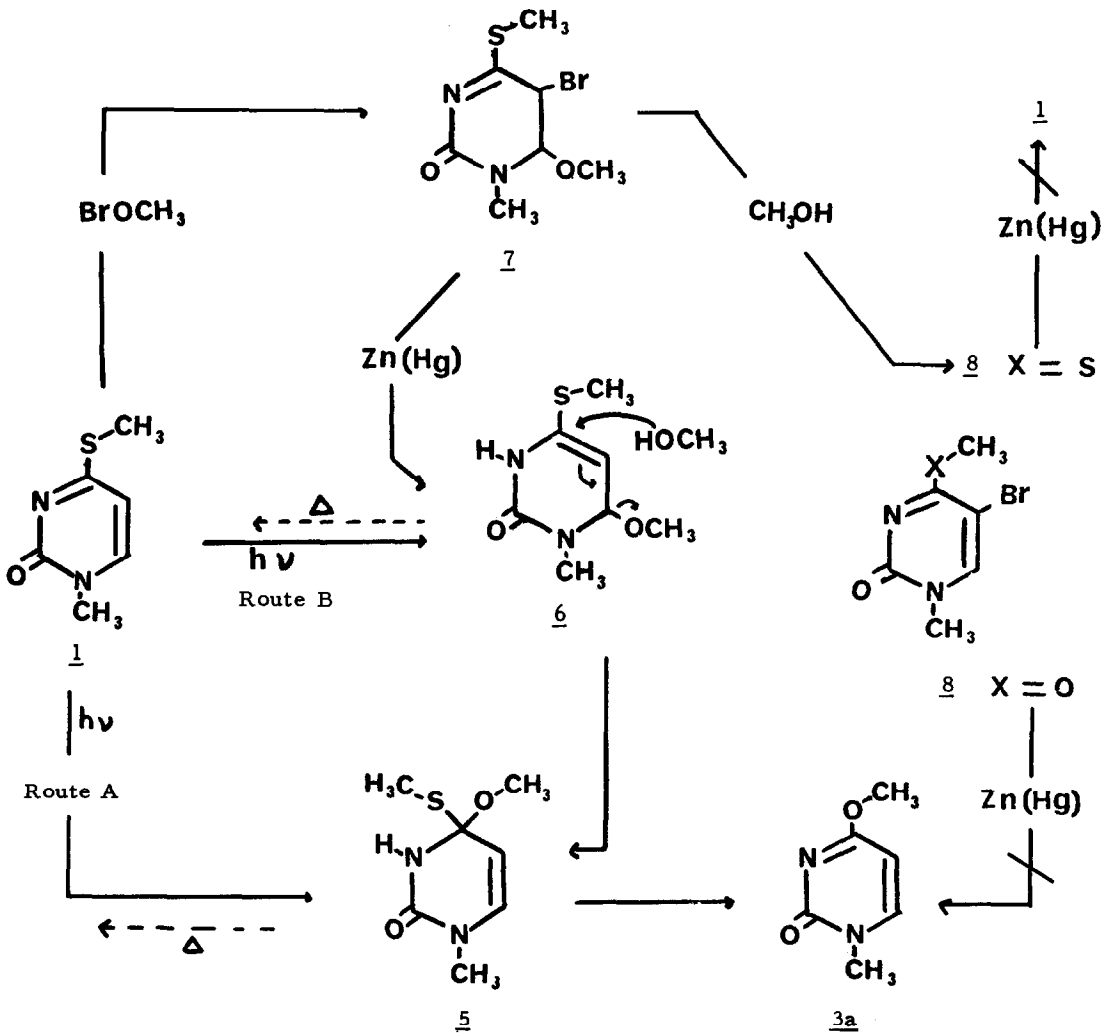
	R'	Yield
3a	CH_3	35 %
3b	CH_2CH_3	30 %
3c	$CH(CH_3)_2$	33 %
3d	$C(CH_3)_3$	40 %

2 R = 

	R'	Yield
4	CH_3	35 %

When irradiated[7] in alcohol (methanol, ethanol, isopropanol, t-butanol) 1-methyl-4-methylthiopyrimidinone 1 disappeared rapidly to give the 4-alkyloxy-1-methylpyrimidinones 3. Compounds 3a-d were identified by direct comparison with samples prepared by reacting the corresponding 2, 4-dialkyloxypyrimidines with methyl iodide (Hilbert-Johnson reaction)[8, 9]. Similarly, when the triacetyl nucleoside 2 was irradiated in methanol we obtained its methoxy analogue 4 (oil) (35 % yield) which was found identical with a substance isolated in minor amount after treatment of triacetyl uridine with CH_2N_2 in methanol[10]

The methoxy pyrimidinone 3a must derive from the thermally unstable 3, 4-dihydropyrimidinone 5. This intermediate may arise either by direct 1, 2- solvent photoaddition on 1 (route A) or by 1, 4-solvent photoaddition producing 6 followed by a methanol addition-elimination step (route B).



The fact that no deuterium incorporation was detected in 1 and 3a by repeating the irradiation in CH_3OD is in agreement with route A ; in the case of route B assuming that the methanol addition and elimination reactions are faster than deuterium exchange at C-5 (tautomerization of 6) this result is not unexpected.

In order to distinguish between the two mechanisms, it would be inadvertent to compare this new photosubstitution reaction with nucleophilic substitution reactions at C-4 of ground state pyrimidinone chemistry. Since such nucleophilic exchange is very easy with 5,6-dihydropyrimidinones it was currently admitted that pyrimidinone could readily undergo these reactions provided a mechanism reminiscent of route B be available. A relevant example is the substitution of the amino group of cytosine by hydroxylamine[11]. However, recently reported evidences suggest that the direct pathway (addition : elimination at C-4) is the most satisfactory[12].

In our effort to test route B we attempted to synthetise derivative 6. For this purpose we prepared compound 7 by adding neutral BrOMe[13] to 1 at -20°C. The former was thermally unstable in neutral methanol and yielded quantitatively the 5-bromo derivative 8 (X=S) which, like its analogue 8 (X=O), could not be reduced by zinc amalgam[14].

When 7 was treated with this reducing agent in methanol at 0°C the 3,6-dihydropyrimidinone 6 could not be obtained. However, work up of the reaction product yielded a 1:2 mixture of compounds 1 and 3a which must be derived from the extremely labile intermediate 6, thus demonstrating that the latter can be a precursor (via 5) of 3a.

In the absence of data concerning the relative electrophilicity of C-4 and C-6 centers of the excited methylthio-4-pyrimidinones we cannot rule out direct photochemical formation of adduct 5 (route A). However, the above ground state chemistry results suggest that alternative route B must be considered and could at least efficiently compete with route A. Significantly, in pyrimidinone photochemistry neutral solvent and, more generally, nucleophile photoaddition always occurs at position C-6[15] ; this has been once again recently illustrated in the case of 4-benzylthio-1-methylpyrimidinone[6,16].

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(3d : δ ppm C-CH_3 : 1.63, N-CH_3 : 3.44, H_5 : 5.76, H_6 : 7.40).

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