Tetrahedron Letters No. 17, pp 1389 - 1390, 1976. Pergamon Press. Printed in Great Britain.

A PECULIAR ALKYLATION REACTION OF ISOALLOXAZINES

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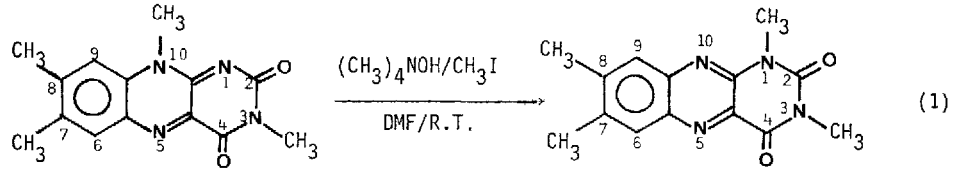
(Received in UK 2 February 1976; accepted for publication 15 March 1976)

Tetramethylammonium hydroxide has been described as an excellent methylating agent for hydantoin derivatives [1]. The same reagent also allows the flash-methylation of barbituric acids [2,3]. We could therefore expect the system $(CH_3)_4NOH/RX$ in a DMF or methanol solution to be efficient for alkylation purposes in the isoalloxazine (flavin) series. In the methylation reaction of 7,8,10-trimethylisoalloxazine (lumiflavin) we not only observed 3,7,8,10-tetramethylisoalloxazine, but also the formation of an important quantity of 1,3,7,8-tetramethylalloxazine (dimethyllumichrome). Reasonably, the first product formed is the methylated isoalloxazine 1, which undergoes a subsequent transformation resulting in the thermodynamically more stable alloxazine 2 (Equation 1).



(1)

1 2

To test this hypothesis and the generality of reaction (1) we carried out the synthesis of alloxazines starting with various fully alkylated isoalloxazines and using different alkyl halides. A summary of the obtained results and some of the physical properties of the products are presented in table I.

The following mechanism accounts for the observations :

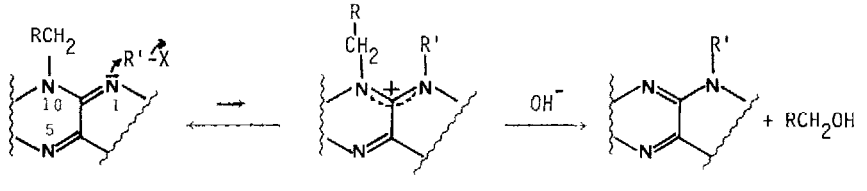


Table 1 : Alkylative rearrangement of isoalloxazines (Equation 1)

Starting isoalloxazine (1)	Reaction conditions RX/solvent/time	% conversion	PRODUCT (2)			
			structure[10]	m.p.(lit.)	λ_{max}(nm)	ε_{max}
$R_3,R_7,R_8,R_{10}=CH_3$	CH_3I/DMF/4 hrs	50	$R_1,R_3,R_7,R_8=CH_3$	256 (254-6)[4,5]	343 388	9100 8700
$R_3,R_7,R_8,R_{10}=CH_3$	$\phi CH_2Br/CH_3OH$/5hrs	30	$R_1=CH_2\phi$ $R_3,R_7,R_8=CH_3$	214°	340 389	8600 7700
$R_3,R_7,R_8,R_{10}=CH_3$	$CH_2=CH-CH_2Br/CH_3OH$/ 22hrs	10	$R_1=CH_2-CH=CH_2$ $R_3,R_7,R_8=CH_3$	209°	343 388	11000 9900
$R_3=CH_3$;R_7,R_8=H $R_{10}=CH_2\phi$	CH_3I/DMF/14hrs	35	$R_1,R_3=CH_3$ R_7,R_8=H	246°	326 382	8500 7100

The mechanism is corroborated by the fact that the N(1) position of isoalloxazines appears to be a hard nucleophilic center both on experimental [6,7] and theoretical [8,9] grounds. The results in Table 1 agree qualitatively with this statement. Indeed going from a hard (methyl iodide) to a soft (benzyl or allyl bromide) alkylating agent we observed a decrease in the percent conversion and an increase in the reaction time.

References and notes

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10) The structure of the products has been assigned on the basis of their characteristic sky-blue fluorescence and their UV-VIS (Pye-unicam 1800), NMR (Jeol MH100) and mass (AEI-MS30) spectra.