A New Alloxazine Synthesis

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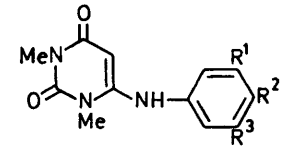
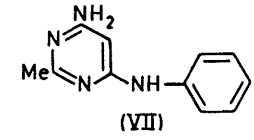
Summary The treatment of 6-anilinopyrimidines with diethyl azodicarboxylate led to the formation of the corresponding alloxazines in a single step.

DIETHYL AZODICARBOXYLATE (DAD) has recently been shown to be a useful reagent as the origin for N-5 in the synthesis of pteridines.[1] We now report a new convenient synthesis of alloxazines, in which DAD is also effective as a nitrogen source for the direct cyclization of 6-anilinopyrimidines.

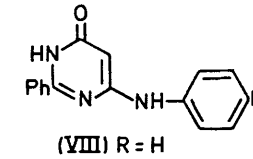
Fusion of 6-anilino-1,3-dimethyluracil (I) with a slight excess of DAD at 160 °C for 1 h, followed by dilution with ether, led to the formation of 1,3-dimethylalloxazine[2] (XI) in quantitative yield. This reaction is equally applicable to other 6-anilinopyrimidine derivatives to give excellent yields of the corresponding alloxazines (see Table).†



(I) $R^1 = R^2 = R^3 = H$
(II) $R^1 = R^3 = H, R^2 = Cl$
(III) $R^2 = H, R^1 = R^3 = Cl$
(IV) $R^1 = H, R^2 = R^3 = Cl$
(V) $R^1 = R^2 = H, R^3 = Me$
(VI) $R^1 = H, R^2 = R^3 = Me$



(VII)



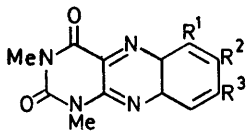
(VIII) R = H
(IX) R = Cl
(X) R = Br

Alloxazine formation by reaction of 6-anilinopyrimidine and DAD

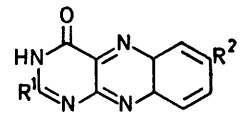
6-Anilinopyrimidine	Reaction conditions (°C, min)	Product	M.p. (°C)	Recrystn. solvent	Yield (%)
(I)	160, 60	(XI)	245	Benzene	95
(II)	170, 30	(XII)	268	Benzene	87
(III)	200, 20	(XIII)	300	Benzene	70
(IV)	200, 20	(XIV)	>300	Benzene	85
(V)	160, 30	(XV)	252	Benzene	98
(VI)	160, 30	(XVI)	254	Benzene	92
(VII)	160, 20	(XVII)	>300	Ethanol	96
(VIII)	180, 40	(XVIII)	>320	DMF	95
(IX)	200, 50	(XIX)	>320	DMF	83
(X)	180, 50	(XX)	>320	DMF	70

The cyclization of 1,3-dimethyl-6-(3-toluidino)uracil (V) by this method gave exclusively 1,3,8-trimethylalloxazine (XV), whereas the nitrosative cyclization[3] of (V) with sodium nitrite in acid gave a mixture of 1,3,8-trimethylalloxazine 5-oxide and 1,3,6-trimethylalloxazine 5-oxide (82:18). This behaviour can be ascribed to steric hindrance

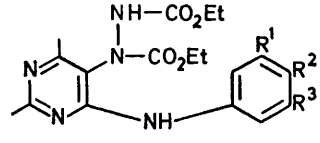
† Satisfactory analytical and spectral data were obtained for all the products.



(XI) $R^1 = R^2 = R^3 = H$
(XII) $R^1 = R^3 = H, R^2 = Cl$
(XIII) $R^2 = H, R^1 = R^3 = Cl$
(XIV) $R^1 = H, R^2 = R^3 = Cl$
(XV) $R^1 = R^2 = H\ R^3 = Me$
(XVI) $R^1 = H, R^2 = R^3 = Me$



(XVII) $R^1 = Me, R^2 = H$
(XVIII) $R^1 = Ph, R^2 = H$
(XIX) $R^1 = Ph, R^2 = Cl$
(XX) $R^1 = Ph, R^2 = Br$



(XXI)

of the bulky 1,2-diethoxycarbonylhydrazino-group at C-5 of the possible intermediate (XXI). Similarly, treatment of 1,3-dimethyl-6-(3,4-xylidino)uracil (VI) with DAD gave 1,3,7,8-tetramethylalloxazine (XVI) as the sole product, whereas the product by nitrosation of (VI) was contaminated with 1,3,6,7-tetramethylalloxazine.

Fusion of 6-amino-4-anilino-2-methylpyrimidine (VII) with DAD gave the deaminated product, 2-methyl-2-deoxyalloxazine (4-hydroxy-2-methylbenzo[*g*]pteridine) (XVII), which was identical in all respects with an authentic sample prepared by the dehydrogenation of 4-hydroxy-2-methylcyclohexa[*g*]pteridine with sulphur.[4] Treatment of 6-anilino-4-hydroxy-2-phenylpyrimidine (VIII) and its analogues (IX and X) with DAD gave the corresponding 2-phenyl-2-deoxyalloxazines[5] (XVIII, XIX, and XX) (Table).

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[1] F. Yoneda, S. Fukazawa, and S. Nishigaki, *Chem. Comm.*, 1971, 83.
[2] E. C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Amer. Chem. Soc.*, 1967, **89**, 3369.
[3] F. Yoneda and M. Ichiba, unpublished results.
[4] S. Nishigaki, S. Fukazawa, K. Ogiwara, and F. Yoneda, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 206.
[5] F. Yoneda, M. Ichiba, K. Ogiwara, and S. Nishigaki, *Chem. Comm.*, 1971, 23.