A New Synthesis of Alloxazines

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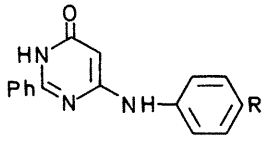
Summary The treatment of 6-anilino-4-hydroxy-5-*p*-nitrophenylazo-2-phenylpyrimidines with 10% concentrated sulphuric acid in glacial acetic acid led to the formation of the corresponding 2-phenyl-2-deoxyalloxazines.

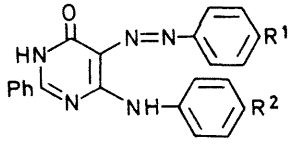
THE direct cyclization of 6-anilinopyrimidines by treatment with various nitrosating agents was discovered independently by Goldner *et al.*[1] and by Taylor's group[2] as a new route to alloxazines and their 5-oxides. We have now examined the utility of the azo-group, which has similar reactivity to the nitroso-group, as an origin for N-5 in the synthesis of alloxazines.

Heating 6-amino-4-hydroxy-2-phenylpyrimidine with an equimolar amount of aniline in the presence of a few drops of concentrated hydrochloric acid afforded 6-anilino-4-hydroxy-5-phenylpyrimidine (I)† (m.p. 206°) in 91% yield. Similarly, 6-*p*-chloroanilino-4-hydroxy-2-phenylpyrimidine (II) (m.p. 190°) and 6-*p*-bromoanilino-4-hydroxy-2-phenylpyrimidine (III) (m.p. 268°) were obtained in 95 and 96% yield, respectively. This procedure is an application of the known exchange amination reaction of pyrimidines.[3] The 6-anilinopyrimidines obtained here were converted into the respective 5-*p*-nitrophenylazopyrimidines (IV), (V), and (VI) (m.p. >320° for all) by the conventional coupling reaction with *p*-nitrobenzenediazonium chloride.

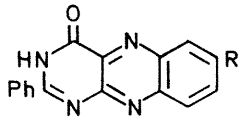
Heating 6-anilino-4-hydroxy-5-*p*-nitrophenylazo-2-phenylpyrimidine (IV) in 10% concentrated sulphuric acid in glacial acetic acid at 130—140° for 3 h, removal of the solvent by partial evaporation, and dilution with water gave 2-phenyl-2-deoxyalloxazine (IX) (m.p. > 320°) in 83% yield, which was in all respects identical with an authentic sample prepared by an alternative route.[4] Similarly, compounds (V) and (VI) under similar conditions yielded 7-chloro- (X) (m.p. > 320°) and 7-bromo-2-phenyl-2-deoxyalloxazine (XI) (m.p. > 320°) in 84 and 92% yield, respectively. On using a more acidic solvent such as 20% concentrated sulphuric acid in acetic acid, the cyclization did not occur, but a sulphuric acid salt of the starting material was obtained. The reaction was likewise not effected by acetic acid or by trifluoroacetic acid alone. Furthermore, all attempts so far to cyclize 5-phenylazo- (VII) (m.p. 302°) and 5-*p*-chlorophenylazo-6-anilino-4-hydroxy-2-phenylpyrimidine (VIII) (m.p. 289°) into the desired alloxazines have been unsuccessful.



(I) R = H
(II) R = Cl
(III) R = Br



(IV) $R^1 = NO_2, R^2 = H$
(V) $R^1 = NO_2, R^2 = Cl$
(VI) $R^1 = NO_2, R^2 = Br$
(VII) $R^1 = H, R^2 = H$
(VIII) $R^1 = Cl, R^2 = H$



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

These facts suggest that the important factors in this reaction are the acidity of the solvent and the presence of a strong electron-attracting group such as the nitro-group in the 5-phenylazo-substituent.

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

[1] H. Goldner, G. Dietz, and E. Carstens, *Annalen*, 1966, **694**, 142.
[2] E. C. Taylor in "Topics in Hetrocyclic Chemistry," ed. R. N. Castle, Wiley-Interscience, New York, 1969, p. 25.
[3] C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, 1960, **82**, 3972.
[4] S. Nishigaki, S. Fukazawa, K. Ogiwara, and F. Yoneda, *Chem. and Pharm. Bull.* (*Japan*), in the press.