

## A NEW, FACILE SYNTHESIS OF 10-ARYLISOALLOXAZINES

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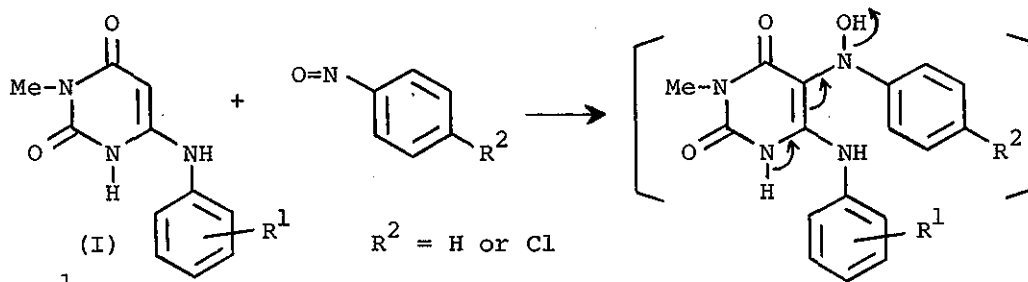
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The condensation of 6-arylaminoouracils with nitroso-benzenes in acetic anhydride gave the corresponding 10-arylisoalloxazines.

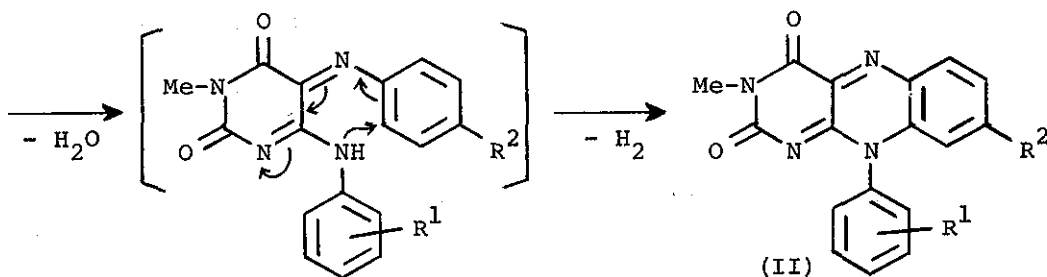
Hydrolysis of simple 3,10-dialkylisoalloxazines provides the corresponding spirohydantoins via nucleophilic addition of hydroxide ion to the 10a-position.<sup>1</sup> By contrast, 3-alkyl-10-arylisoalloxazines, which are sterically hindered at the 10a-position, undergo the initial hydrolytic scission at the 4-position to lead the quinoxalone derivatives;<sup>2</sup> thus, 10-arylisoalloxazines are useful in determining the importance of the availability of the 10a-position to nucleophilic addition. Furthermore, 10-arylisoalloxazines have been found to undergo photocyclization giving benzimidazo[1,2,3-ij]benzo[g]pteridine-6(5H),8(7H)-diones.<sup>3</sup>

The only known synthetic method for the preparation of 10-arylisoalloxazines has involved the condensation of alloxans with

2-aminodiphenylamines.<sup>2-5</sup> We now report a new, facile synthesis of 10-arylisalloxazines involving treatment of 6-arylaminoouracils (Ia-f) with nitrosobenzenes in acetic anhydride.



- a;  $\text{R}^1 = \text{H}$   
 b;  $\text{R}^1 = 3\text{-Me}$   
 c;  $\text{R}^1 = 3,4\text{-Me}_2$   
 d;  $\text{R}^1 = 4\text{-Cl}$   
 e;  $\text{R}^1 = 3,4\text{-Cl}_2$   
 f;  $\text{R}^1 = 4\text{-CN}$



(IV)

(II)

- a;  $\text{R}^1 = \text{R}^2 = \text{H}$   
 b;  $\text{R}^1 = 3\text{-Me}, \text{R}^2 = \text{H}$   
 c;  $\text{R}^1 = 3,4\text{-Me}_2, \text{R}^2 = \text{H}$   
 d;  $\text{R}^1 = 4\text{-Cl}, \text{R}^2 = \text{H}$   
 e;  $\text{R}^1 = 3,4\text{-Cl}_2, \text{R}^2 = \text{H}$   
 f;  $\text{R}^1 = 4\text{-CN}, \text{R}^2 = \text{H}$   
 g;  $\text{R}^1 = \text{H}, \text{R}^2 = \text{Cl}$   
 h;  $\text{R}^1 = 4\text{-Cl}, \text{R}^2 = \text{Cl}$

The starting materials (Ia-f) were prepared by fusion of 6-chloro-3-methyluracil with the respective anilines according to the reported procedure.<sup>6</sup>

Refluxing of Ia (0.003 mole) with excess nitrosobenzene (0.009 mole) in acetic anhydride (70 ml) for 20 min afforded 3-methyl-10-phenylisoalloxazine (IIa),<sup>2</sup> which is isolated by concentration of the reaction mixture and addition of ethanol. Other 10-arylisoalloxazines (IIb-h) were similarly prepared by refluxing I with a nitrosobenzene in acetic anhydride.

TABLE 10-Arylisoalloxazine formation by the reaction of 6-arylamino-3-methyluracils with nitrosobenzenes

Starting materials	10-Arylisoalloxazines	M.p./°C <sup>a</sup>	Yield/%
Ia <sup>6</sup> + Nitrosobenzene	IIa <sup>2</sup>	>360	51
Ib <sup>7</sup> + Nitrosobenzene	IIb	326	56
Ic <sup>8</sup> + Nitrosobenzene	IIc	347	46
Id <sup>7</sup> + Nitrosobenzene	IID	>360	36
Ie + Nitrosobenzene	IIe	>360	48
If + Nitrosobenzene	IIf	>360	42
Ia <sup>6</sup> + p-Chloronitrosobenzene	IIg <sup>9</sup>	>360	75
Id <sup>7</sup> + p-Chloronitrosobenzene	IIh	>360	70

<sup>a</sup> Recrystallized from acetic acid.

This synthesis apparently involves the initial formation of a 5-hydroxylamine intermediate (III), whose dehydration to the diimine (IV) is facilitated by the presence of acidic hydrogen at the 1-position of the uracil. Cyclization and hydrogen transfer would then give the 1,5-dihydroisoalloxazine, which is dehydrogenated

with excess nitrosobenzene to lead the isoalloxazine.

It is noted that the known nitrosative cyclization<sup>10</sup> of 6-N-alkylanilinouracils to 10-alkylisoalloxazines could not be applied to the synthesis of 10-arylisoalloxazines, because the intermediary 6-N-arylanilinouracils were not available by the usual condensation of 6-chlorouracils with diphenylamines.

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#### REFERENCES

- 1 F. Yoneda, Y. Sakuma, and K. Shinozuka, J. C. S. Chem. Comm., 1977, 175.
- 2 S. B. Smith and T. C. Bruice, J. Am. Chem. Soc., 1975, 97, 2875.
- 3 W.-R. Knappe, Chem. Ber., 1974, 107, 1614.
- 4 R. Kuhn and F. Weygand, Chem. Ber., 1935, 68, 1282.
- 5 L. Main, G. J. Kasperek, and T. C. Bruice, Biochemistry, 1972, 11, 3991.
- 6 H. Goldner, G. Dietz, and E. Carstens, Annalen, 1966, 694, 142.
- 7 F. Yoneda, S. Matsumoto, Y. Sakuma, and S. Fukazawa, J. C. S. Perkin I, 1975, 1907.
- 8 Y. Sakuma, S. Matsumoto, T. Nagamatsu, and F. Yoneda, Chem. Pharm. Bull. (Tokyo), 1976, 24, 338.
- 9 F. Yoneda, Y. Sakuma, and K. Shinozuka, J. C. S. Chem. Comm., Com 655, in press.
- 10 F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, J. Am. Chem. Soc., 1976, 98, 830.

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