

Fumio Yoneda,* Kazuo Shinozuka and Kinshiro Tsukuda

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto 862, Japan

Akira Koshiro

Department of Pharmacy, Yamaguchi University Hospital, Kogushi, Ube 755, Japan

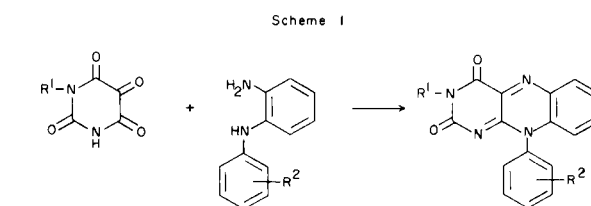
Received April 16, 1979

The condensation of 6-arylamino- and 6-alkylaminouracils with nitrosobenzenes in a mixture of acetic anhydride and acetic acid gave the corresponding 10-aryl- and 10-alkylisoalloxazines (flavins).

J. Heterocyclic Chem., **16**, 1365 (1979).

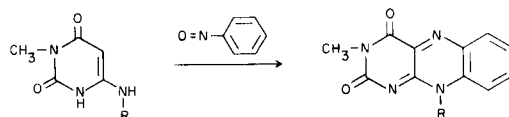
Hydrolysis of simple 3,10-dialkylisoalloxazines provides the corresponding spirohydantoin *via* nucleophilic addition of hydroxide ion to the 10a-position (1). By contrast, 3-alkyl-10-arylisoalloxazines, which are sterically hindered at the 10a-position, undergo the initial hydrolytic scission at the 4-position to lead the quinoxalones (2); 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-6,8(5*H*,7*H*)diones (3).

The only known synthetic method for the preparation of 10-arylisoalloxazines has involved the condensation of alloxans with 2-aminodiphenylamines (2-5) (Scheme I). We now report a new, general synthesis of 10-arylisoalloxazines



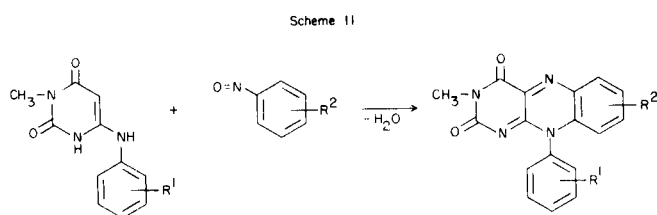
involving the condensation of 6-arylamino- and 6-alkylaminouracils with nitrosobenzenes (6) (Scheme II), whose process is a successful application of the known 10-alkylisoalloxazine synthesis (7). Additionally, we wish to record some 10-alkylisoalloxazines synthesized by this process.

Table I



Compound No.	R	Yield (%)	M.p. (a) (°C)	Ms m/e (M*)	Formula	Analysis (%)					
						Calcd.		Found			
					C	H	N	C	H	N	
IIa (4)	C ₆ H ₅	62	>360	304	C ₁₇ H ₁₂ N ₄ O ₂	67.09	3.98	18.41	67.34	3.86	18.71
IIb	3-CH ₃ -C ₆ H ₄	57	326	318	C ₁₈ H ₁₄ N ₄ O ₂	67.91	4.43	17.60	67.83	4.35	17.33
IIc	3,4-(CH ₃) ₂ -C ₆ H ₃	67	347	332	C ₁₉ H ₁₆ N ₄ O ₂	68.66	4.85	16.86	68.54	5.10	16.99
IId	4-Cl-C ₆ H ₄	59	>360	338	C ₁₇ H ₁₁ ClN ₄ O ₂	60.27	3.27	16.54	60.17	2.98	16.42
IIe	3,4-Cl ₂ -C ₆ H ₃	42	>360	393	C ₁₇ H ₁₀ Cl ₂ N ₄ O ₂	54.71	2.70	15.01	54.80	2.88	15.22
IIf	4-CN-C ₆ H ₄	53	>360	329	C ₁₈ H ₁₁ N ₅ O ₂	65.65	3.37	21.27	65.79	3.41	21.00
IIg	C ₆ H ₅ -CH ₂	67	284	318	C ₁₈ H ₁₄ N ₄ O ₂	67.91	4.43	17.60	67.80	4.62	17.88
IIh	C ₆ H ₅ -CH ₂ CH ₂	74	314	332	C ₁₉ H ₁₆ N ₄ O ₂	68.66	4.85	16.86	68.69	4.77	16.68
IIi	CH ₃ CO-OCH ₂ CH ₂	50	225	314	C ₁₅ H ₁₄ N ₄ O ₄	57.32	4.49	17.83	57.61	4.57	18.04
IIj	CH ₃ CO-OCH ₂ CH ₂ CH ₂	45	226	328	C ₁₆ H ₁₆ N ₄ O ₄	58.53	4.91	17.07	58.40	5.11	17.41
IIk (7)	CH ₃ CH ₂ CH ₂	69	332	270	C ₁₄ H ₁₄ N ₄ O ₂						
III (7)	CH ₃ CH ₂ CH ₂ CH ₂	70	315	284	C ₁₅ H ₁₆ N ₄ O ₂						
IIl	HO-CH ₂ CH ₂	87	294	272	C ₁₃ H ₁₂ N ₄ O ₃	57.35	4.44	20.58	57.42	4.40	21.11
		(from IIi)									
IIl	HO-CH ₂ CH ₂ CH ₂	85	269	286	C ₁₄ H ₁₄ N ₄ O ₃	58.73	4.93	19.57	58.61	5.12	19.72
		(from IIj)									

(a) All products were recrystallized from a mixture of ethanol and dimethylformamide (1:1).



The starting materials, 6-arylamino- (Ia-f) and 6-alkylamino-3-methyluracils (Ig-l), were prepared by the treatment of 6-chloro-3-methyluracil with the respective arylamines or alkylamines according to the reported procedure (8,9) (Table III).

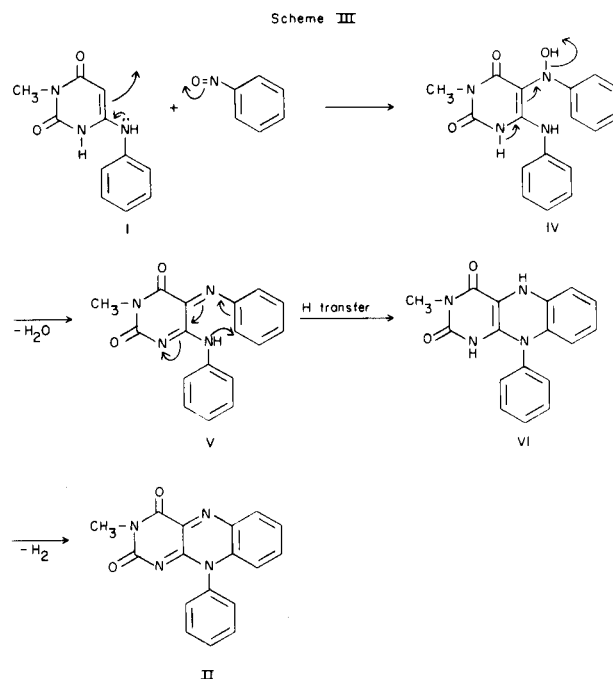
Refluxing of the compounds Ia-l with excess nitrosobenzene in a mixture acetic anhydride and acetic acid (4:1) afforded the corresponding 10-aryl- (IIa-f) and 10-alkylisoalloxazines (IIg-l) (Table I). In the case of the reaction of 6-hydroxyalkylamino-3-methyluracils (Ii,j) with nitrosobenzene, the 10-acetoxyalkylisoalloxazines (Iii,j) were obtained. The latter compounds were treated with methanolic ammonia to give the corresponding 10-hydroxyalkylisoalloxazines (IIm,n) by elimination of acetyl group.

Similarly, 10-aryl-3,6-dimethylisoalloxazines (IIIa,b) were prepared by the condensation of the respective 6-arylamino-3-methyluracils (Ia,c) with 2-nitrosotoluene under the same conditions.

The light absorption spectra (Table II) show one band in the 440 nm region, another in 330-350 nm region, and one in the uv region (in ethanolic solution) which are typical of flavins.

This isoalloxazine synthesis probably involves the initial formation of a 5-hydroxylamine intermediate (IV), whose dehydration to the diimine (V) 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 (VI), which is dehydrogenated with excess nitrosobenzene or with air to lead the final isoalloxazines (Scheme III).



It is noted that the known nitrosative or nitrative cyclization (7) of 6-(*N*-alkylanilino)uracils to 10-alkylisoalloxazine 5-oxides could not be applied to the synthesis of 10-arylisoalloxazines, because the intermediary 6-(*N*-arylanilino)uracils were not available by the usual condensation of 6-chlorouracils with diphenylamines.

EXPERIMENTAL

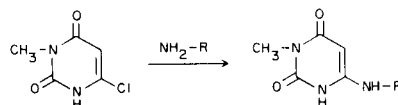
Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Uv spectra were recorded on a UVIDEC-1 spectrophotometer, 1-cm quartz cells being employed. Ident-

Table II

Visible and Uv Maxima of Isoalloxazines

Compound No.	λ max (Ethanol) nm (log ϵ)									
IIa	271	(4.65),	344	(4.02),	4.22 sh	(4.10),	4.39	(4.15),	470 sh	(3.95)
IIb	264	(4.44),	332	(3.86),	4.28 sh	(3.89),	4.40	(3.92),	463 sh	(3.89)
IIc	264	(4.52),	336	(3.97),	4.29 sh	(4.03),	4.40	(4.06),	461 sh	(3.95)
IId	263	(4.39),	337	(3.91),	4.22 sh	(3.95),	4.37	(4.00),	461 sh	(3.89)
IIe	265	(4.34),	332	(3.80),	4.24 sh	(3.80),	4.37	(3.84),	461 sh	(3.71)
IIf	266	(4.46),	323	(3.96),	4.21 sh	(3.91),	4.37	(3.95),	465 sh	(3.78)
IIg	236 sh	(4.31),	264	(4.24),	3.05	(4.08),	4.36	(3.91)		
IIh	263	(4.43),	336	(3.91),	4.22 sh	(4.10),	4.40	(3.93),	461 sh	(3.95)
IIi	264	(4.40),	334	(3.82),	4.33 sh	(3.87),	4.36	(3.91),	456 sh	(3.80)
IIj	263	(4.50),	333	(4.01),	4.19 sh	(4.05),	4.36	(4.19),	455 sh	(4.00)
IIm	265	(4.35),	332	(3.84),	4.21 sh	(3.82),	4.37	(3.86),	456 sh	(3.76)
IIn	264	(4.40),	331	(3.92),	4.15 sh	(4.01),	4.37	(3.95),	455 sh	(3.87)
IIIa	270	(4.35),	304 sh	(3.72),	3.56	(3.77),	4.23 sh	(3.72),	4.43	(3.78), 471 sh (3.64)
IIIb	271	(4.34),	358	(3.78),	4.30 sh	(3.70),	4.44	(3.75),	468 sh	(3.63)

Table III



Compound No.	R	Yield (%)	M.p. (a) (°C)	Ms m/e (M ⁺)	Formula	Analysis (%)					
						Calcd. C	Calcd. H	N	Found C	Found H	N
Ia (9)	C ₆ H ₅	89	338	217	C ₁₁ H ₁₁ N ₃ O ₂						
Ib (11)	3-CH ₃ -C ₆ H ₄	88	291	231	C ₁₂ H ₁₃ N ₃ O ₂						
Ic (10)	3,4-(CH ₃) ₂ -C ₆ H ₃	89	278	245	C ₁₃ H ₁₅ N ₃ O ₂						
Id (11)	4-Cl-C ₆ H ₄	74	297	251	C ₁₁ H ₁₀ ClN ₃ O ₂						
Ie	3,4-Cl ₂ -C ₆ H ₃	69	335	285	C ₁₁ H ₉ Cl ₂ N ₃ O ₂	46.17	3.17	14.69	46.09	3.27	14.70
If	4-CN-C ₆ H ₄	63	357	242	C ₁₂ H ₁₀ N ₄ O ₂	59.50	4.16	23.13	59.61	4.10	23.27
Ig (8)	C ₆ H ₅ -CH ₂	78	302	231	C ₁₂ H ₁₃ N ₃ O ₂						
Ih	C ₆ H ₅ -CH ₂ CH ₂	87	238	245	C ₁₃ H ₁₅ N ₃ O ₂	63.66	6.16	17.13	63.69	6.14	17.09
Ii	HO-CH ₂ CH ₂	81	248	185	C ₇ H ₁₁ N ₃ O ₃	45.40	5.99	22.69	45.17	6.12	23.11
Ij	HO-CH ₂ CH ₂ CH ₂	79	233	199	C ₈ H ₁₃ N ₃ O ₃	48.23	6.58	21.10	48.06	6.41	21.51
Ik	CH ₃ CH ₂ CH ₂	78	243	183	C ₈ H ₁₃ N ₃ O ₂	52.44	7.15	22.94	52.30	7.08	23.10
Il (8)	CH ₃ CH ₂ CH ₂ CH ₂	67	244	197	C ₉ H ₁₅ N ₃ O ₂						

(a) All products are colorless needles and were recrystallized from ethanol.

tity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-1A spectrophotometer.

6-Arylamino-3-methyluracils (Ia-f).

Heating of 6-chloro-3-methyluracil (1.6 g., 0.01 mole) with an arylamine (0.03 mole) at 160-170° (oil bath) for 10 minutes, followed by cooling and then dilution with ether caused the separation of crystals, which were filtered off and washed with water. Recrystallization from ethanol gave colorless needles (Table III).

6-Alkylamino-3-methyluracils (Ig-1).

A mixture of 6-chloro-3-methyluracil (1.6 g., 0.01 mole) and an alkylamine (0.03 mole) in *n*-butanol (50 ml.) was refluxed for 3 hours. The mixture was evaporated in vacuo and the residue was treated with ether to separate crystals which were filtered off and washed with water. Recrystallization from ethanol gave colorless needles (Table III).

10-Aryl- (IIa-f) and 10-Alkyl-isoalloxazines (IIg-1). General Procedure.

Compounds Ia-1 (0.01 mole) and nitrosobenzene (0.03 mole) were added to a mixture of acetic anhydride and acetic acid (4:1) (20 ml.) and the mixture was refluxed for 20 minutes. The mixture was evaporated in vacuo and the residue was diluted with ethanol. Crystals thus separated were filtered off and recrystallized from ethanol to give yellow to orange needles (Table I).

3,6-Dimethyl-10-phenylisoalloxazine (IIIa).

A mixture of compound Ia (2.2 g., 0.01 mole) and *o*-nitrosotoluene (3.6 g., 0.03 mole) were added to a mixture of acetic anhydride and acetic acid (4:1) (20 ml.) and the mixture was treated as described above to give IIIa, yellow needles (2.45 g., 77%), m.p. > 360° (from ethanol); ms: m/e 318 (M⁺).

Anal. Calcd. for C₁₈H₁₄N₄O₂: C, 67.91; H, 4.43; N, 17.60. Found: C, 68.21; H, 4.51; N, 17.74.

3,6-Dimethyl-10-(3,4-xylyl)isoalloxazine (IIIb).

A mixture of compound Ic (2.8 g., 0.01 mole) and *o*-nitrosotoluene (3.6 g., 0.03 mole) were added to a mixture of acetic anhydride and acetic acid (4:1) (20 ml.) and the mixture was treated as above to give IIIb, yellow needles (2.7 g., 72%), m.p. > 360° (from ethanol); ms: m/e 346 (M⁺).

Anal. Calcd. for C₂₀H₁₈N₄O₂: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.47; H, 5.47; N, 15.94.

Deacetylation of 10-Acetoxyalkylisoalloxazines (IIi,j). Preparation of 10-Hydroxyalkylisoalloxazines (IIm,n).

To a suspension of compounds IIIi,j (0.01 mole) in methanol (50 ml.) in an autoclave, dry ammonia was introduced until saturation under cooling with ice. After closing the autoclave, the mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated in vacuo and the residue was recrystallized from ethanol to give yellow needles (Table I).

Acknowledgement.

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture. The authors are indebted to Miss Miyeko Hirashima for her technical assistance.

REFERENCES AND NOTES

- (1) F. Yoneda, Y. Sakuma and K. Shinozuka, *J. Chem. Soc., Chem. Commun.*, 175 (1977).
- (2) S. B. Smith and T. C. Bruice, *J. Am. Chem. Soc.*, **97**, 2875 (1975).
- (3) W.-R. Knappe, *Chem. Ber.*, **107**, 1614 (1974).
- (4) R. Kuhn and F. Weygand, *ibid.*, **68**, 1282 (1935).
- (5) L. Mair, G. J. Kasperek and T. C. Bruice, *Biochemistry*, **11**, 3991 (1972).
- (6) Preliminary report, F. Yoneda, K. Shinozuka, Y. Sakuma and Y. Nitta, *Heterocycles*, **9**, 7 (1978).
- (7) F. Yoneda, Y. Sakuma, M. Ichiba and K. Shinomura, *J. Am. Chem. Soc.*, **98**, 830 (1976).
- (8) H. Goldner, G. Dietz and E. Carstens, *Ann. Chem.*, **691**, 142 (1966).
- (9) H. Goldner, G. Dietz and E. Carstens, *ibid.*, **694**, 142 (1966).
- (10) Y. Sakuma, S. Matsumoto, T. Nagamatsu and F. Yoneda, *Chem. Pharm. Bull.*, **24**, 338 (1976).
- (11) F. Yoneda, S. Matsumoto, Y. Sakuma and S. Fukazawa, *J. Chem. Soc., Perkin Trans. I*, 1907 (1975).