Photochemistry of heterocycles XXIV.* Synthesis and photochemistry of 3-(2-, 3-, and 4-pyridyl)-substituted fused isoxazolines

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Dedicated to Professor P. Kristian, in honour of his 60th birthday

1,3-Dipolar cycloaddition of 2-, 3-, or 4-pyridinecarbonitrile oxide with 2,5-dihydrofuran, 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2,2,1]hept-2-ene, and 2*H*,4*H*,7*H*-1,3-dioxepin is described. UV light irradiation of the thus prepared condensed isoxazolines furnished unstable enamino aldehydes. Quantum yields of the photolysis of the condensed isoxazolines increase in the series 2-, 4-, 3-pyridyl-substituted derivatives. Chemical structures of the condensed isoxazolines were inferred from the ^{13}C NMR spectral data and the DQ COSY experiment in ^{1}H NMR spectra.

Описано 1,3-диполярное циклоприсоединение 2-, 3- или 4-пиридинкарбонитрилоксида к 2,5-дигидрофурану, 5,6-бис(метоксикарбонил)-7-оксабицикло[2,2,1]гепт-2-ену и 2*H*,4*H*,7*H*-1,3-диоксепину. Действие УФ-облучения приводит к образованию из полученных конденсированных изоксазолинов неустойчивых енаминоальдегидных продуктов. Были измерены величины квантовых выходов фотолиза полученных изоксазолинов, возрастающие в ряду 2-пиридил, 4-пиридил, 3-пиридилзамещенных производных. Структура полученных изоксазолинов была установлена с помощью ^{13}C ЯМР и эксперимента DQ COSY в ^{1}H ЯМР спектроскопии.

Isoxazolines have been recognized as suitable synthetic precursors to β-hydroxy ketones, β-hydroxy nitriles, and γ-amino alcohols [1]. We have found [2—8] that the presence of an oxygen atom in the β-position to the isoxazoline oxygen of fused isoxazolines (*I*, *III*, *V*) facilitated a highly selective, photoinduced rearrangement, leading to cyclic enamino aldehydes (*II*, *IV*, *VI*) with an oxygen in the ring. Rearrangements $I \rightarrow II$, $III \rightarrow IV$, and $V \rightarrow VI$ exemplify the process (Scheme 1).

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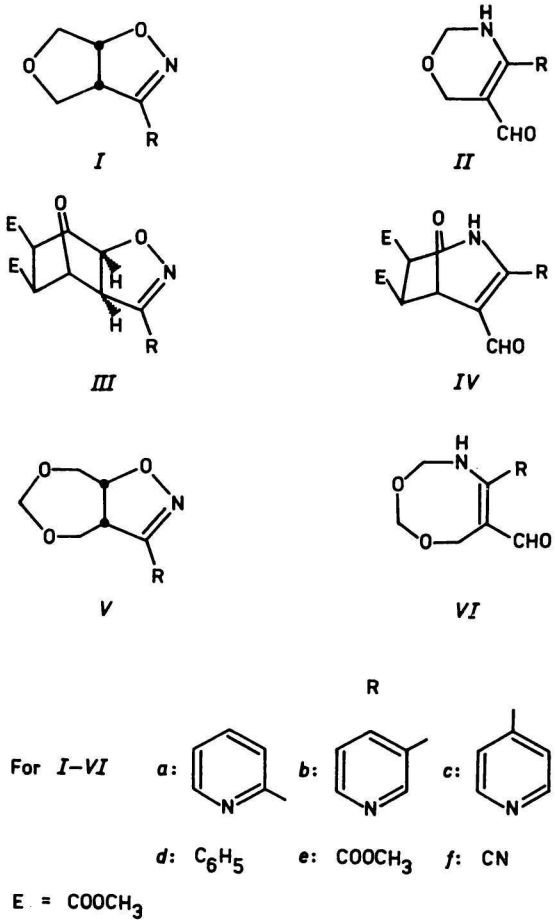

Scheme 1

Substituents R in the position 3, such as phenyl [2—6], methoxycarbonyl [8] or cyano group [7] do not degrade the selectivity of the process. α- and β-Naphthyl-substituted derivatives of condensed isoxazolines *I*, *III*, and *V* on the other hand proved to be photostable, when irradiated with the practically monochromatic light at $\lambda = 254$ nm [9]. Irradiation with a polychromatic light of a high-pressure mercury lamp succeeded in converting naphthyl-substituted derivatives into enamino aldehyde products *II*, *IV*, and *VI*, respectively, or to their decomposition products. Derivatives *I*, *III*, *V*, incorporating a 9-anthryl residue [10], underwent upon irradiation with $\lambda = 254$ nm UV light, a photodegradation to unidentifiable products. In case of these derivatives (*I*, *III*, *V*) selectivity of the photoarrangement depends on the character of the substituent R.

We now report on the preparation and photochemical properties of the condensed isoxazolines, substituted in position 3 with a 2-, 3-, and 4-pyridyl residue, respectively. Target fused isoxazolines were prepared by the well-established 1,3-dipolar cycloaddition of the requisite pyridinecarbonitrile oxides with 2,5-dihydrofuran, 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2,2,1]hept-2-ene, and 2*H*,4*H*,7*H*-1,3-dioxepin, respectively. The corresponding fused isoxazolines *Ia*—*Ic*, *IIIa*—*IIIc*, and *Va*—*Vc* (Tables 2—4) were obtained in 15—30 % yields. Pyridinecarbonitrile oxides were prepared *in situ* from the corresponding carboximidoyl chlorides dissolved in dichloromethane and treated by aqueous sodium carbonate in the presence of the heterocyclic dipolarophiles. Low yields of cycloadducts, accompanied by great amounts of nitrile oxide dimers (up to 60 %) testify that the reactivity of the latter lies below that of benzonitrile oxide [2—6]. Similar cycloadditions with benzonitrile oxide gave 50—95 % yields.

Cycloadditions of pyridinecarbonitrile oxides reported so far in the literature concerned the reaction of 4-pyridinecarbonitrile oxide [11], generated from an oxime by the hypochlorite method, with a norbornene derivative (50 % yield).

Table 1

Characterization of the prepared fused isoxazolines *I*, *III*, and *V*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p. °C	λ_{max}/nm log ε	$M^{+\bullet}$ m/z
Ia	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	30	89—92[a]	279	190
	190.2	63.21	5.28	14.75			2.72	
Ib	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	25	103—105[b]	262	190
	190.2	63.10	5.48	14.64			2.65	
Ic	$C_{10}H_{10}N_2O_2$	63.15	5.30	14.73	30	91—94[c]	271	190
	190.2	63.18	5.45	14.60			2.85	
IIIa	$C_{16}H_{16}N_2O_6$	57.83	4.85	8.43	20	174—176	281	332
	332.3	57.64	4.92	8.51			2.73	
IIIb	$C_{16}H_{16}N_2O_6$	57.83	4.85	8.43	23	213—215	263	332
	332.3	57.86	4.90	8.53			2.70	
IIIc	$C_{16}H_{16}N_2O_6$	57.83	4.85	8.43	15	217—220	272	332
	332.3	57.60	4.71	8.49			2.78	
Va	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72	20	104—107	376	220
	220.2	59.80	5.63	12.65			2.72	
Vb	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72	18	160—162	263	220
	220.2	60.07	5.47	12.81			2.63	
Vc	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72	20	189—191	272	220
	220.2	59.94	5.53	12.76			2.71	

According to Ref. [12]: *a*) m.p. = 104 °C, *b*) m.p. = 118 °C, *c*) m.p. = 117—118 °C.

Cycloadditions of 2-, 3-, and 4-pyridinecarbonitrile oxide, liberated from *N*-hydroxy-(2-, 3-, and 4-pyridine)carboximidoyl chlorides by triethylamine, with 2,5-dihydrofuran [12] proceeded not only in higher yields (33—56 %), but gave also derivatives *Ia*—*Ic* with different melting points. Authors [12] assigned to their cycloaddition products structures one would expect from the type of reaction, and supported their assumption only by elemental analyses. Our fused isoxazolines *Ia*—*Ic* were purified by column chromatography and characterized by spectral data.

Structure assignment of the prepared fused isoxazolines was carried out based on ^{1}H and ^{13}C NMR spectral data (Tables 1—4 and 5—7, respectively), as well as by analogy with the corresponding 3-phenyl-substituted derivatives [2—6] *Id*, *IIId*, *Vd*. For configuration assignment (*cis*) of the bridge hydrogens, signals of other hydrogen atoms, and coupling constants, NMR spectra (300 MHz) were used. Heterocorrelated ^{1}H and ^{13}C NMR spectra confirmed the signals assignment.

Table 2

^{1}H NMR spectral data of 3-(2-, 3-, and 4-pyridyl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles *I*

Compound	δ/ppm . *J*/Hz						
	H-3a	H^{A}-4	H^{B}-4	H^{A}-6	H^{B}-6	H-6a	H_{arom}
Ia	4.09	4.44	3.79	4.10	3.79	5.38	*a*
	9.3	6.9, 1.5	6.6, 9.3	10.8	6.6, 9.3	3.6, 9.3	
Ib	3.94	4.09	3.64	4.53	3.74	5.40	*b*
	9.3	10.8	3.6, 10.8	8.1, 8.1	6.6, 9.3	3.3, 9.3	
Ic	3.64	4.13	3.95	4.45	3.80	5.54	*c*
	3.9, 10.8	10.8	9.1	1.8, 6.6	6.6, 9.3	3.6, 9.3	

a) 7.38 7.43 and 8.57 8.62 (m, 4H).
b) 7.59 (dd, 1H), 8.19 (d, 1H), 8.65 (d, 1H).
c) 8.87 (s, 1H).

Capitalizing on our previous successful photochemical conversions of isoxazoline derivatives to enamino aldehydes, we attempted the phototransformation of derivatives *Ia*—*Ic* to *IIa*—*IIc* (4-(2-, 3-, and 4-pyridyl)-5-formyl-2,3-dihydro-6*H*-1,3-oxazine), *IIIa*—*IIIc* to *IVa*—*IVc* (2-formyl-3-(2-, 3-, and 4-pyridyl)-6,7-bis(methoxycarbonyl)-8-oxa-4-azabicyclo[3,2,1]oct-2-ene), and *Va*—*Vc* to *VIa*—*VIc* (6-(2-, 3-, and 4-pyridyl)-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocine) as well. Irradiation of methanolic (acetonitrile, benzene, ether) solutions by UV light at $\lambda = 254$ nm was carried out in the same manner as in our previous experiments [2—8]. In contrast to the smooth phototransformation of the aryl-

Table 3

^{1}H NMR spectral data of 3,4-bis(methoxycarbonyl)-7-(2-, 3-, and 4-pyridyl)-9,10-dioxa--8-azatricyclo[4,3,0,1^{2,5}]dec-7-enes *III*

Compound	δ/ppm J/Hz							
	H-1	H-2	H-3	H-4	H-5	H-6	CH_3	H_{arom}
IIIa	5.02	4.95	3.40	3.21	4.90	4.19	3.54	*a*
	8.1		9.6	9.6			3.55	
IIIb	5.04	4.89	3.40	3.23	4.77	4.26	3.53	*b*
	8.1		9.6	9.6		8.1	3.55	
IIIc	5.09	4.90	3.39	3.25	4.76	4.21	3.54	*c*
	8.1		9.6	9.6			3.56	

a) 7.42 (m, 1H), 7.85 (m, 2H), 8.66 (m, 1H).
b) 7.50 (m, 1H), 8.10 (d, 1H), 8.61 (m, 1H).
c) 7.68—7.75 and 8.65—8.75 (m, 4H).

Table 4

^{1}H NMR spectral data of 8-(2-, 3-, and 4-pyridyl)-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-enes *V*

Compound	δ/ppm J/Hz						
	H-1	H^A-2	H^A-4	H^B-4	H^A-2, H^A-6	H^B-6, H-7	H_{arom}
Va	4.90	4.58	4.82	4.39	4.12—4.24	3.85—3.91	*a*
	2.0, 12.9	3.6, 12.9	6.9	6.9			
Vb	4.90	4.28	4.83	4.39	4.20—4.23	3.88—3.92	*b*
	2.7—12.0	2.7, 12.0	6.6	6.6			
Vc	4.94	4.17—4.24	4.83	4.39	4.17—4.24	3.83—3.92	*c*
	2.0, 12.0	2.0, 12.0	6.6	6.6			

a) 7.40 (m, 1H), 7.83 (m, 2H), 8.58 (d, 1H).
b) 7.49 (m, 1H), 8.02 (d, 1H), 8.64 (m, 1H), 8.85 (m, 1H).
c) 7.59 7.79 and 8.62 8.73 (m, 4H).

(*Id*, *IIId*, *Vd*), methoxycarbonyl- (*Ie*, *IIIe*, *Ve*), and cyano-substituted (*If*, *IIIf*, *Vf*) derivatives, irradiation of pyridyl-substituted fused isoxazolines gave rise only to tarry products. When however the irradiation of dilute solutions of isoxazolines (c = 0.1 mmol dm^{-3}) was monitored by UV spectroscopy, characteristic absorption maxima of enamino aldehydes at λ = 310 nm [2—6] could be observed indicating that the primary mechanism of the photoreaction followed the same

Table 5

^{13}C NMR chemical shifts of 3-(2-, 3-, and 4-pyridyl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles *I*

Compound	δ/ppm							
	C-3	C-3a	C-4	C-6	C-6a	C_{arom}		
Ia	158.20	53.42	71.80	75.65	86.61	121.84	124.66	137.35
						148.35	149.50	
Ib	155.10	52.98	71.38	75.67	87.12	125.28	125.75	136.38
						146.16	149.31	
Ic	155.48	52.11	70.88	75.15	86.83	120.43	135.49	150.06
						150.52		

Table 6

^{13}C NMR chemical shifts of 3,4-bis(methoxycarbonyl)-7-(2-, 3-, and 4-pyridyl)-9,10-dioxa--8-azatricyclo[4,3,0,1^{2,5}]dec-7-enes *III*

Compound	δ/ppm									
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CH_3	C=O	C_{arom}
IIIa	86.00	84.07	57.48	49.54	80.11	45.87	156.02	51.93	170.84	*a*
								51.92	170.71	
IIIb	86.01	84.11	56.90	49.57	79.61	46.00	153.14	52.01	170.85	*b*
								51.90	170.79	
IIIc	86.62	83.93	56.31	49.44	79.55	45.90	153.64	51.90	170.66	*c*
								51.78	170.57	

a) 121.83, 124.86, 137.27, 148.11, 149.60.
b) 124.29, 124.65, 134.31, 147.53, 150.92.
c) 120.99, 121.13, 135.93, 150.08.

Table 7

^{13}C NMR chemical shifts of 8-(2-, 3-, and 4-pyridyl)-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-enes *V*

Compound	δ ppm						
	C-1	C-2	C-4	C-6	C-7	C-8	C_{arom}
Va	83.82	70.60	98.43	67.88	51.93	157.50	*a*
Vb	83.37	70.51	98.24	67.29	51.57	155.31	*b*
Vc	84.06	70.49	98.33	67.37	51.18	155.99	*c*

a) 121.87, 124.57, 137.16, 149.01, 149.36.
b) 124.25, 134.49, 147.43, 150.47.
c) 121.24, 136.80, 150.31.

pathway as in previous cases, but primary photoproducts — heterocyclic enamino aldehydes were too unstable to be intercepted and isolated. Similar phenomenon was recorded in the irradiation of 9-anthryl-substituted isoxazolines [10].

Photochemical quantum yields Φ, related to the consumption of isoxazoline derivative (up to the total 10 % conversion) were determined for *Ia* (0.01), *Ib* (0.04), *Ic* (0.01); *IIIa* (0.023), *IIIb* (0.09), *IIIc* (0.04); *Va* (0.004), *Vb* (0.04), and *Vc* (0.008). Photoreactivity of pyridyl-substituted fused isoxazolines, assessed on the basis of the above Φ values decreases in the order 3-, 4-, 2-pyridyl derivatives. Generally, Φ values were smaller than those of phenyl-, methoxycarbonyl- or cyano-substituted analogues. It should be pointed out that no study of the photochemistry of pyridyl-substituted isoxazolines has been published yet.

Parallelism in thermal reactions between substituted pyridines and nitrobenzenes is both well documented and often pointed out. 4- and 3-Nitrophenyl-substituted, analogous derivatives *I*, *III*, and *V* are photostable [13, 14].

Experimental

Melting points were determined with a Kofler apparatus and are corrected. ^{1}H and ^{13}C NMR spectra were obtained from hexadeuterodimethyl sulfoxide solutions, relative to tetramethylsilane, on a Varian VX 300 instrument (300 MHz). Ultraviolet spectra were obtained on a spectrophotometer M-40 (Zeiss, Jena), in methanol. Values of ε are given in $m^2 mol^{-1}$. Mass spectra were determined on an MS 902 S spectrometer with direct inlet system, at ionization energy 70 eV and capture current 100 μA. Infrared spectra of KBr pellets (1 mg/300 mg) were obtained on a spectrophotometer M-80 (Zeiss, Jena), calibrated with a polystyrene film.

N-Hydroxy-(2-, 3-, and 4-pyridine)carboximidoyl chlorides were prepared according to Ref. [12]. Irradiation experiments were carried out at 20 °C in a 300 cm^3 onion-type quartz reactor, equipped with a 15 W low-pressure Hg-lamp (Toshiba GL-15) [15]. Determination of quantum yields was described elsewhere [16].

Synthesis of isoxazolines

The *N*-hydroxy-(2-, 3-, and 4-pyridine)carboximidoyl chlorides (0.01 mol) were dissolved in 20 cm^3 of dichloromethane, together with 3—5 equivalents of the respective dipolarophile. The stirred solutions were kept at 5 °C for 1 h, and an aqueous solution of sodium carbonate (0.01 mol; 1.06 g) was added. The reaction mixture was then stirred at laboratory temperature overnight. Organic layer was separated and combined with dichloromethane extracts (2 × 20 cm^3) of the aqueous layer, dried over Na_2SO_4 and evaporated. Products were isolated by column chromatography (silica gel/chloroform).

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