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Photochemistry of Condensed Isoxazolines

V. Ondruš[1], L'. Fišera[1,*], and N. Prónayová[2]

[1] Department of Organic Chemistry, Slovak Technical University, SK-81237 Bratislava, Slovakia
[2] Central Laboratory of Chemical Techniques, Slovak Technical University, SK-81237 Bratislava, Slovakia

Summary. The condensed bridged isoxazolines **4** are rearranged on irradiation with a low-pressure mercury lamp exclusively into condensed derivatives of tetrahydropyridine **5**. The selectivity of the rearrangement is due to a stabilization of the biradical **8** by the overlap of the radical-electrons with π-electrons of the C=C double bond and the heterocyclic ring. Quantum yields of the photorearrangement, established from the consumption of the starting materials **4**, were determined.

Keywords. Photochemistry; Condensed isoxazolines.

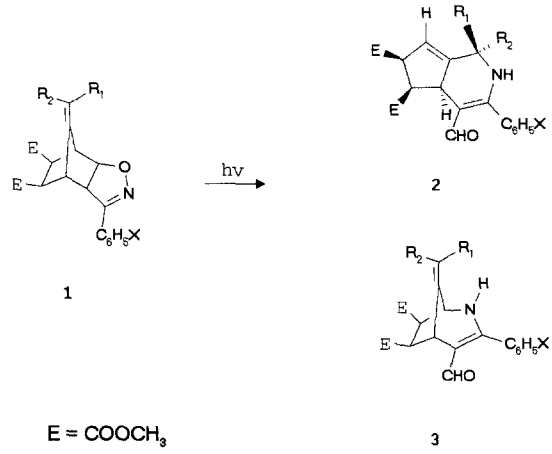
Photochemie kondensierter Isoxazoline

Zusammenfassung. Die kondensierten überbrückten Isoxazoline **4** werden durch Bestrahlen mit einer Niederdruckquecksilberlampe ausschließlich zu kondensierten Tetrahydropyridinderivaten (**5**) umgelagert. Die Selektivität der Umlagerung beruht auf der Stabilisierung des Diradikals **8** durch Überlappung der ungepaarten Elektronen mit π-Elektronen der C=C-Doppelbindung und des Heterocyclus. Aus dem Verbrauch an Ausgangsmaterial (**4**) wurden Quantenausbeuten der Photoumlagerung bestimmt.

Introduction

The high synthetic versality of 2-isoxazolines (4,5-dihydroisoxazoles) is based on their potential to serve as synthetic equivalents of β-hydroxy ketones [1] and other related functions [2], γ-amino alcohols [3], and enaminoaldehydes [4]. In previous papers, we have shown that photochemical rearrangements of isoxazolines, which are known to be usually non-selective [5], proceed unusually selectively to give the heterocyclic enaminoaldehydes if a structural element is introduced which allows a fragmentation of the primary biradical [6–9]. Recently, we have found that the dimethyl 10-(diphenylmethylene)-3-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]deca-4-ene-8,9-dicarboxylates (**1**) afforded dimethyl-2,2-diphenyl-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylates (**2**) as sole products on irradiation [10]. The selectivity of the photorearrangement of isoxazolines **1** to enaminoaldehydes **2** is due to an allylic stabilization of the biradical of type **8** increased by the phenyl rings. This paper [11] is aimed to investigate the influence of a heterocyclic substituent such as 2-furyl or 2- and 3-thienyl instead of phenyl on the direction of the photorearrange-

ment and to estimate the ability of heterocyclic rings to stabilize a radical electron by the measurement of quantum yields of the photorearrangement.



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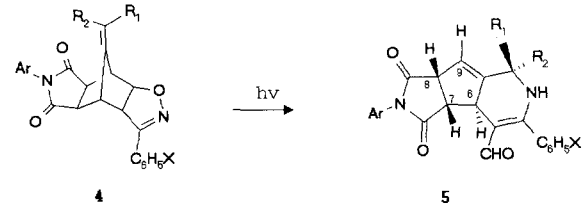

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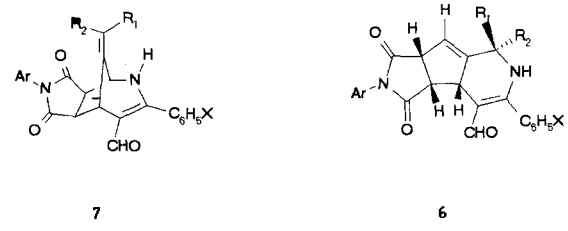

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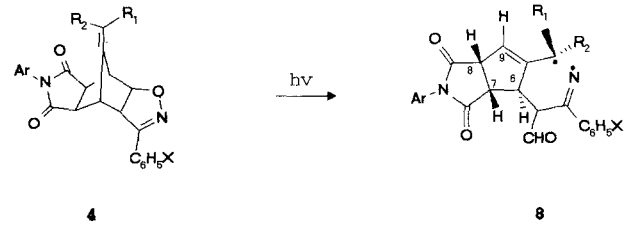
Ar= 3,5-diCl-C_6H_3



4 8

Substituents of compounds **4** and **5**

	R^1	R^2	4-*X*
a	Ph	Ph	Cl
b	2-Th	2-Th	CH_3
c	2-Th	2-Th	Cl
d	2-Th	Ph	Cl
e	Ph	2-Th	Cl
f	2-Th	CH_3	CH_3
g	CH_3	CH_3	Cl
h	2-Fu	CH_3	Cl
i	2-Fu	H	Cl
j	Ph	H	Cl
k	2-Th	H	Cl
l	3-Th	H	Cl

Results and Discussion

The preparative photochemical reactions were carried out in benzene, methanol or acetonitrile by means of monochromatic radiation ($\lambda_{max} = 254$ nm) [6–10]. The photolyses of the corresponding solutions of substituted 10-(R^1,R^2-methylene)-3-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]deca-4-enes **4a–h** (where R^1 and R^2 are phenyl, methyl, 2-furyl, 2-thienyl, and H) on irradiation yielded the rearrangement products, the 2,2-R^1,R^2-disubstituted 4-aryl-5-formyl-3-azabicyclo[4,3,0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)imides **5a–h**. The second possibility, the enaminoaldehyde **7** was not detected in the crude reaction mixture.

The photolyses were carried out until the starting materials **4** disappeared (proved by TLC), so that subsequent photochemical reactions of the derivatives **5** could be prevented which would lead to polymeric materials. The structure of the heterocyclic condensed enaminoaldehydes **5** was determined from ^1H and ^{13}C NMR spectral data on the basis of the analogy with the corresponding phenyl derivatives **2** [10]. The ^1H NMR spectra of the enaminoaldehydes **5** exhibit a singlet for the aldehydic proton in the region of 8.82–9.22 ppm whose presence was also confirmed by the doublet at 188.20–189.69 ppm in the ^{13}C NMR spectrum. The occurrence of a doublet of doublets in the olefinic region (H-9, 5.21–5.96 ppm) and a singlet for C-2 at 50.53–66.73 ppm is inconsistent with the alternative structure of the enaminoaldehyde **3**. The distinction between the arrangements of H-6, H-7 and H-8 is based on spectroscopic data, in particular using $J_{6,7}$ and $J_{7,8}$ coupling constants and NOE experiments (cf. Experimental). The coupling constant $J_{7,8}$ (6.4–8.7 Hz) provides an evidence for a *cis*-arrangement of H-7 and H-8 which is the same as in the starting materials **4**.

Theoretically, two diastereomeric products **5** and **6** could be formed. Proton NMR analysis of isolated enaminoaldehydes **5a–c** and **5f–h** revealed that each diastereomer has a H-6, H-7 *anti* relationship. In **5g**, for example, irradiation of H-8 (4.10 ppm) enhanced the intensity of the signals for H-9 by 12% and H-7 by 17.6%,

Table 1. Photorearrangement quantum yields ϕ (dioxane)

Compound	**4a**	**4e**	**4g**	**4i**	**4j**	**4k**	**4l**
ϕ	0.018	0.057	0.019	0.040	0.018	0.016	0.360

and irradiation of H-6 enhanced the intensity of the signal of H-9 (4.2%), thus proving a H-6, H-7 *anti* relationship.

In the case of **5f** (R^1 = 2-thienyl, R^2 = methyl) and **5h** (R^1 = 2-furyl, R^2 = methyl), the configuration of substituents R^1 and R^2 relative to H-6 was confirmed by NOE difference spectroscopy. Irradiation of the methyl group caused NOEs at H-6, which suggested that these groups were on the same side of the molecule. Similarly, the photolysis of 10-phenyl-10-(2-thienyl) substituted isoxazoline **4d**, which consists of two inseparable stereoisomers, affords the enaminoaldehyde as a mixture of stereoisomers **5d** and **5e** (H-6 *cis* and *trans* to the 2-thienyl group), both possessing a H-6, H-7 *anti* relationship.

Interestingly enough, when the mixture of regioisomers **4** ($R^1 \neq R^2$) was irradiated in addition to photoproducts **5** the unreacted starting compounds possessing a R^1 substituent (R^1 = phenyl, 2-furyl, 2-thienyl) in the *anti* relationship to the isoxazoline oxygen were always isolated. The corresponding starting *syn* derivatives **4** have not been detected in the crude reaction mixture after photolysis. This phenomenon can be rationalized by the fact that the *syn* derivatives **4** exhibit higher quantum yields ϕ than the *anti* derivatives **4**. A similar dependence of ϕ on the *exo-endo* configuration of the condensed isoxazolines has also been observed in other cases [12].

We suppose that the rearrangements of the imides **4** and esters **1**, whose mechanism was dealt with in detail in our previous paper [10], proceed by the same mechanism. In this case, too, the formation of enaminoaldehydes **5** must be caused by the intervention of an intermediate biradical **8** in which one of the radical centers can be stabilized by the overlap of the radical-electron with π-electrons of the C=C double bond and by the R^1 aromatic or heterocyclic substituent.

The quantum yield ϕ of all the photorearrangements of **4** does not depend on the presence or absence of oxygen, which indicates a singlet mechanism. A detailed attention has been paid to the effect of the substituent in position 10 on the quantum yield of the photo reaction, since the ϕ values can give a measure of the ability of various aromatic and heterocyclic groups to stabilize the transition state leading to a biradical intermediate. Table 1 contains the results of measurements of the photorearrangement quantum yields. A comparison of the radical-stabilizing ability of the substituents under investigation with the phenyl group showed that the 3- and 2-thienyl as well as 2-furyl groups are also very effective radical stabilizing groups.

Experimental

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian VXR 300 (300 MHz) and Tesla BS 487 C (80 MHz) spectrometers, respectively, and ^{13}C NMR spectra on a Varian VXR 300 spectrometer at 75 MHz (*TMS* as internal standard, $CDCl_3$, δ values in ppm, J in Hz). The starting model compounds **4a–o** (where R^1, R^2 are phenyl, methyl, 2-furyl, 2- and 3-thienyl, and H) were prepared by 1,3-dipolar cycloaddition reaction of arylnitrile oxides to the *Diels-Alder* adducts of the corresponding fulvenes and N-(3,5-dichlorophenyl)-maleimide according to Ref. [13].

The preparative reactions were carried out at 25 °C in a quartz reactor (300 ml) with a forced circulation of the solution and irradiation by a low pressure mercury lamp [6]. The measurement of the quantum yields was performed as already described [11]. **5a–f** gave satisfactory elemental analyses (C, H, N).

2,2-Diphenyl-4-(4-chlorophenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5a**; $C_{35}H_{23}Cl_3N_2O_3$)

Yield 38%; m.p. 307–310 °C; UV: 303 (3.05); ^{1}H NMR: 3.95 (dd, 1H, H-6, $J_{6,7} = 6.7$ Hz, $J_{6,9} = 2.7$ Hz), 4.10 (m, 1H, H-8, $J_{7,8} =$ Hz, $J_{8,9} = 2.7$ Hz), 4.20 (dd, 1H, H-7), 5.29 (dd, 1H, H-9), 5.51 (s, 1H, NH), 6.90–7.55 (m, 17H, aromat. and vinyl. H), 8.90 (s, 1H, CHO); ^{13}C NMR: 42.44 (d, C-7), 46.41 (d, C-8), 53.65 (d, C-6), 66.73 (s, C-2), 110.96, 124.90, 126.96, 128.51, 128.59, 129.00, 129.06, 132.92, 133.71, 135.29, 137.03, 140.57, 142.03, 150.70, 157.26 (aromat. and vinyl. C), 173.78 (s, C=O), 176.00 (s, C=O), 188.71 (d, CHO).

2,2-Bis-(2-thienyl)-4-(4-methylphenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5b**; $C_{32}H_{22}Cl_2N_2S_2O_3$)

Yield 22%; m.p. 266–269 °C; UV: 302 (3.06); ^{1}H NMR: 2.40 (s, 3H, CH_3), 4.12 (m, 2H, H-6 and H-8, $J_{6,7} = 7.0$ Hz, $J_{7,8} = 8.7$ Hz, $J_{8,9} = 2.7$ Hz), 4.28 (dd, 1H, H-7), 5.57 (dd, 1H, H-9), 5.41 (s, 1H, NH), 6.72–7.55 (m, 13H, aromat., thienyl. and vinyl. H), 9.15 (s, 1H, CHO); ^{13}C NMR: 15.27 (q, CH_3), 42.22 (d, C-7), 46.43 (d, C-8), 53.58 (d, C-6), 61.33 (s, C-2), 110.84, 123.37, 125.10, 125.97, 126.31, 126.92, 127.40, 127.72, 128.66, 129.46, 130.65, 133.86, 135.26, 141.35, 146.03, 147.32, 150.46, 157.59 (aromat., thienyl. and vinyl. C), 173.61 (s, C=O), 175.01 (s, C=O), 189.69 (d, CHO).

2,2-Bis-(2-thienyl)-4-(4-chlorophenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5c**; $C_{31}H_{19}Cl_3N_2S_2O_3$)

Yield 34%; m.p. 292–293 °C; UV: 303 (3.10); ^{1}H NMR: 4.10–4.15 (m, 2H, H-6 and H-8, $J_{6,7} = 6.9$ Hz, $J_{7,8} = 8.5$ Hz, $J_{8,9} = 2.7$ Hz), 4.28 (dd, 1H, H-7), 5.59 (dd, 1H, H-9), 5.34 (s, 1H, NH), 6.75–7.59 (m, 13H, aromat., thienyl. and vinyl. H), 9.09 (s, 1H, CHO); ^{13}C NMR: 42.13 (d, C-7), 46.44 (d, C-8), 53.58 (d, C-6), 65.85 (s, C-2), 111.57, 123.68, 125.07, 126.42, 127.00, 127.16, 127.51, 128.75, 129.16, 130.65, 131.92, 135.31, 137.25, 145.74, 147.82, 150.03, 155.97 (aromat., thienyl. and vinyl. C), 173.71 (s, C=O), 174.84 (s, C=O), 189.21 (d, CHO).

2-Phenyl-2-(2-thienyl)-4-(4-chlorophenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5d** + **5e**; $C_{33}H_{24}Cl_3N_2SO_3$)

Yield 37%; m.p. 269–272 °C; UV: 305 (3.02); ^{1}H NMR: 3.95–4.30 (m, 6H, 2xH-6, 2xH-7 and 2xH-8), 5.38 (s, 2H, 2xNH), 5.62 and 5.65 (dd, 2H, 2xH-9), 6.45–7.60 (m, 30H, aromat., thienyl. and vinyl. H), 8.82 (s, 1H, CHO); 8.87 (s, 1H, CHO); ^{13}C NMR: 41.73 (d, C-7), 43.00 (d, C-7), 45.65 (d, C-8), 46.35 (d, C-8), 53.19 (d, C-6), 53.22 (d, C-6), 64.33 (s, C-2), 64.39 (s, C-2), 125.09, 125.66, 126.09, 126.71, 127.12, 127.21, 127.25, 127.54, 127.67, 128.06, 128.35, 128.65, 128.85, 128.92, 129.28, 129.92, 130.36, 130.75, 130.87, 131.80, 133.36, 133.44, 133.79, 134.16, 134.30, 135.20, 135.32, 136.62, 136.93, 140.45, 141.08, 146.63, 147.35, 148.84, 149.18 (aromat., thienyl. and vinyl. C), 172.92 (s, C=O), 173.84 (s, C=O), 174.81 (s, C=O), 174.93 (s, C=O), 188.20 (d, CHO), 188.46 (d, CHO).

2-Methyl-2-(2-thienyl)-4-(4-methylphenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5f**; $C_{29}H_{22}Cl_2N_2SO_3$)

Yield 27%; m.p. 308–310 °C; UV: 306 (3.09); ^{1}H NMR: 1.95 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.01 (m, 1H, H-8, $J_{7,8} = 8.7$ Hz, $J_{8,9} = 3.0$ Hz), 4.29 (dd, 1H, H-6, $J_{6,7} = 6.3$ Hz, $J_{6,9} = 3.0$ Hz), 4.33 (dd, 1H, H-7),

5.21 (dd, 1H, H-9), 4.96 (s, 1H, NH), 7.15–7.26 (m, 10H, aromat., thienyl. and vinyl. H), 9.22 (s, 1H, CHO); ^{13}C NMR: 21.41 (q, CH_3), 25.75 (q, CH_3) 41.86 (d, C-7), 46.47 (d, C-8), 53.28 (d, C-6), 57.55 (s, C-2), 109.49, 121.34, 125.09, 125.51, 126.19, 127.07, 128.60, 129.40, 130.86, 133.08, 135.19, 141.10, 146.37, 151.70 (aromat., thienyl. and vinyl. C), 173.73 (s, C=O), 175.31 (s, C=O), 189.54 (d, CHO).

2,2-Dimethyl-4-(4-chlorophenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5g**; $C_{25}H_{19}Cl_3N_2O_3$)

Yield 31%; m.p. 280–283 °C; UV: 304 (3.00); ^{1}H NMR: 1.44 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 4.10 (m, 1H, H-8, $J_{7,8} = 8.7$ Hz, $J_{8,9} = 2.7$ Hz), 4.15 (dd, 1H, H-6, $J_{6,7} = 6.6$ Hz, $J_{6,9} = 2.7$ Hz), 4.27 (dd, 1H, H-7), 5.63 (dd, 1H, H-9), 4.62 (s, 1H, NH), 7.27–7.40 (m, 8H, aromat. and vinyl. H), 9.15 (s, 1H, CHO); ^{13}C NMR: 25.95 (q, CH_3), 26.95 (q, CH_3), 41.61 (d, C-7), 46.12 (d, C-8), 52.84 (s, C-2), 53.69 (d, C-6), 109.49, 117.35, 124.88, 128.44, 128.93, 132.52, 133.69, 135.08, 136.88, 150.98 (aromat. and vinyl. C), 173.85 (s, C=O), 175.41 (s, C=O), 188.69 (d, CHO).

2-(2-Furyl)-2-methyl-4-(4-chlorophenyl)-5-formyl-3-azabicyclo[4.3.0]-nona-4,9-diene-7,8-dicarboxylic N-(3,5-dichlorophenyl)-imide (**5h**; $C_{28}H_{19}Cl_3N_2O_4$)

Yield 23%; m.p. 280–283 °C; UV: 304 (3.12); ^{1}H NMR: 1.73 (s, 3H, CH_3), 4.02 (m, 1H, H-8, $J_{7,8} = 8.7$ Hz, $J_{8,9} = 2.1$ Hz), 4.14 (dd, 1H, H-6, $J_{6,7} = 6.3$ Hz, $J_{6,9} = 2.1$ Hz), 4.23 (dd, 1H, H-7), 5.91 (d, 1H, H-9), 5.13 (s, 1H, NH), 6.20–7.43 (m, 10H, aromat., furyl. and vinyl. H), 9.00 (s, 1H, CHO); ^{13}C NMR: 24.73 (q, CH_3), 41.79 (d, C-7), 46.13 (d, C-8), 53.70 (d, C-6), 54.92 (s, C-2), 105.67, 110.52, 120.67, 124.93, 125.51, 127.93, 128.54, 129.03, 129.12, 132.16, 133.67, 135.13, 135.59, 137.02, 142.61, 147.51, 154.84, 157.67 (aromat., furyl. and vinyl. C), 173.87 (s, C=O), 175.16 (s, C=O), 189.13 (d, CHO).

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