Journal of Photochemistry and Photobiology A: Chemistry 206 (2009) 198–204

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Photoreactivity of triazolopyridinones, including the drug trazodone, in aqueous solution

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ARTICLE INFO

Article history:
Received 20 April 2009
Received in revised form 29 June 2009
Accepted 3 July 2009
Available online 24 July 2009

Keywords:
Triazolopyridinone
Cyclobutane
Cage compound
[2+2] photocycloaddition
[4+4] photocycloaddition

ABSTRACT

Irradiation of triazolo[4,3-a]pyridin-3-ones at 310 nm has been investigated in water/acetonitrile (7%). Cis-cisoid-fused cyclobutanes are generally obtained. Cage products are found starting from derivatives bearing (piperazin-1-yl)aryl moiety under dilute conditions (10^{-3} M). Two different routes appear to be involved in the formation of the observed photoproducts. A plausible mechanistic explanation is reported.

1. Introduction

In the field of organic chemistry photochemical reactions of unsaturated molecules receive much attention from both mechanistic and synthetic perspectives since they often represent the best routes for cyclic compounds, particularly for highly strained systems as cage compounds [1]. Recently, we obtained a cage-like product by irradiation in water of the triazolopyridinone drug trazodone (**1a**), Fig. 1, by sunlight or by artificial lamps with a maximum at λ 310 nm [2]. Its OH-aryl substituted **1b** was considered an intermediate of the transformation [2]. In a previous paper it was reported that simple [1,2,4] triazolo[4,3-a]pyridin-3(2H)-ones give cis-cisoid-fused cyclobutanes when irradiated at 360 nm in organic solvent (THF) [3]. Although the cage product from trazodone was produced in low yield [2], we were intrigued by the peculiar trend observed in aqueous solution and decided to extend investigation to various triazolopyridinones in order to gain more mechanistic insight. Irradiation was carried out at λ 310 nm using compounds **1a–c** and other simple derivatives **1d**,**e**. Compound **1c** was prepared by methylation of **1b** while **1e** was obtained from the commercially available **1d** by a reported method [4].

All compounds **1** exhibit comparable absorptions in the λ range 300–400 nm due to the triazolpyridinone system (Fig. 2) [5].

2. Experimental

2.1. Chemicals

Trazodone (**1a**), analytical standard grade (99%) (Aldrich), compound **1d** (Alfa-Aesar) and bromopentane (Aldrich) were commercially available and used without further purification.

2.2. General procedures

NMR spectra were recorded on a Varian Inova-500 instrument operating at 499.6 and 125.62 MHz for ^{1}H and ^{13}C, respectively, and referenced with deuterated solvents. ESI/MS spectra were obtained in 0.1% formic acid–acetonitrile (1:1) on an Agilent 1100 MSD instrument. UV/vis spectra were recorded in methanol on a PerkinElmer Lambda 7 spectrophotometer. IR spectra were recorded on a Jasco FT/IR-430 instrument equipped with single reflection ATR, samples were dissolved in MeOH and deposited on the ZnSe crystal.

Irradiations at 310 or 254 nm were performed by a photoreactor (Helios Italquartz) equipped with six 15 W lamps with a maximum at 310 or at 254 nm. Pyrex or quartz tubes (20 cm × 1 cm, 25 ml) were used. The course of the reactions was monitored by HPLC [Synergy Polar-RP 80-A column, 4 μm, 250 mm × 4.6 mm].

Analytical and preparative TLC were made on Kieselgel 60 F_{254} plates with 0.2 mm and 0.5 or 1 mm layer thickness, respectively (Merck).

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1010-6030/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.jphotochem.2009.07.003

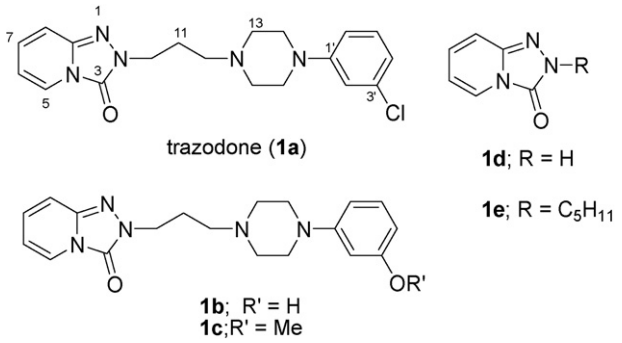

Fig. 1. Compounds investigated.

2.3. Experimental procedures

2.3.1. Synthesis of compound *1c*

Compound **1b** (100 mg) was dissolved in methanol (0.5 ml) and ethereal diazomethane was added. The solution was then kept under stirring at rt. After 24 h, solvents were evaporated and the residue was chromatographed on preparative TLC ($CHCl_3$/hexane/MeOH, 3:6:1) to afford compound **1c** (60% yield): oil; IR (ZnSe): ν_{max} 2922, 2818, 1697, 1433, 1166 cm^{-1}; UV λ_{max} (MeOH) nm: 259 ($\log \varepsilon$ 3.41), 326 ($\log \varepsilon$ 3.3); ^{1}H NMR: δ_H (500 MHz, CD_3OD) 7.77 (1H, d, *J* 7.2 Hz, H-5), 7.16 (1H, t, *J* 8.4 Hz, H-5′), 7.10 (2H, overlapped, H-7 and H-6′), 6.52 (1H, dd, *J* 8.4, 2.0 Hz, H-8), 6.49 (1H, td, *J* 7.2, 2.0 Hz H-6), 6.45 (1H, br s, H-2′), 6.42 (1H, br d, *J* 8.0 Hz, H-4′), 4.1 (2H, t, *J* 7.0 Hz, H-10), 3.79 (3H, s, OCH_3), 3.10 (4H, m, H-14), 2.56 (4H, m, H-13), 2.48 (2H, m, H-12), 2.07 (2H, m, H-11); δ_C (125 MHz, CD_3OD) 160.1 (C-3′), 148.1 (C-3), 150.0 (C-1′), 141.9 (C-9), 129.7 (C-7), 129.7 (C-5′), 123.7 (C-5), 115.3 (C-6′), 110.5 (C-6), 108.8 (C-8), 104.1 (C-4′), 102.2 (C-2′), 55.5 (OCH_3), 55.1 (C-12), 53.0 (C-13), 50.8 (C-14), 44.2 (C-10), 29.7 (C-11).

2.3.2. Synthesis of compound *1e*

A solution of triazolpyridinone **1d** (500 mg, 3.7 mmol) in dry xylene (15 ml) was added to a mixture of NaH (210 mg, 8.7 mmol; 50% in oil suspension washed three times with xylene under nitrogen) in 10 ml of xylene, and the resulting mixture was kept under reflux for 2 h. After cooling at rt, a solution of bromopentane (1.6 mmol) in xylene (20 ml) was added dropwise. The mixture was then heated at 150 °C under stirring for 24 h. After cooling, the mixture was filtered and the mother liquor was washed with 2% NaOH to remove any unreacted triazolopyridinone **1d**. The organic layer was evaporated under reduced pressure, and the residue was chromatographed on silica gel (hexane/CH_2Cl_2, 95:5) to give product **1e** with 30% yield: oil; IR (ZnSe): ν_{max} 2948, 1702, 1635, 1544, 1354 cm^{-1}; UV λ_{max} (MeOH) nm: 258 ($\log \varepsilon$ 3.39), 326 ($\log \varepsilon$ 3.28); ^{1}H NMR: δ_H (500 MHz, CD_3OD) 7.79 (1H, dd, *J* 7.0, 1.0 Hz, H-5), 7.23 (1H, ddd, *J* 8.5, 6.5, 1.0 Hz, H-7), 7.16 (1H, dd, *J* 8.5, 1.0 Hz, H-8), 6.45 (1H, td, *J* 7.0, 1.0 Hz, H-6), 3.96 (2H, t, *J* 7.0, H-10), 1.82 (2H, m, H-11), 1.30 (4H, m, H-12 and H-13), 0,89 (3H, t, *J* 7.0, H-14); δ_C (125 MHz, CD_3OD) 150.5 (C-3), 143.6 (C-9), 132.2 (C-7), 125.0 (C-5), 116.5 (C-8), 113.0 (C-6), 47.3 (C-10), 30.2 (C-11), 29.9 (C-12), 23.7 (C-13), 14.8 (C-14).

2.3.3. Irradiation of compounds *1* at 310 nm in water/CH_3CN (15:1)

(a) Solutions of compounds **1** (10^{-2} M; 40 mg in 11 ml for **1a**–**c**, 30 mg in 20 ml for **1d**, 40 mg in 18 ml for **1e**) were irradiated in open quartz tubes with six 15 W lamps with a maximum at 310 nm. After 4 h the solutions were analysed by HPLC [H_2O/CH_3OH/CH_3CN (3:1:1 for **1a**–**c** and 4:3:3 for **1d**,**e**]. After solvent evaporation each residue was analysed by ^{1}H NMR and purified on preparative TLC (1 mm).

Preparative TLC [benzene/acetone/triethylamine (2:2:1)] of the mixture from **1a** gave the starting **1a** (10 mg), compound **1b** (8 mg), compound **2a** (4 mg) and a crude product (6 mg) which by TLC [0.5 mm; $CHCl_3$/CH_3OH (7:3) saturated with 2 parts of water] gave compound **2a**′ (4 mg).

The irradiation mixture from compound **1b** treated as for **1a** gave starting **1b** (10 mg) and a mixture (3 mg) consisting of **2b** and **3b** in ca. 1:1 molar ratio (^{1}H NMR). Due to its low concentration selected data of **2b** were obtained by ^{1}H NMR spectrum of this mixture after subtracting the signals of known [2] product **3b**: δ_H (500 MHz, CD_3OD) 6.78 (d), 6.24 (d), 6.20 (d), 5.25 (dd), 5.11 (t).

Preparative TLC [$CHCl_3$/hexane/MeOH (4:5:1)] of the mixture from **1c** afforded 25 mg of starting **1c**, 3 mg of compound **3c** and 8 mg of compound **2c**.

The irradiation mixture of **1d** led by preparative TLC [$CHCl_3$/MeOH (9:1)] to the dimer **2d** (22 mg) and the starting material (6 mg).

Irradiation mixture of **1e**, purified by TLC [CH_2Cl_2/MeOH (9:1)], gave **1e** (15 mg) and **2e** (23 mg).

(b) Solutions of compounds **1** (10^{-3} M, 50 mg in 130 ml for **1a**–**c**, 30 mg in 200 ml for **1d**, 40 mg in 190 ml for **1e**) were irradiated for 4 h as above. Each solution was analysed and treated as above. Preparative TLC [benzene/acetone/triethylamine (2:2:1)] of the residue from **1a** gave compound **1b** (38 mg) and cage product **3b** (6 mg).

The residue of **1b** by preparative TLC [benzene/acetone/triethylamine (2:2:1)] gave the unreacted compound **1b** (40 mg) and cage compound **3b** (5 mg).

Preparative TLC [$CHCl_3$/hexane/MeOH (4:5:1)] of **1c** gave starting **1c** (40 mg) and cage compound **3c** (5 mg).

The residue of **1d** by preparative TLC [$CHCl_3$/MeOH (9:1)] led to starting **1d** (12 mg), cyclobutane **2d** (10 mg), intractable material (7 mg).

The irradiation mixture of **1e** was separated by preparative TLC [CH_2Cl_2/MeOH (9:1)] into starting **1e** (10 mg), cyclobutane **2e** (12 mg) and intractable material (15 mg).

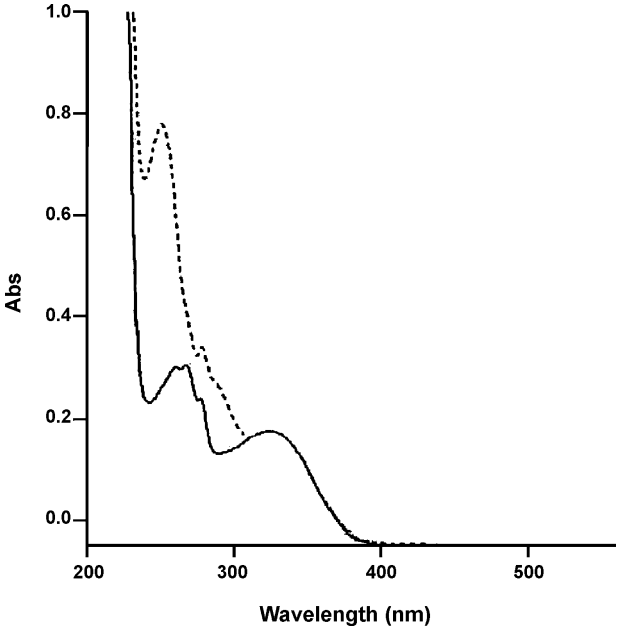

Fig. 2. UV spectra of representative triazolopyridinones **1b** (dashed line) and **1d** (continuous line) in methanol.

Table 1
^{13}C and ^{1}H NMR spectral data of representative cis-cyclobutanes **2** (CD_3OD, 125 MHz for ^{13}C and 500 MHz for ^{1}H NMR, δ in ppm J in Hz).

Position	**2a**		**2d**[a]		**2e**	
	^{13}C[b]	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
3	153.7 (q)[c]		152.5 (q)		153.7 (q)	
5	48.1 (t)	5.13 (t, 8.8)	45.1 (t)	4.99 (t, 9.0)	48.2 (t)	5.14 (t, 8.5)
6	43.7 (t)	3.84 (o[d])	41.5 (t)	3.73 (dt, 2.5, 8.8)	43.9 (t)	3.82 (o)
7	134.0 (t)	6.24 (dd, 10.7, 3.9)	131.7 (t)	6.08 (dd, 10.0, 4.0)	133.9 (t)	6.25 (1H, dt, 9.9, 3.9)
8	115.8 (t)	6.17 (d, 10.7)	114.6 (t)	6.14 (d, 10.0)	116.1 (t)	6.13 (1H, br d, 9.9)
9	142.1 (q)		140.9 (q)		142.0 (q)	
10/10′	45.2/45.0 (s)	3.80 (o)			46.8/46.6 (s)	3.86–3.55 (o)
11/11′	27.2/27.1 (s)	1.98/1.89, 1.82 (m)			30.2 (s)	1.74–1.56 (m)
12/12′	56.9/56.8 (s)	2.54/2.46 (m)			30.1 (s)	1.74–1.56 (m)
13/13′	54.5 (s)	2.66 m			23.8 (s)	1.37 (m)
14/14′	46.6 (s)	3.20 m			14.8 (p)	0.92 (t, 6.8)
1″/1‴	154.3 (q)					
2″/2‴	117.6 (t)	6.91/6.90 (t, 1.0)				
3″/3‴	136.4 (q)					
4″/4‴	115.8 (t)	6.79 (br d, 8.8)				
5″/5‴	131.8 (t)	7.13 (t, 8.8)				
6″/6‴	120.8 (t)	6.85/6.83 (br d, 8.8)				
3′	152.0 (q)		150.9 (q)		152.1 (q)	
5′	120.8 (t)	6.74 (d, 7.8)	118.8 (t)	6.65 (d, 8.0)	120.9 (t)	6.74 (d, 8.0)
6′	109.8 (t)	5.42 (dd, 7.8, 5.8)	107.3 (t)	5.32 (dd, 8.0, 5.0)	109.6 (t)	5.43 (dd, 8.0, 6.0)
7′	34.8 (t)	3.75 (o)	32.2 (t)	3.64 (dt, 5.9, 8.8)	34.8 (t)	3.78 (o)
8′	37.8 (t)	4.00 (br t, 7.8)	35.8 (t)	3.86 (dt, 2.1, 9.5)	37.9 (t)	4.00 (dt, 2.9, 9.0)
9′	140.0 (q)		138.7 (q)		139.9 (q)	

[a] Recorded in $(CD_3)_2SO$. Previous ^{1}H NMR data were run at 100 MHz [3].
[b] Assigned by HSQC and HMBC experiments.
[c] Letters, p, s, t and q, in parentheses indicate, respectively, the primary, secondary, tertiary and quaternary carbons, assigned by DEPT.
[d] Signal overlapped.

*2.3.4. Spectral data of photoproducts **2**–**3***

*2.3.4.1. Compound **2a**.* Oil, UV λ_{max} (CH_3OH): 211 ($\log\varepsilon$ 4.7), 256 ($\log\varepsilon$ 4.5), 291 ($\log\varepsilon$ 3.7) nm. IR (ZnSe): ν_{max} 2923, 2815, 1693, 1594, 1482, 1386, 1237 cm^{-1}. ESI-MS m/z (%): 743 (100), 745 (70), 747 (18). ^{1}H and ^{13}C NMR data are listed in Table 1.

*2.3.4.2. Compound **2a′**.* Oil, UV λ_{max} (CH_3OH): 213 ($\log\varepsilon$ 4.4), 254 ($\log\varepsilon$ 4.2), 293 ($\log\varepsilon$ 3.9) nm; IR (ZnSe): ν_{max}($CHCl_3$) 2926, 2818, 1693, 1585, 1438, 1382, 1258 cm^{-1}; ESI-MS m/z (%): 725 (100), 727 (34). δ_H (500 MHz, CD_3OD) 7.14/7.08 (2H, t, J 8.5 Hz, H-5″/H-5‴), 6.84/6.37 (2H, d, J 1.5 Hz, H-2″/H-2‴), 6.79 and 6.78 (3H, d, J 8.5 Hz, H-5′, H-4″ or H-4‴ and H-6″ or H-6‴), 6.46 (1H, br d, J 8.5 Hz, H-6″ or H-6‴), 6.31 (1H, dd, J 8.5, 1.5 Hz, H-4″ or H-4‴), 6.11 (1H, d, J 10.2 Hz, H-8), 6.07 (1H, dd, J 10.2, 3.0 Hz, H-7), 5.25 (1H, dd, J 7.5, 6.0 Hz, H-6′), 5.10 (1H, t, J 8.5, Hz, H-5), 4.1–3.6 (7H, m, H-6, H-7′, H-8′, H-10 and H-10′), 3.15 (8H, m, H-14 and H-14′), 2.57 (8H, m, H-13 and H-13′), 2.48/2.39 (4H, m, H-12/H-12′), 1.98/1.80 (4H, m, H-11 and H-11′); δ_C (125 MHz, CD_3OD) 157.7/135.0 (C-3″/C-3‴), 153.2/152.8 (C-1″/C1‴), 153.0 (C-3), 150.0 (C-3′), 139.9 (C-9), 136.7 (C-9′), 130.1/129.9 (C-7, C-5″/C-5‴), 120.2 (C-5′), 118.9/108.3 (C-6″/C-6‴), 115.6/102.9 (C-2″/C-2‴), 113.8/106.5 (C-4″/C4‴), 55.3/55.2 (C-12/C-12′), 52.9 (C-13, C-13′), 48.8/48.5 (C-14/C-14′), 46.1 (C-5), 43.5 (C-6, C-10, C10′), 36.3 (C-8′), 32.9 (C-7′), 25.8 (C-11, C-11′).

*2.3.4.3. Compound **2c**.* Viscous oil; UV λ_{max} (CH_3OH): 252 ($\log\varepsilon$ 3.8), 292 ($\log\varepsilon$ 3.8) nm; IR (ZnSe): ν_{max}($CHCl_3$) 2922, 2818, 1705, 1593, 1442, 1202 cm^{-1}; ESI-MS m/z (%): 735 (100). δ_H (500 MHz, CD_3OD): 7.12 (2H, t, J 8.8 Hz, H-5″, H-5‴), 6.73 (1H, d, J 8.0 Hz, H-5′), 6.55 (2H, br d, J 8.0 Hz, H-6″, H-6‴), 6.46 (2H, d, J 8.0 Hz, H-4″, H-4‴), 6.41 (2H, d, J 1.5 Hz, H-2″ or H-2‴), 6.23 (1H, dd, J 10.5, 3.5 Hz, H-7), 6.16 (1H, dd, J 10.5, 1.8 Hz, H-8), 5.41 (1H, dd, J 7.5, 5.5 Hz, H-6′), 5.12 (1H, t, J 8.5, Hz, H-5), 4.0–3.6 (7H, m, H-6, H-7′, H-8′, H-10 and H-10′), 3.74 (6H, s, OMe), 3.15 (8H, m, H-14 and H-14′), 2.62 (8H, m, H-13 and H-13′), 2.49/2.41 (4H, m, H-12/H-12′), 1.99/1.82 (4H, m, H-11 and H-11′); δ_C (125 MHz, CD_3OD) 162.5 (C-3″, C-3‴), 154.4 (C-3, C-3′, C-1″, C-1‴), 142.0 (C-9), 140.1 (C-9′), 134.0 (C-7), 131.2 (C-5″, C-5‴), 120.8 (C-5′), 110.6 (C-6″, C-6‴), 106.6 (C-4″, C4‴), 104.2 (C-2″, C-2‴), 57.1/56.8 (C-12/C-12′), 56.1 (OMe), 54.6 (C-13, C-13′), 50.1 (C-14, C-14′), 48.3 (C-5), 45.2/45.0 (C-10, C10′), 43.7 (C-6), 37.8 (C-8′), 34.9 (C-7′), 27.3 (C-11, C-11′).

*2.3.4.4. Compound **3c**.* Oil; UV λ_{max} (CH_3OH) nm: 214 ($\log\varepsilon$ 4.6), 252 ($\log\varepsilon$ 4.1); IR (ZnSe): ν_{max}($CHCl_3$) 2922, 2818, 1701, 1585, 1445, 1202 cm^{-1}; ESI-MS m/z (%): 735 (100). δ_H (500 MHz, CD_3OD): 7.12 (2 H, t, J 8.8 Hz, H-5″, H-5‴), 6.52 (1H, dd, J 8.0, 1.9 Hz, H-6″, H-6‴), 6.47 (2H, t, J 1.9 Hz, H-2″, H-2‴), 6.42 (2H, dd, J 8.0, 1.9 Hz, H-4″, H-4‴), 5.31 (2H, dd, J 9.0, 7.8 Hz, H-5, H-5′), 4.46 (2H, dd, J 9.0, 7.8 Hz, H-8, H-8′), 3.80 (4H, m, H-10, H-10′), 3.75 (6H, s, OMe), 3.52 (2H, m, H-6, H-6′), 3.33 (4H, obscured, H-7, H-7′), 3.17 (8H, m, H-14, H-14′), 2.52 (8H, m, H-13, H-13′), 2.37/2.24 (4H, m, H-12/H-12′), 1.87 (4H, m, H-11, H-11′); δ_C (125 MHz, CD_3OD) 162.6 (C-3″, C-3‴), 154.4 (C-3, C-3′, C-1″, C-1‴), 143.4 (C-9), 140.1 (C-9′), 134.0 (C-7), 131.3 (C-5″, C-5‴), 110.4 (C-6″, C-6‴), 106.5 (C-4″, C4‴), 104.2 (C-2″, C-2‴), 57.1 (C-12/C-12′), 56.1 (OMe), 54.7 (C-13, C-13′), 50.5 (C-14, C-14′), 50.0 (C-5, C-5′), 45.3 (C-10, C10′), 39.3 (C-8, C-8′), 36.9 (C-6, C-6′), 32.7 (C-7, C-7′), 26.8 (C-11, C-11′).

*2.3.5. X-ray structure analysis of compound **2d***

Data collection was performed at ambient temperature on a Bruker–Nonius kappaCCD diffractometer (graphite-monochromated Mo Kα radiation, λ = 0.71073 Å). Crystal data: $C_{12}H_{10}N_6O_2$, M = 270.26 g/mol, triclinic, P-1, Z = 2, a = 6.7000(6), b = 6.8860(9), c = 14.053(2) Å, α = 79.71(1), β = 85.455(8), γ = 63.98(1)°, V = 573.3(1) $Å^3$, D_{calc} = 1.566 g/cm^3, μ = 0.114 mm^{-1}. 8088 reflections collected, θ_{max} = 27.5°, 2568 independent reflections (R_{int} = 0.0313). The final refinement converged to R_1 = 0.0397 [$I > 2\sigma(I)$] and R_1 = 0.0625 (all reflections). Largest difference peak and hole were +0.237 and −0.188 e$Å^{-3}$.

The structure was solved by direct methods and anisotropically refined by the full matrix least-squares method on F^2 against all independent measured reflections using SHELX-97 software package. H atoms were placed in calculated positions (except those bounded to N atoms that were found in difference Fourier maps) and refined according to a riding model. All crystallographic data

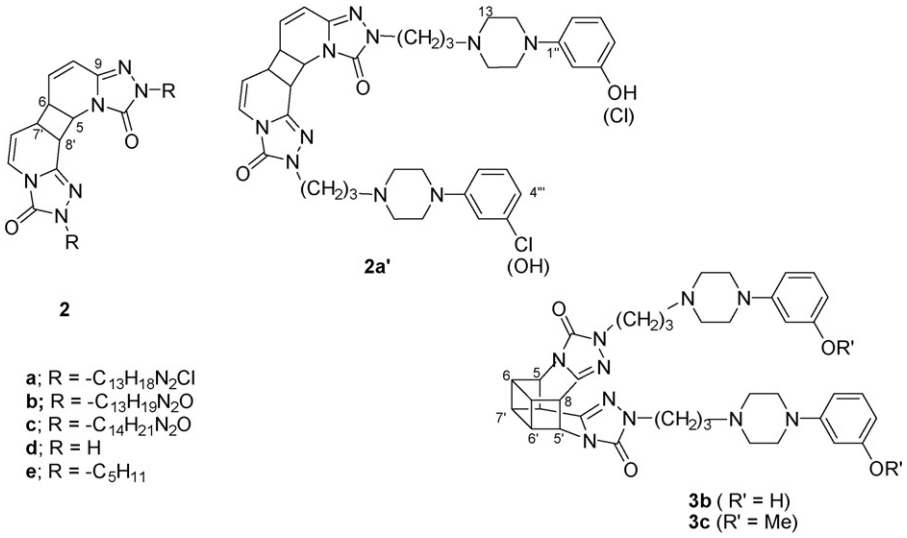

Fig. 3. Photoproducts from **1**.

have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Deposition number is CCDC 721840. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

2.3.6. Evaluation of quantum yield

The quantum yields of compounds **1** (10^{-2} and 10^{-3} M solutions in water/CH_3CN 15:1) were measured in quartz tubes (1 cm optical path) by means of the photoreactor (Helios Italquartz) equipped with six 15 W lamps with a maximum at 310 nm. The light flux (1.90×10^{-7} Es^{-1}) was measured by *o*-nitrobenzaldehyde [6]. The chemical conversion of compounds **1** was determined by HPLC [column: Synergy Polar RP 80A, eluent: $H_2O/CH_3OH/CH_3CN$ (4:3:3) using UV detector at 254 nm].

*2.3.7. Irradiation of cyclobutanes **2** at 310 and 254 nm in water/CH_3CN (15:1)*

Solutions of cyclobutanes **2** (10 ml, 10^{-3} M) were irradiated in an open quartz tubes for 4 h at 310 nm. After solvents evaporation, ^{1}H NMR and TLC analyses of each irradiation mixture showed only the presence of compounds **1**.

The irradiation at 254 nm gave the same results.

*2.3.8. Irradiation of cage products **3** at 310 and 254 nm in water/CH_3CN (15:1)*

Solutions of compounds **3** (10 ml, 10^{-3} M) were irradiated in open quartz tubes for 4 h at 310 nm. After solvents evaporation, ^{1}H NMR and TLC analyses of each irradiation mixture showed the presence of unidentified products.

The irradiation at 254 nm gave the same results.

*2.3.9. Irradiation at 254 nm in water/CH_3CN (15:1) of compounds **1a**,**d***

A solution of each compound (10 ml, 10^{-3} M) was irradiated in open quartz tubes for 4 h at 254 nm. After solvents evaporation, each residue was analysed by ^{1}H NMR and TLC and showed only starting material and unidentified compounds.

*2.3.10. Irradiation at 310 nm of compounds **1a**,**d** in organic solvents at 10^{-3} M*

Solution of each compound in CH_3CN (10 ml, 10^{-3} M) was irradiated for 4 h in open quartz tube at 310 nm. After solvent evaporation, each residue was analysed by TLC and ^{1}H NMR. Both analyses revealed complex mixtures of unidentified products among which Solution of each compound in CH_3CN (10 ml, 10^{-3} M) was irradiated for 4 h in open quartz tube at 310 nm. After solvent evaporation, each residue was analysed by TLC and ^{1}H NMR. Both analyses revealed complex mixtures of unidentified products among which the starting **1a** and **1d** the corresponding photoproducts **2a** and **2d** were present in traces.

The same results were obtained using dry benzene as solvent or benzene in the presence of benzophenone (0.1 equiv. respect to **1**).

3. Results

Due to the low solubility of **1d** and **1e** in water, acetonitrile was used as co-solvent (CH_3CN/H_2O 1:15 v/v, ca. 7%). As assumed for the most part, the use of acetonitrile does not interfere with the photochemistry, but may decrease the quantum efficiency of reaction by decreasing the polarity of the medium [7,8].

Irradiation was carried out with a set of lamps with a maximum at 310 nm in water/CH_3CN (15:1, ca. 7%) using 10^{-2} and 10^{-3} M solutions. Quantum yields (Φ) of compounds **1** were measured at both concentrations (Table 2), and show that the values are similar and are not affected by N-2 substitution nor by concentration.

The irradiation reactions were monitored by ^{1}NMR and HPLC after 4 h. The products isolated are shown in Fig. 3. All of them were characterized by their physical data.

The percentages of products (Table 3) have been deduced by HPLC and confirmed by chromatography.

As shown in Table 3, the formation of cyclobutanes **2** is common to all products **1**. Cage-like products **3** are found only starting from compounds **1a**–**c** in dilute solutions. In particular, according to previous results [2], **1a** converts to its OH-aryl substituted **1b** and this in turn affords **2b**. It is significant that a monophenoxyl cyclobutane **2a**′ is found in 10^{-2} M solution, so showing that under this condition chlorine displacement by OH group is slow.

Table 2
Quantum yields of compounds **1**.

Compound	Φ^a ($\times 10^3$)	Φ^b ($\times 10^3$)
1a	4.8	3.3
1b	5.1	2.2
1c	1.0	2.6
1d	7.0	2.8
1e	4.8	5.7

[a] 10^{-2} M solutions.
[b] 10^{-3} M solutions.

Table 3
Irradiation of triazolopyridinones (**1**) at 310 nm.

Starting compound	Condition	Products (%)[b]		
		1	**2**	**3**
1a	10^{-2} M	54 (21)[c]	11 (14)[d]	–
	10^{-3} M	90[c]	–	10[e]
1b	10^{-2} M	80	11	9
	10^{-3} M	83	–	17
1c	10^{-2} M	72	20	8
	10^{-3} M	81	–	19
1d	10^{-2} M	27	73	–
	10^{-3} M	55	45	–
1e	10^{-2} M	38	62	–
	10^{-3} M	43	57	–

[a] Six UV lamps setted at 310 nm, solvent: H_2O/CH_3CN 15/1, irradiation time: 4 h.
[b] Deduced by HPLC.
[c] It refers to product **1b**.
[d] It refers to product **2a**′.
[e] It refers to product **3b**.

Cis-cisoid-fused cyclobutane dimers of triazolopiridines are reported to give cage-like products by irradiation at 254 nm [9]. Accordingly, cyclobutanes **2** were irradiated at 254 and also at 310 nm, but, under both conditions, they reverted to starting **1** and no cage-like products could be detected. Similar irradiations using cage-like products **3b**,**c** resulted in the formation of intractable material.

Experiments using **1a** and **1d** as representative were carried out in the sole organic solvent (CH_3CN). Under these conditions quantum yields at 310 nm could not be determined. Indeed, although compounds **1a**,**d** and their respective photoproducts **2a**,**d** were present in traces, the irradiation mixtures were too complex to be investigated by HPLC analysis due to the formation of other unidentified products and polymeric materials. These results were also confirmed by ^{1}H NMR analysis. Moreover, no cage product was found by irradiating **1a**,**d** at 310 nm in dry benzene [10] nor in dry benzene in the presence of benzophenone as photosensitizer [11], conditions that have been previously reported to favor cage-like products formation.

3.1. Identification of products

The photoproducts were identified by ^{1}H-, ^{13}C-, and 2D-NMR as well as ESI-MS analyses except for **2b** which was obtained in mixture with **3b** (see Section 2). All of them exhibit molecular peaks of dimeric systems.

A molecular formula of $C_{38}H_{44}Cl_2N_{10}O_2$ was assigned to the compound **2a** by the pseudo molecular ion peak at *m*/*z* 743 $[M+H]^+$ in ESI-MS. The ^{1}H NMR spectrum (Table 1) displayed signals corresponding to eight aromatic protons of two 1,3-disubstituted phenyl rings (δ 6.79, br d, J = 8.8 Hz; 6.85/6.83, br d, J = 8.8 Hz; 6.91/6.90, t, J = 1.0 Hz; and 7.13, t, J = 8.8 Hz), four olefinic protons of two disubstituted double bonds (δ 6.74, d, J = 7.8 Hz; 6.24, dd, J = 10.7, 3.9 Hz; 6.17, d, J = 10.7 Hz; 5.42, dd, J = 7.8, 5.8 Hz), and four aliphatic methines (δ 5.13, t, J = 8.8 Hz; 4.00, br t, J = 7.8 Hz; 3.84 and 3.75). Furthermore, the spectrum showed signals of two propyl chains and two piperazine rings. The ^{13}C NMR spectrum (Table 1) showed only 26 signals. The DEPT spectrum showed eight methylenes and twelve methines, which were correlated to the corresponding protons by a HSQC experiment. In a HMBC experiment, the following correlations were observed: H-5′ with C-3′, C-9′, and C-7′; H-6′ with C-8′, C-7′, C-6 and C-5′; H-7 with C-7′, C-6 and C-5; H-8 with C-9, C-7, and C-6; H-5 with C-9, C-9′ and C-3; and H-8′ with C-9′, C-7′, C-6′, C-6 and C-5. Thus, the structure of a [2+2] cycloaddition adduct, derived from different double bonds of the two dihydropyridine rings, was established for compound **2a**. The cis-cyclobutane structure was assigned by analysis of the NOESY spectrum which evidenced NOEs between the H-6′ proton with H-7 and H-5 proton with H-7′ and H-8′.

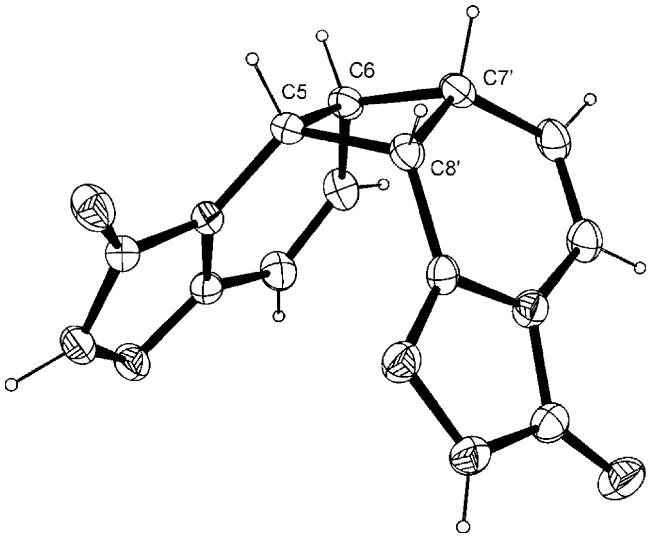

Fig. 4. Ortep view of compound **2d**. Ellipsoids are drawn at 30% probability level.

A molecular formula of $C_{38}H_{45}ClN_{10}O_3$ was assigned to the compound **2a**′ by the pseudo molecular ion peak at *m*/*z* 725 $[M+H]^+$ in ESI-MS. The ^{1}H NMR spectrum displayed signals corresponding to six aromatic protons of two 1,3 disubstituted phenyl rings (δ 6.79, 6.78, 6.84, and 7.14; 6.31, 6.37, 6.46, and 7.08) identified as a 3-*N*-hydroxyphenyl group and a 3-*N*-chorophenyl group. Furthermore, the spectrum showed signals of four olefinic protons of two disubstituted double bonds, four aliphatic methines, two propyl chains and two piperazine rings. These data and those of the ^{13}C NMR spectrum closely resembled those of compound **2a** so that the structure **2a**′ was attributed to this substance.

Compound **2c** showed the pseudo molecular ion peak at *m*/*z* 735 $[M+H]^+$ in ESI-MS. Comparison of its ^{1}H and ^{13}C NMR data with those of **2a** suggested an identical cis-cisoid-fused cyclobutane dimer for **2c**.

The molecular formula of **2d**, that was obtained as colorless crystals with m.p. 232–3 °C (lit. 230 °C dec.; [3]), was determined to be $C_{12}H_{10}N_6O_2$ by pseudo molecular ion peak at *m*/*z* 271 $[M+H]^+$ in ESI-MS and twelve signals in the ^{13}C NMR spectrum (Table 1). These data suggested a dimeric structure for this compound. A close inspection of ^{1}H NMR signals (Table 1) including COSY, NOESY, HSQC and HMBC spectra allowed to attribute a cis-cyclobutane structure of compound **2d**. Its structure and stereochemistry (cisoid-fused cyclobutane ring system) was confirmed by X-ray analysis (Fig. 4).

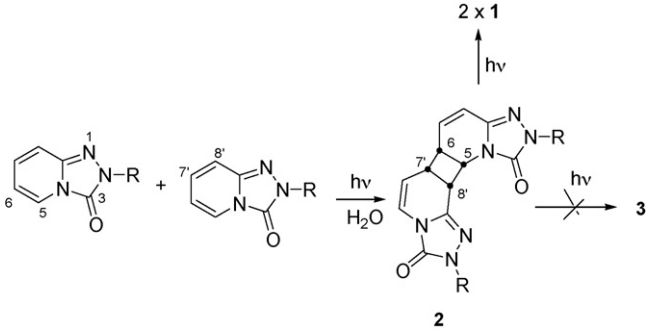

Fig. 5. Photo-induced selective route for cyclobutanes **2** and their photochemical conversion.

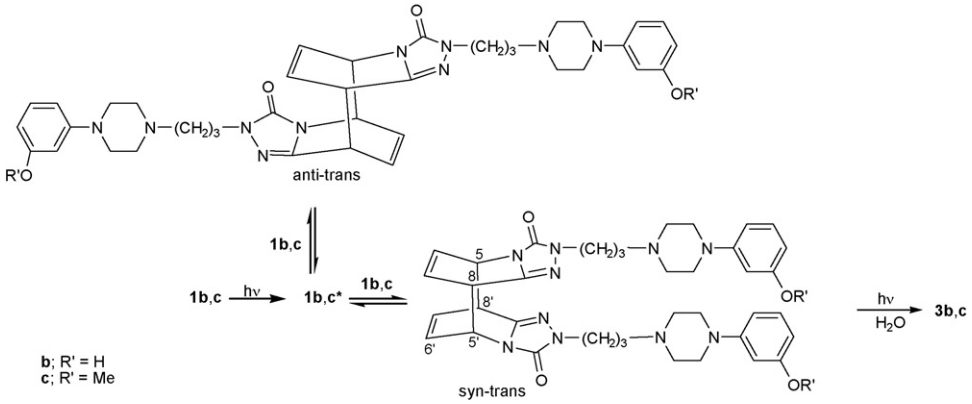

Fig. 6. Suggested photo-induced pathway for cage products **3b**,**c**.

Compound **2e** showed the pseudomolecular ion peak at *m*/*z* 411 $[M+H]^+$ in ESI-MS. The ^1H and ^{13}C data (Table 1) close resembled that of compound **2d**, except for the signals of *n*-pentyl chains, denoting a cis-cyclobutane structure also for **2e**.

Photoproduct **3b** was identified by comparison of its spectral data with those previously reported [2]. The ^1H and ^{13}C NMR spectra of compound **3c** close resembled that of **3b**. In particular, it exhibited signals at δ 5.31, 3.52, 3.33 and 4.46 correlated to the carbons at δ 50.4, 37.0, 32.7, and 39.3 due to the saturated cage-functionality. ^1H–^1H COSY and HMBC correlations and NOESY spectrum allowed to assign the proposed structure.

4. Discussion

Triazolopyridinones **1** in water undergo a regio- and stereoselective asymmetric [2+2] photocycloaddition between different double bonds (5,6- and 7′,8′ bonds) of the two dihydropyridine rings, as reported previously in organic solvents [3]. Only cis-cisoid cyclobutanes have been isolated, and their formation increases with concentration. The selectivity could be due to a π-stacking preorientation, which aligns the molecules in a head-to-head fashion so that the excited-state triazolopyridinone **1** can readily interact with the adjacent ground-state **1** to give a cis-cisoid-fused cyclobutane **2** [12]. Cisoid [2+2] adducts are favored at high concentration and, mainly, in polar media [12–14]. It is to be noted that irradiation of compound **1d** in our conditions (0.01 M water/acetonitrile) affords the corresponding cyclobutane **2d** in 67% (isolated yield) in 4 h versus 50% yield after 72 h in 0.05 M solution of THF [3].

Formation of cage-like products **3** seems not to be related to the primary formation of cyclobutanes **2**. Indeed these compounds by irradiation do not undergo an intramolecular [2+2] cycloaddition but revert to the starting **1** (Fig. 5). Formation of **3** seems instead to be related to the presence of the (piperazin-1-yl)aryl moiety since they are present only in the irradiation mixtures of derivatives **1b**,**c**, and limited to aqueous dilute solutions. It is probable that this moiety promotes intermediate charge species, favored by the polar protic solvent water. Under dilute conditions where cyclobutane formation is disadvantaged, these species could give cage-like products **3** through a [4+4] cycloaddition followed by an intramolecular [2+2] cycloaddition (Fig. 6) [15]. Photodimerization via [4+4] cycloaddition has been found in the irradiation of polycyclic aromatic compounds [16], pyridine derivatives, namely 2-aminopyridines [17] and 2-pyridones [17,18] and, also, triazolopyridines [19]. Anti-trans configuration has been generally observed, which cannot lead to cage-like products, with only small amounts of syn-trans-adducts. In our case once more the protic solvent water could play a role in the suitable alignment for syn-trans dimerization [18] as well as could do secondary interactions of the (piperazin-1-yl)aryl moiety [15]. The chlorine displacement by OH group observed for drug **1a** agrees with the formation of charge species which are often invoked in the photodehalogenation of aryl halides involving amines [20]. Under dilute conditions this OH-substitution is faster than dimerization, and conversion to **1b** is the primary reaction observed (Table 3) [2].

5. Conclusion

Triazolopyiridinones undergo selective [2+2] cycloaddition at 5,6- and 7′,8′-bonds in aqueous solution as well as in organic solvents [3] giving syn-cis-cyclobutane dimers. The latter do not undergo further cycloaddition. Formation of peculiar cage-like products appears to depend on the presence of (piperazin-1-yl)aryl moiety, aqueous medium and dilute solution.

Investigation shows how the complexity of drug structures may not permit to foresee the photochemical behavior by comparison with simple analogues and highlights a possible peculiar role of a highly polar solvent as water in photochemical processes.

Acknowledgements

NMR experiments were performed at CIMCF (Centro Interdipartimentale di Metodologie Chimico-Fisiche) on a Varian 500 Inova spectrometer of Consortium INCA (Consorzio Interuniversitario Nazionale Chimica per l'Ambiente). Thanks are due to Prof. Angela Tuzi (Dipartimento di Chimica "Paolo Corradini"-Università di Napoli Federico II) for providing us with X-ray data.

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