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

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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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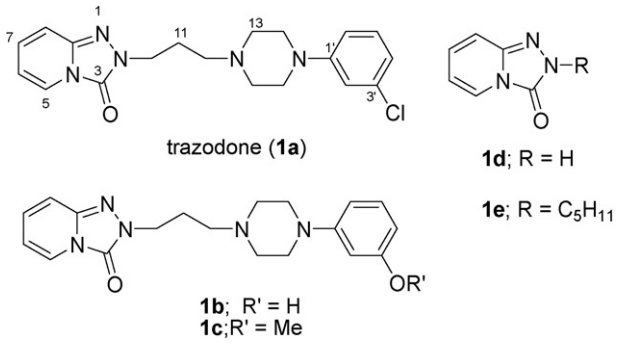

Fig. 1. Compounds investigated.

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).

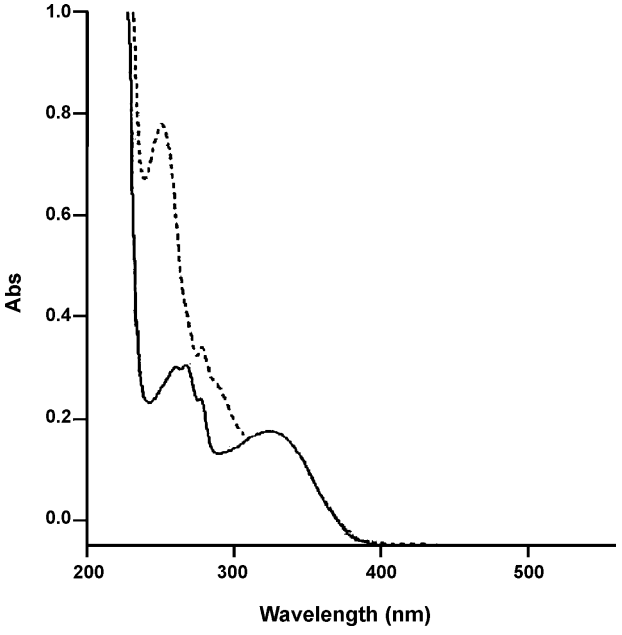

Fig. 2. UV spectra of representative triazolopyridinones **1b** (dashed line) and **1d** (continuous line) in methanol.