Short communication

The Crystal Structure of Lacidipine Phototransformation Product[1]

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Abstract

Diethyl (E)-4-[2-[2-(tert-butoxycarbonyl)vinyl]phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate or lacidipine (**1**) is a drug used for treatment of hypertension. The literature data for the undesired daylight phototransformation of compound **1** was confirmed for UV light as well. The main product, (1α,1aα,4aα,8bα,8cα) 1-(1,1-dimethylethyl) 4,8c-diethyl 1a,2,4a,8b-tetrahydro-1a,3-dimethyl-2-azacyclobuta[jk]fluorene-1,4,8c(1*H*)-tricarboxylate was isolated and the crystal structure was determined.

Keywords: 1,4-dihydropyridines, lacidipine, phototransformation, crystal structure

1. Introduction

Diethyl (E)-4-[2-[2-(tert-butoxycarbonyl)vinyl] phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate or lacidipine (compound **1** in Figure 1) is a member of Hantzsch dihydropyridine type Ca antagonists group[1] used as a drug for the treatment of mild to moderate hypertension.[2, 3]

Phototransformation of lacidipine (**1**) to cis analogue **2** was described.[3] The study of phototransformation by the artificial sun light was repeated later in more details[4] as an important parameter for drug handling. There the phototransformation pathway was extended to compound **3** (Figure 1).

This kind of phototransformation of lacidipine (**1**) has been confirmed in our group as well for the transformation in UV light. In addition in this short communication we present the results x-ray analysis of the final product (**3**).

2. Results and Discussion

The solution of **1** in acetonitrile was irradiated using UV light (λ = 300–410 nm) of low-pressure mercury lamp. The conversion was monitored by HPLC. The products were isolated and identified as compounds **2** and **3**. This confirms the identity of UV light transformations carried out in our laboratory to day-light transformation described in the literature.[4]

Although the structure of compound **3** was suggested,[4] we were able to confirm its very interesting basket-like structure by X-ray analysis (Figure 2). The appropriate crystals were prepared after removing the solvent from the reaction mixture and crystallization of oily residue from the mixture of hexane and ethyl acetate (9/1, v/v).

This intramolecular conversion is interesting from the synthetic point of view, since the only examples of intermolecular photochemical [2+2] cycloadditions of much less substituted 1,4-dihydropyridines with acrylonitrile and some other unsaturated nitriles have been described.[5]

1 part of this work was preliminary reported in Slovenski kemijski dnevi 2001, 20 and 21th September 2001, Maribor, Slovenia, Zbornik referatov s posvetovanja, p. 339.

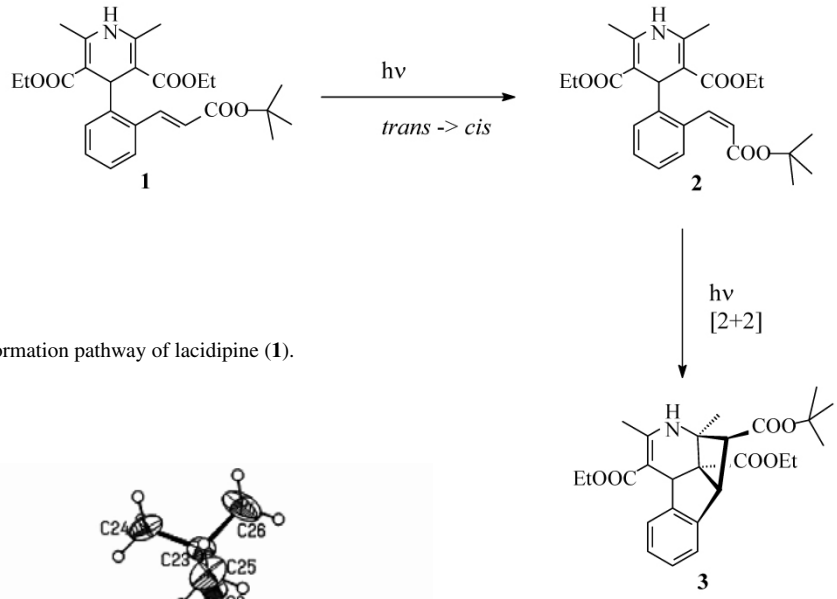

Figure 1. Phototransformation pathway of lacidipine (**1**).

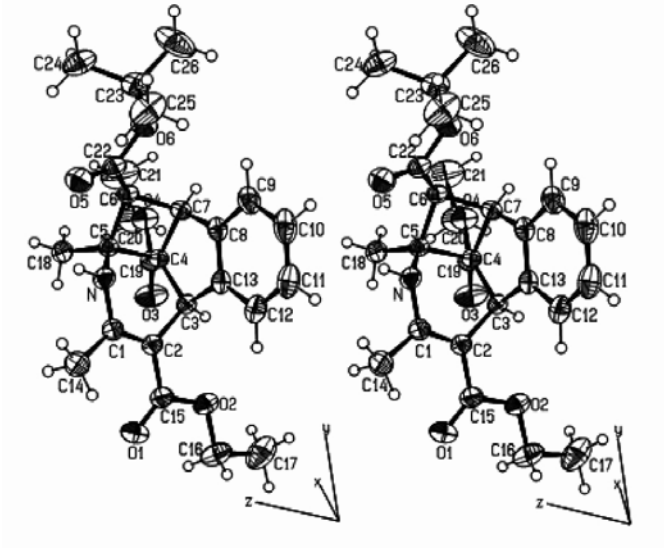

Figure 2. Ortep stereoview of the molecule of compound **3** with labelling of nonhydrogen atoms. Ellipsoids at 40% probability level.

2. 1. X-ray Structure Determination of Compound 3

The stereoview of the asymmetric unit of compound **3** is shown in Figure 2. The crystallographic data are presented in Table 1. The structure was solved by direct methods using the SIR92[6] program. The positions of hydrogen atoms were obtained from difference Fourier map. We employed full-matrix least-squares refinement on F magnitudes with anisotropic displacement factors for all nonhydrogen and isotropic for hydrogen atoms. The correction for secondary extinction[7] was applied with g = $5(1)\cdot10^4$. The Xtal3.4[8] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII[9] program was used to produce molecular graphics. Additional crystallographic data for the structure reported have been deposited at the Cambridge Crystallographic Data Centre with quotation number CCDC 214530 and are available free of charge on request.[10]

3. Experimental

The starting substance (**1**) was prepared by the procedure described in the literature.[3] All solvents and reagents were of p. a. grade. Irradiations were carried out in a photochemical chamber reactor Rayonet RPR-200, equipped with Rayonet Merry-Go-Round RMA-400 in quartz vessels Rayonet RQV-5 (volume 15 ml), closed with a rubber septum. As a light source 16 "black light" low-pressure mercury lamps (nominal power 8 W) were used. The spectral distribution of lamps is from 300 to 410 nm with a maximum at about 350 nm.

Reaction was monitored by HPLC using Bio-Dimension "fast-scan" UV-VIS monitor as detection unit, Nova-Pak Phenyl 3,9 · 150 mm column as stationary phase and mixture acetonitrile/methanol/0,01M ammonium acetate (36/24/40, v/v/v) as mobile phase. For the identification of different components the retention times and UV absorption spectra in the range 200 to 360 nm obtained by "fast-scan" UV-VIS monitor was used. For the identification and comparision of the compounds with the literature data NMR spectra were obtained on a Varian VXR-300 spectrometer, MS spectra on a Micromass AutospecQ, and elemental analyses for C, H, and N on a Perkin-Elmer CHN Analyser 240.

3. 1. Procedure for the Phototransformation of Lacidipine (1)

The solution of 50 mg (0,11 mmol) of lacidipine (**1**) in 10 ml of acetonitrile is charged in reaction vessel RQV-5. The solutions were irradiated and samples were taken every 15 minutes. HPLC analysis were showed the trans-

Table 1. Crystallographic Data for Compound **3**.

Compound	**3**
Crystal data	
Chemical formula	$C_{26}H_{33}NO_6$
Formula relative weight	455.55
Crystal system	triclinic
Space group	P –1, No. 2
a (Å)	9.794(1)
b (Å)	10.836(1)
c (Å)	13.663(2)
α (°)	69.27(2)
β (°)	77.76(1)
γ (°)	68.22(1)
V (Å^3)	1253.8(3)
Z	2
Calc. density D_x (Mg m^{-3})	1.207
Radiation type	Mo Kα
Wavelength (Å)	0.71069
No. of refl. for cell parameters	75
θ range (°)	8.39–15.79
μ (mm^{-1})	0.0852
Temperature (K)	293(1)
Crystal shape	prism
Crystal size (mm)	0.56 · 0.40 · 0.32
Crystal colour	colourless
Data collection	
Diffractometer	Enraf Nonius CAD-4
Data collection method	ω-2θ scans
Absorption correction	None
No. of measured refl.	9915
No. of independent refl.	6352
No. of observed refl.	4089
Criterion of observed refl.	$I > 2.5\sigma(I)$
R_{int}	0.0073
θ_{max} (°)	28.5
Range of h, k, l	$-9 \rightarrow h \rightarrow 13$ $-13 \rightarrow k \rightarrow 14$ $-17 \rightarrow l \rightarrow 18$
No. of standard refl.	3
Frequency of standard refl.	Every 333.3 min of scan. time
Intensity decay (%)	0.10
Refinement	
Refinement on	F
R	0.042
wR	0.054
No. of contributing refl.	5379
No. of parameters	431
$(\Delta/\sigma)_{max}$	0.0036
$\Delta\rho_{max}$	0.321
$\Delta\rho_{min}$	–0.263

formation of compound **1** through compound **2** to compound **3** after 240 min of irradiation. For the isolation and identification of componds **2** and **3** the procedure was repeated and the product isolated at their maximal appearances after 60 and 240 minutes respectivelly. The isolation was done by evaporation of the solvent and fractional crystallization from the mixture of heptan and ethyl acetate for compound **2** and by simple crystallization from the same mixture for compound **3**.

4. Conclusions

On the basis of identification of all reaction components the degradation pathway of lacidipine (**1**) is explained in the following way (Scheme 1): lacidipine (**1**), a compound with a trans-cinnamoic moiety is first subjected to photochemical trans-cis transformation. The obtained cis analogue (diethyl (Z)-4-[2-[2-(tert-butoxycarbonyl)vinyl] phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, compund **2**) is further transformed by intramolecular [2+2] photochemical cycloadditon affording (1α,1aα,4aα, 8bα,8cα) 1-(1,1-dimethylethyl) 4,8c-diethyl 1a, 2,4a,8b-tetrahydro-1a,3-dimethyl-2-azacyclobuta-[jk]fluorene-1,4,8c(1*H*)-tricarboxylate (compound **3**). The crystal structure was determined by the x-ray analysis.

5. Acknowledgement

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6. References

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Povzetek

Dietil (*E*)-4-[2-[2-(tert-butoksikarbonil)vinil]fenil]-2,6-dimetil-1,4-dihidropiridin-3,5-dikarboksilat ali lacidipin (**1**) je zdravilo, ki se uporablja za zdravljenje hipertenzije. Potrdili smo, da prihaja do identične neželjene fotokemične degradacije kot na dnevni svetlobi tudi v UV svetlobi. Glavni produkt te pretvorbe, (1α,1aα,4aα,8bα,8cα) 1-(1,1-dimetiletil) 4,8c-dietil 1a,2,4a,8b-tetrahidro-1a,3-dimetil-2-azaciklobuta[jk]fluoren-1,4,8c(1*H*)-trikarboksilat, smo izolirali in mu določili kristalno strukturo.