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Research Article

Photoinduced Aromatization of Asymmetrically Substituted 1,4-Dihydropyridine Derivative Drug Cilnidipine

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The antihypertensive drug Cilnidipine (**1**) is photolabile under UV-A light. Irradiation of a chloroform solution of Cilnidipine under aerobic and anaerobic conditions produces a common photoproduct which was isolated as 2-methoxyethyl-3-phenyl-2-propenyl pyridine dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate (**2**). The formation of products was explained by photochemical aromatization of Cilnidipine.

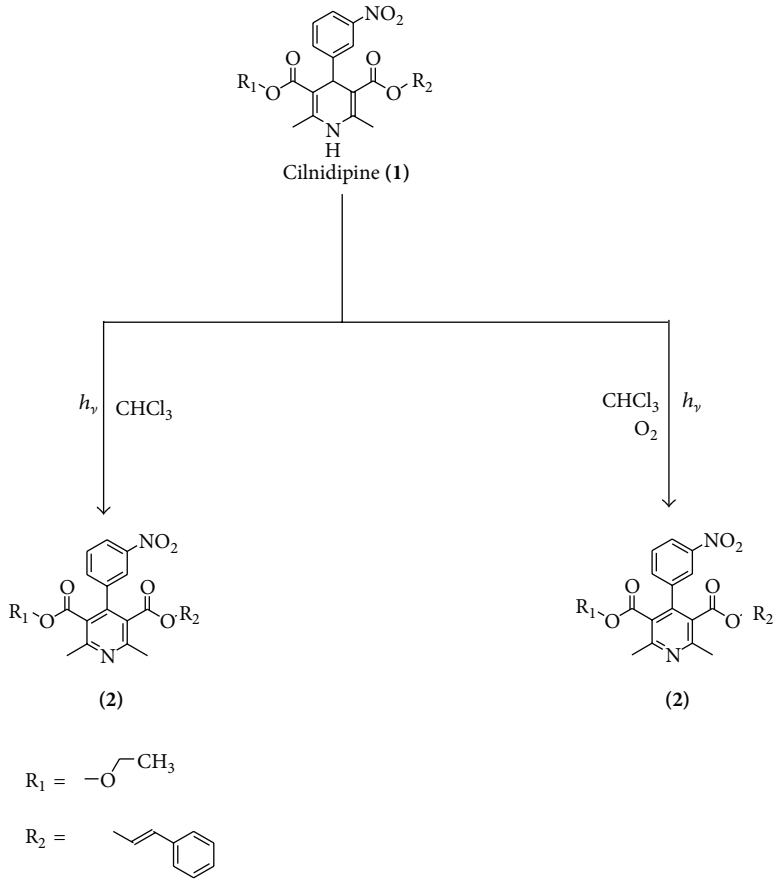
1. Introduction

The last few years have witnessed a growing interest of the scientific community in photoinitiated reactions of drugs [1]. This has been motivated by photobiological reasons, connected to the increasing number of cases of drug-photoinduced disorders but it has also attracted considerable attention from a more fundamental photochemical standpoint [2]. Thus it is worthy to stress that studies performed on drugs bearing either simple or complex chromophoric structures have provided remarkable contributions to the broad area of the molecular mechanisms of photoinitiated reactions [3, 4].

Derivatives of 1,4-dihydropyridines (DHPs) are drugs belonging to the class of pharmacological agents known as calcium channel blockers [5]. They inhibit calcium ion penetration inside cells and weaken the contractility of the cardiac muscle [6]. These compounds have been shown to be very effective vasodilators and are useful in the treatment of hypertension, ischemic heart disease, and other cardiovascular disorders [7, 8]. The 1,4-dihydropyridines show fast photochemical decomposition, which lead to chemical changes responsible for weakening the therapeutic effect [9, 10]. During the use of the DHPs, some side effects have been reported, of which the most common are associated with the vasodilatory action. But recently, besides these phenomena, more and more phototoxic effects on the skin are observed, indicating that they can cause skin photosensitivity reactions [11, 12].

Cilnidipine is a newly synthesized dihydropyridine calcium antagonist that has a slow onset and long duration of action. It can regulate the catecholamine secretion closely linked to intracellular Ca^{2+} levels [13, 14]. Comparing with other calcium antagonists, it has a slow onset, long-lasting antihypertensive effect, and unique inhibitory actions on sympathetic neurotransmission [15]. It shifts the lower limits for autoregulation of the cerebral blood flow downward, which may remain intact even if excessive hypotension is induced by Cilnidipine [16]. Hence, Cilnidipine has high potentials in the therapy of hypertension. Cilnidipine also exhibits photosensitive reaction [17].

The main goal was to investigate the photochemical reactivity and to correlate with its clinical photosensitization. Herein we have examined the photochemistry of a newly synthesized dihydropyridine calcium antagonist Cilnidipine under mild conditions similar to those encountered in biological systems, namely, oxygenated media, as well as under argon atmosphere. The irradiation of Cilnidipine with UV-A light under both conditions gives the same photoproduct identified as **2** from their spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra) properties (Scheme 1). The products are formed by photochemical aromatization of Cilnidipine.



Scheme 1: Photodegradation products of Cilnidipine.

2. Experimental

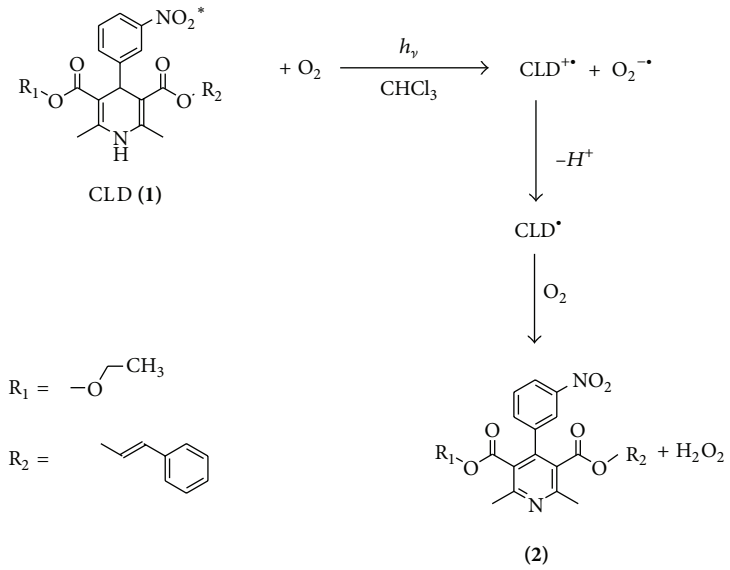
2.1. Apparatus and Chemicals. All chemicals used were of analytical grade. Pure Cilnidipine was obtained from Sigma Aldrich (India); IR spectra were recorded as KBr discs on a Perkin Elmer model spectrum RXI. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance-DRX-300 Spectrometer using TMS as internal standard and CD_3OD as solvent. High resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 eV ionization voltage. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (60–120 mesh).

2.2. Photoirradiation Procedure. Cilnidipine (265 mg) was dissolved in 400 mL chloroform and irradiated at room temperature for 1 hr in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co. Model RPR-208 equipped with four RUL-300 nm fluorescence lamps) for the complete conversion of the reactants. Progress of the reaction was monitored by thin layer chromatography (chloroform-methanol, 98 : 2). Irradiation was carried out under both aerobic and anaerobic conditions. At the end of reaction the formation of a number of products was indicated on TLC and the photoproduct was isolated by eluting with chloroform and petrol (60 : 40, v/v) on silica column. Under both aerobic and anaerobic conditions **2** is obtained as major photoproduct and identified as 2-methoxyethyl-3-phenyl-2-propenyl pyridine dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate **(2)** from the following spectral properties.

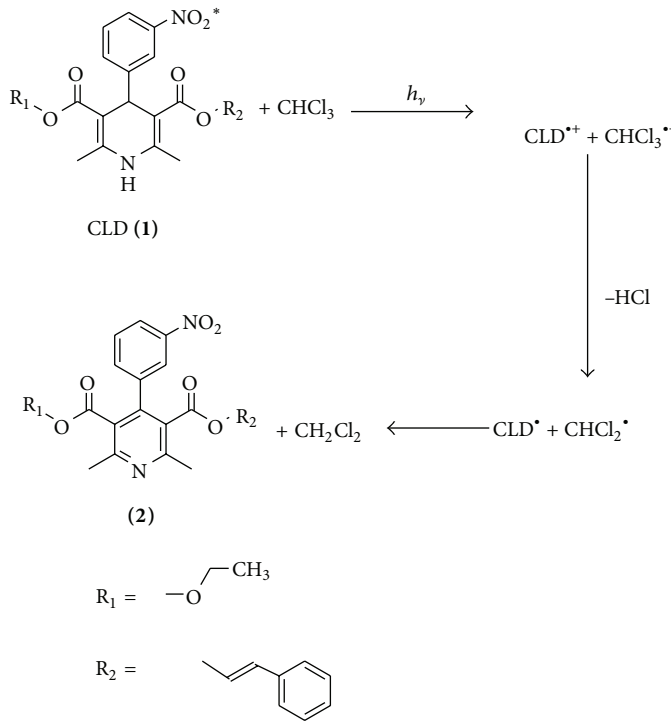
2-Methoxyethyl-3-phenyl-2-propenyl Pyridine Dihydro-2,6-dimethyl-4-(3-nitrophenyl) Pyridine-3,5-dicarboxylate (2). Yield: 125 mg (47%) HRMS calcd. For $C_{27}H_{26}N_2O_7$ 490.5045 found 490.5040; IR (KBr): 1680 (CO), 1350 (NO_2), 1530 (NO_2) cm^{-1}; ^{1}H-NMR (CD_3OD, δ, ppm) 7.84–8.40 (m, phenyl H), 2.5 (s, CH_3), 3.23 (s, OCH_3); ^{13}C-NMR (CD_3OD, δ, ppm) 1660 (CO), 148.8, 138.5, 133.4, 130.2, 122.0, 121.4 (Phenyl), 18.6 (CH_3); MS: m/z: 490 (M^+), 461 (M^+–OCH_3), 444 (M^+–NO_2).

3. Results and Discussion

Irradiation of Cilnidipine in chloroform under both aerobic and anaerobic conditions with Corex filtered light followed by purification of crude product by silica gel column chromatography afforded one major photoproduct, which was identified by their spectral studies as 2-methoxyethyl-3-phenyl-2-propenyl pyridine dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate (Scheme 1).



Scheme 2: Mechanistic pathway of photochemical aromatization of Cilnidipine under aerobic condition.



Scheme 3: Mechanistic pathway of photochemical aromatization of Cilnidipine under anaerobic condition.

The photoproduct formation can be rationalized by the involvement of different mechanism under aerobic and anaerobic conditions. Photoproduct formation under aerobic condition is purposed as photoinduced single electron transfer from Cilnidipine (CLD) to molecular oxygen results in the formation of a radical cation ($CLD^{+\bullet}$) and a superoxide radical anion ($O_2^{-\bullet}$). The generated $CLD^{+\bullet}$ cation radical may undergo fast deprotonation to give the $CLD^{\bullet}$ radical. The $CLD^{\bullet}$ radical further reacts with molecular oxygen to yield the pyridine photoproduct (**2**) and H_2O_2 (Scheme 2).

Under anaerobic condition photoproduct formed according to the proposed mechanism; excited Cilnidipine donates an electron to chloroform resulting in the formation of radical cation ($CLD^{+\bullet}$) and $CHCl_3^{-\bullet}$. Elimination of HCl from both intermediates leads to the formation of a radical pair of Cilnidipine ($CLD^{\bullet}$) and dichloromethyl ($CHCl_2^{\bullet}$)

radicals. Hydrogen abstraction by $CHCl_2^{\bullet}$ radical completes the reaction by formation of the photoproduct **2** and dichloromethane (Scheme 3).

The most interesting aspect of dihydropyridines can be attributed to the coenzyme reduced nicotinamide adenine dinucleotide (NADH). The importance of the oxidative reaction of these compounds is due to their similarity to the oxidative metabolism of these compounds with pharmaceutical activity in the liver to form pyridine derivatives, which become biologically inactive [18]. Hence, a convenient method for the conversion of 1,4-dihydropyridines to pyridine derivatives is important for the investigation of their metabolism and the result of the present investigation provides two suitable methods for the aromatization of 1,4-dihydropyridine.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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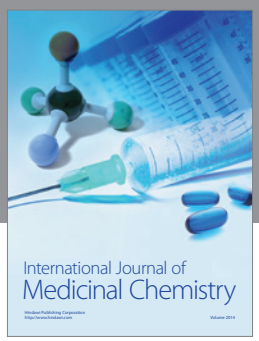

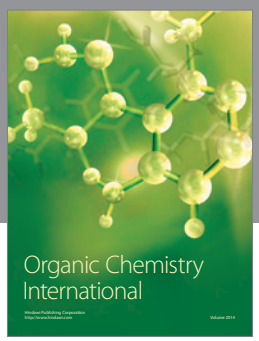

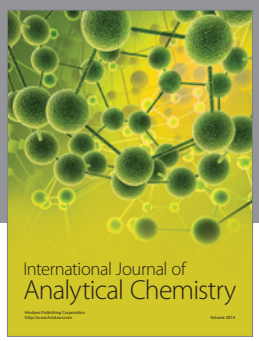

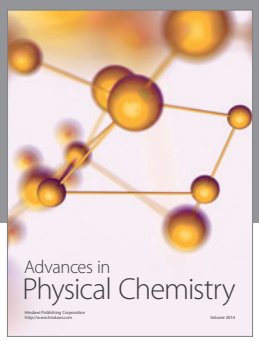

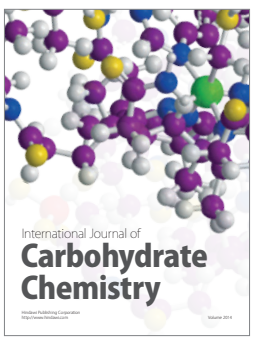

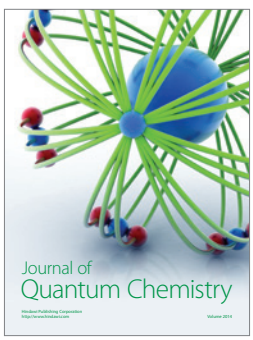

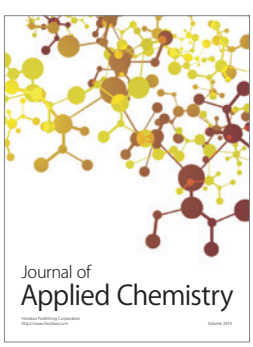

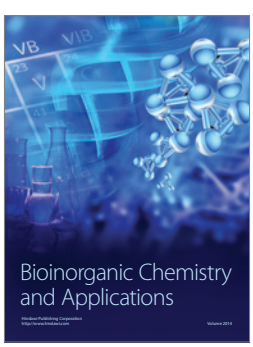

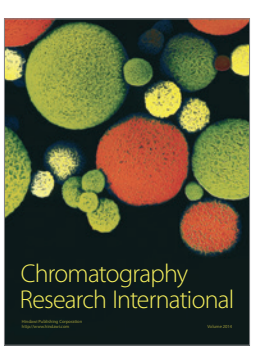

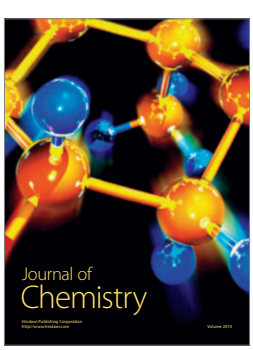

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