

Photodegradation of tenoxicam and lornoxicam

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ABSTRACT

Tenoxicam (**TNX**) and Lornoxicam (**LRX**) are nonsteroidal anti-inflammatory drugs (NSAIDs) that undergo photodegradation when photoirradiated with 254 nm radiation in methanol for 7 hours. Five main photodegradation products were isolated and characterized using different spectroscopic tools. A plausible mechanism to explain formation of these products is also presented.

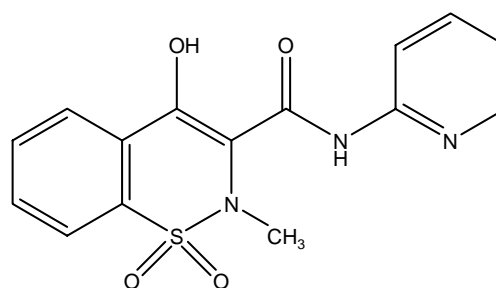
KEYWORDS: photodegradation, nonsteroidal anti-inflammatory, oxicams, tenoxicam, lornoxicam

INTRODUCTION

Oxicams are nonsteroidal anti-inflammatory drugs (NSAIDs) used for the treatment of rheumatic arthritis, osteoarthritis and post-operative inflammations [1, 2]. Several other functions of this group of drugs have been reported which include UV-protection and sensitization, chemoprevention and chemosuppression of cancer and finally their function as effective anti-oxidants [3-7].

Since 1980 when Piroxicam (**PRX**) (Scheme 1) was first launched as a lead compound of the oxicams into the European market for clinical use [8], new members of these pharmaceutical agents have been synthesized based on structure-activity relationships (SARs) and the isosteric substitution concept, which starts by substituting the lead compound with moieties of similar stereoelectronic features which might improve the pharmacological efficacy and other pharmacokinetic properties [9]. Several studies on

oxicams reported that, the pharmaceutical agents have some adverse skin reactions including, photoallergy and abnormal photosensitivity [2, 10]. These drawbacks were attributed to some of the photodegradation products or metabolite end products of the pharmaceutical agent [10-12]. Contradictory data concerning the photostability of the oxicams can be found in the literature. An aqueous solution of Piroxicam was found to be stable when exposed to sunlight for 72 hours [13]. On the other hand, Tenoxicam showed 50% loss of the drug when exposed to sunlight for 3 hours [14]. These diverse results prompted us to study the photodegradation of oxicams as part of ongoing research. Therefore, in this study we report the photodegradation of Tenoxicam (**TNX**) and Lornoxicam (**LRX**) as members of this pharmaceutical group of drugs into five main products. The photodegradation products were characterized using different spectroscopic tools. A plausible mechanism to explain formation of these products is also presented.



PRX

Scheme 1

EXPERIMENTAL

Instrumentation and chemicals

The NMRs were recorded on a 500 MHz NMR spectrometer (Bruker, DRX500). EI GC/MS spectra were recorded using a Shimadzu GC17A/GCMS-QP 5050A mass spectrometer equipped with a standard EI source. UV/VIS spectra were recorded on a Perkin Elmer Lambda 40 UV/VIS spectrometer. Melting points were measured on a Buchi B-540 and are given uncorrected. Photochemical reactions were performed with a RPR-100 Rayonet Photochemical Chamber Reactor (Southern New England Ultraviolet Company, Branford, USA) at 254 nm using quartz tubes. Tenoxicam and Lornoxicam were purchased from Kemprotec Limited United Kingdom and used directly without any further purification. All the chromatographic separations were performed on 20 x 20 cm or 5 x 20 cm Merck glass plates covered with silica gel 60 F254 layer thicknesses 0.25 mm.

General photolysis procedure

Tenoxicam (TNX) and Lornoxicam (LRX) 100 mg were dissolved in 100 mL methanol and irradiated at 254 nm in a RPR-100 Rayonet Photochemical Chamber Reactor for 7 hours. After concentration, the residue was subjected to chromatography on silica gel plates with 1% methanol in chloroform. The R_f values of the appropriate zones are given below.

N-Methyl-*N'*-(pyridin-2-yl) oxalamide (1)

It was obtained in 18-22% conversion as colorless powder after sublimation at 60-65°C under 60 mbar vacuum, and crystallization from diethyl ether and n-pentane (1:1), $R_f = 0.33$, mp: 120-121°C. IR (KBr): $\nu = 3350$ (NH), 1679 (C=O), 1685 (C=O) cm^{-1} . ^1H NMR (CDCl_3): $\delta = 3.59$ (s, 3H, CH₃), 7.14 (m, 1H), 7.51 (s, 1H), 7.77 (m, 1H), 8.20 (d, 1H), 8.38 (s, 1H, NH), 9.75 (s, 1H, NH). ^{13}C NMR (CDCl_3): $\delta = 26.5$, 77.5, 133.9, 120.8, 138.4, 148.4, 149.9, 157.9, and 159.9. MS: m/z (%) = 179 (M^+), 121 (100), 94 (21), 78 (44), 58 (23).

Methyl (pyridin-2-yl carbamoyl) formate (2)

It was obtained in 12-15% conversion as colorless powder after sublimation at 60-65°C under

60 mbar vacuum, and crystallization from diethyl ether and n-pentane (1:1), $R_f = 0.63$, mp: 102-103°C. IR (KBr): $\nu = 3364$ (NH), 1733 (C=O) 1700 (C=O) cm^{-1} . ^1H NMR (CDCl_3): $\delta = 4.00$ (s, 3H, CH₃), 7.14 (m, 1H), 7.79 (m, 1H), 8.26 (d, 1H), 8.37 d, 1H), 9.43 (s, 1H, NH). ^{13}C NMR (CDCl_3): $\delta = 54.1$, 114.3, 121.1, 138.7, 148.3, 149.8, 153.9, and 160.6. MS: m/z (%) = 180 (M^+) (16), 121 (84), 78 (100), 78 (45), 58.

N-Methyl-*N'*-(pyridin-2-yl carbamoyl) methanethioamide (3)

It was obtained in 12-14% conversion as pale yellow powder after sublimation at 60-65°C under 60 mbar vacuum, and crystallization from diethyl ether and n-pentane (1:1), $R_f = 0.78$, mp: 133-134°C. IR (KBr): $\nu = 3265$ (NH), 1683 (C=O) cm^{-1} . ^1H NMR (CDCl_3): $\delta = 3.33$ (s, 3H, CH₃), 7.78 (m, 1H), 8.22 (m, 1H), 8.41 (m, 1H), 9.56 (s, 1H, NH), 10.59 (s, 1H, NH). ^{13}C NMR (CDCl_3): $\delta = 33.1$, 113.7, 120.8, 138.4, 148.5, 150.0, 156.2, and 186.4. $\text{C}_8\text{H}_9\text{N}_3\text{OS}$ Mwt = 195.24 and m/z (%) = 197 ($\text{M}^+ + 2$), 196 ($\text{M}^+ + 1$), 195 (M^+) (14), 121 (100), 94 (17), 78 (30) %.

N-Methyl-3-oxo-thieno [3,2-d]-1,2-thiazole 1,1-dioxides (4)

These compounds were detected and identified by GC-MS:

4a; $\text{C}_6\text{H}_5\text{NO}_3\text{S}_2$ to give MS: m/z (%) = 203 (50), 139 (65), 110 (100), 82 (50).

4b; $\text{C}_6\text{H}_6\text{ClNO}_3\text{S}_2$ to give MS: m/z (%) = 239 (40), 209 (30), 176 (75), 145 (100), 109 (65), 81 (75).

Methyl thiophene-2-carboxylates (5)

These compounds were detected and identified by GC-MS:

5a; $\text{C}_6\text{H}_6\text{O}_2\text{S}$ to give 142.18, MS: m/z (%) = 142 (50), 111 (100), 83 (23), 39 (40).

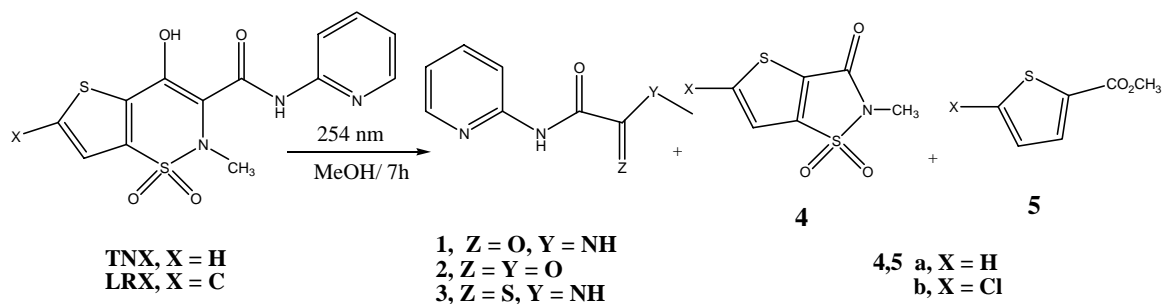
5b; $\text{C}_6\text{H}_4\text{ClO}_2\text{S}$ to give 176.62, MS: m/z (%) = 176 (50), 145 (100), 117 (20), 81 (15), 73 (45).

RESULTS AND DISCUSSION

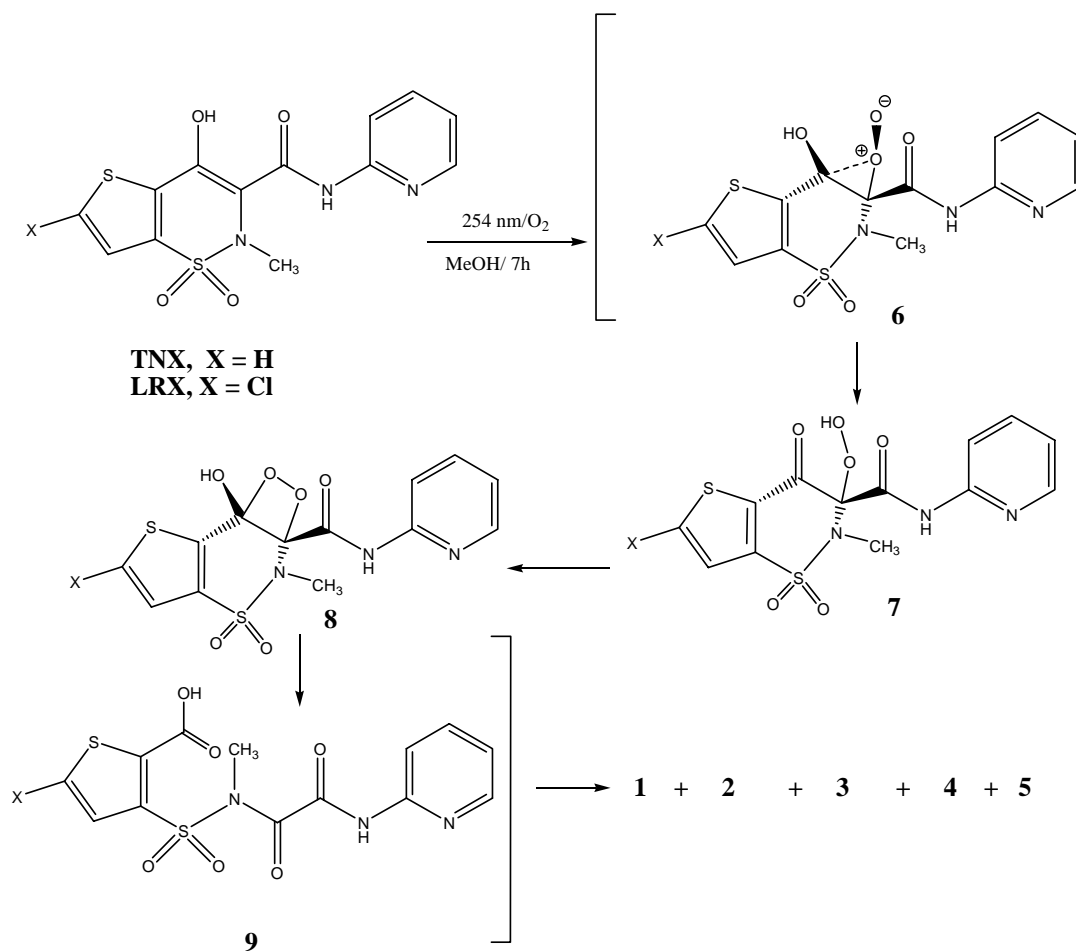
In a previous photochemical study dealing with Piroxicam and its synthesized analogues we reported the photodegradation of the pharmaceutical agent to the *N*-methyl saccharin as a main product. On the other hand, a new photochemical isomerization was noticed with the synthesized

analogues and the 1,2-benzothiazine ring system converted into the 1,3-benzothiazine ring system [15]. In this short communication we report the photolysis of Tenoxicam (TNX) and Lornoxicam (LRX) as a part of an ongoing photochemical

research project dealing with oxicams and analogues. From the chemical structure point of view, Tenoxicam and Lornoxicam are thienothiazine oxicams. However the Piroxicam (PRX), Meloxicam (MLX) and Droxicam (DRX) the other members



Scheme 2



Scheme 3

of the group are benzothiazine oxicams, i.e. the thiazine ring is the common ring system of all oxicams. Now, when the methanolic solution of TNX and LRX irradiated at 254 nm for 7 hours, five main photodegradation products were isolated and identified namely *N*-methyl-*N'*-(pyridin-2-yl) oxalamide (1), methyl (pyridin-2-yl carbamoyl) formate (2), *N*-methyl-*N'*-(pyridin-2-yl carbamoyl) methanethioamide (3), *N*-Methyl-3-oxo-thieno[3,2-d]-1,2-thiazole1,1-dioxide (4) and methyl thiophene-2-carboxylates (5a, b) (Scheme 2).

The structures of the photodegradation products were assigned by ¹H-NMR, ¹³C-NMR, 2D-NMR, IR and GC-MS. A plausible mechanism that explains the formation of these photolysis products is depicted in (Scheme 3).

Now, photoexcited oxicam (TNX or LRX) reacts with singlet oxygen to form perepoxide **6** which rearranges to dioxetane intermediate **8** via intermediate **7**. The assumption of the perepoxide intermediate formation from the interaction of singlet oxygen and oxicam prior to dioxetane intermediate (2+2 cycloaddition product) in solvents with the largest π^* values was reported in PRX photolysis and explained in terms of solvent-substrate interactions [16-17]. Direct formation of **7** via an en-type reaction of the excited substrate with singlet oxygen also can't be rolled out. Subsequent ring cleavage leads to **9**. The later intermediate undergoes either nucleophilic attack by the solvent lone pair to form **2** and **4** or extrusion of sulphur dioxide and methylation to yield **1** and **5**. The formation of these products is in compatible with reported data of oxidation of oxicams by leukocyte peroxidases and hydrogen peroxide [18, 19]. Finally, the formation of photoproduct **3** is quiet abnormal for such photodegradation and was not detected or reported as one of the oxidation products or metabolites of such oxicams.

In conclusion, this is a preliminary result concerning the photolysis of Tenoxicam and Lornoxicam as thienothiazine oxicams. The behavior is nearly compatible with that of Piroxicam at the same condition from the products point of view. Products **1** and **2** were previously reported [20] as photodegradation products of Piroxicam with *N*-methyl saccharin which is the

analogue of **4** in the presented study. However, products **3**, **4** and **5** are novel photodegradation products which are not previously reported under such conditions. Therefore, a more detailed study concerning formation of these products, the mechanistic pathways and solvent effect is under way.

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