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Der Chemica Sinica, 2012, 3(3):753-758

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Photochemical behavior and photobiological action of photosensitive drug Tolbutamide

Anamika Gupta*, Mohd. Rehan Zaheer, Waseem Ahmad and Jawaid Iqbal

Department of Chemistry, Aligarh Muslim University, Aligarh(U.P.), India

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ABSTRACT

*Irradiation of sulfonamide derived oral antidiabetic drug, tolbutamide (N-[(butylamino) carbonyl]-4-methylbenzenesulfonamide,***1***) in a phosphate buffered solution under aerobic atmosphere afforded two photoproducts by cleavage of S-N and C (O)-N bonds of urea units. When irradiated with linoleic acid it photoinduced lipid peroxidation. The insignificant decrease in lipid peroxidation test under argon atmosphere indicates that tolbutamide is capable of photosensitizing lipids through a process where oxygen does not play a principal role. Also the efficient inhibition of lipid peroxidation by well established radical scavengers GSH, confirmed the involvement of a type I mechanism*

Keywords: Tolbutamide, photochemistry, phototoxicity, lipid peroxidation.

INTRODUCTION

Biological photosensitization induced by drugs has been the object of a considerable amount of attention especially in the last decade. Such interest has been promoted by the fact that even though many drugs are excellent therapeutically agents but they are also known to often cause phototoxic and/or photo allergic phenomena. Phototoxic disorders have a high incidence, whereas photoallergic reactions are much less frequent in human population [1]. The primary event in any photosensitization process is the absorption of a photon, and the following free radical and singlet oxygen generation by photoexcited drug molecules may seem to be the principal intermediate species in the phototoxic response [2,3]. Several reviews concerning the mechanisms of both drug photodegradation and photosensitization were recently published [4,5] However, little information is available for other widely used photosenstizing drugs [6] whose exact molecular mechanism of their phototoxicity are not as well understood.It is therefore important to study the photochemistry of each individual photosensitizing drug that may be exposed to UV light.

The sulfonamide group is considered as a chromophores which is present in a number of biologically active molecules, have been clinically used for many years and found to posses a large number of biological activities, including antimicrobial [7,8], carbonic anhydrase inhibitors [9-11], anti-cancer [12] and as an anti-inflammatory agents [13]. Benzene sulphonamide, derived from sulphonamide family have attracted intense interest in recent years as they are important clinical agents, mainly are used in the treatment of gastro-intestinal – duodenal ulcers, neurological disorders, glaucoma, altitude sickness and for some forms of tumor [14] and some benzene sulphonamide is also clinically used as a antidibetic agent has been associated in some patient with the appearance

of phototoxic effect such as erythema, flaring and urticarial weal [15]. These compound have been recognized as a very good photo sensitizers in clinical test and in cell culture[16]. Although it is very useful but it can produced adverse photo biological effect such as clinical photosensitization which occurs on the skin of patient [17].

Tolbutamide (1) is a benzene sulphonamide derivative and it is a first generation potassium channel blocker, oral hypoglycemic drug [18-20]. It is structurally similar to acetohexamide, chlorpropamide and tolazamide. This drug may be used in the management of type II diabetes if diet alone is not effective. Tolbutamide stimulates the secretion of insulin by the pancreas. Since the pancreas must synthesize insulin in order for this drug to work, it is not effective in the management of type I diabetes. It generally has a short duration of action due to its rapid metabolism, and is therefore safe for use in elderly diabetics [21]. Tolbutamide with sulfonamide chromophores is expected to be photolabile and probable photo sensitizer of biological substrate and is exhibited phototoxic effect in patient treated with this drug [22,23]. In continuation of our previous work we became interested in investigating the photochemical behavior of the tolbutamide under aerobic condition in UV- B light for an appropriate correlation to its phototoxicity. Photolysis of tolbutamide in presence of oxygen resultant in the formation of two degradation products identified as **2** and **3** from their spectral (^{1}H-NMR, ^{13}C-NMR, IR and mass spectra) properties. Scheme-1 Product2 and 3 presumably produced by the cleavage of CO-N bond of tolbutamide (1).

MATERIALS AND METHODS

Apparatus and Chemicals

All chemicals used were of analytical and pharmaceutical grade. Tolbutamide (1) was extracted from commercial medicament Rastinone Aventis Pharma Limited (India) .The purity of drug extracted was checked by TLC and comparing its melting point with the literature value. Rose Bengal and gluthione (GSH) were purchased from Sigma Aldrich, India. Photochemical reactions were carried out in quartz fitted immersion well photochemical reactor equipped with 400W medium pressure mercury vapour lamp with continuous supply of water. UV spectra were recorded on a Shimadzu 160 A Instrument. IR spectra were recorded in KBr discs on a Perkin Elmer model spectrum RXI. ^{1}H-N.M.R and ^{13}C-N.M.R Spectra were recorded on a Bruker Avance –DRX -300 Spectrometer using $SiMe_4$ as internal standard and $CDCl_3$ as solvent. E/MS were obtained on a VG-ZAB-HS mass spectrometer. High resolution mass spectra were determined with a VG-ZAB-BEQ 9 spectrometer at 70 eV ionization voltages. Column chromatography was performed on silica gel 60 (70-230mesh).thin layer chromatography (TLC) was carried on Merck silica gel60 F_{254}(0.2mm thick plates).

Photoirradiation procedure

Tolbutamide (1) 285 mg (1.06 mM) was dissolved in 400 ml methanol and irradiated at room temperature in the Rayonet photochemical reactor. Progress of the reaction was monitored by thin layer chromatography (chloroform-methanol, 98:2). After the irradiation of mixture for 71 hr the solvent was removed in a rotary evaporator and crude product was subjected to silica gel column chromatography elution with CH_3CN/H_2O (30:70,v/v) on silica column gave 2 and 3 as products which exhibited following spectral properties.

Butanamine-1 (2):

Yield:60mg (21.8 %); UV λ_{max} (MeOH) 210 nm ; HRMS calcd. for (M^+) $C_4H_{11}N$ 73.33,found 73.20, IR(KBr): 2880, 2967, 3350, 800,1090 cm^{-1},^{1}HNMR($CDCl_3$, δ,ppm) δ 2.7 (t, J=7,2H, H-1), 1.43 (m,4H,H-3&H-4), 1.16 (s,2H, NH_2), 0.92(t, J=7 Hz,3H, H-4) ; ^{13}C-NMR($CDCl_3$,δ,ppm) δ 41.8 (C-1), 35.0 (C-2), 19.9 (C-3), 13.8 (C-4), MS: m/z: 73 (M^+), 30(M^+-CH_2=$^+NH_2$).

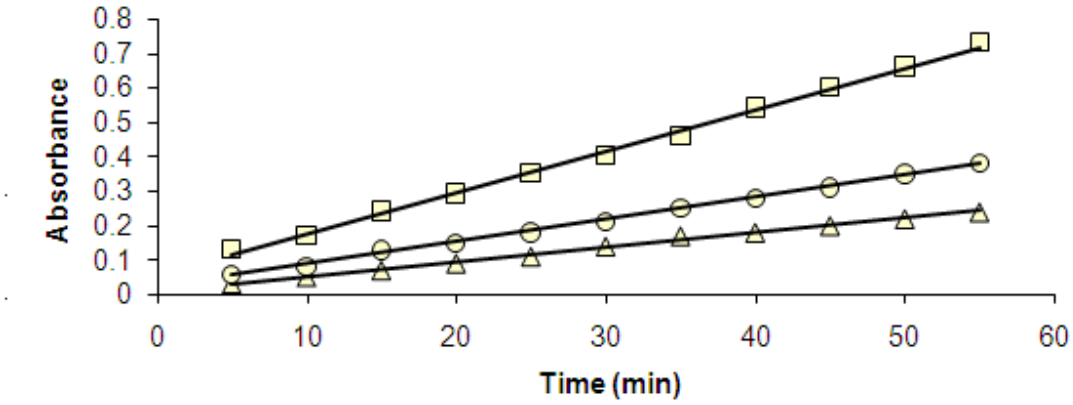
N-tosylformamide (3):

Yield: 95mg(34.5 %); UV λ_{max} (MeOH) 261 nm and 210 nm ; HRMS calcd. for (M^+) $C_8H_9NO_3S$ 199.2270, found 199.2268; IR(KBr): 3359, 3325cm^{-1}(NH), 1340, 1160cm^{-1} (SO_2); ^{1}H-NMR ($CDCl_3$, δ, ppm) δ 8.75(s,1H,CHO) 7.82 (d, J=7.9 Hz,2H,tolyl H-3 and H-5) 7.32 (d, J=7.9Hz ,2H,tolyl H-2 and H-6),2.38 (s,3H tolyl,CH_3), 2.0(s,1H,NH), ^{13}C- NMR ($CDCl_3$, δ, ppm)δ 175.01 (CO,CHO),142.6,136.9, 129.8 128.3, 23.4, (C-1,C-4, C-2 and C-6, C-3andC-5,$CH_3$of the toluene moiety). MS: m/z: 199(M^+), 185(M^+-CH_3), 170(M^+-HCO), 155(M^+-HCONH), 92(M^+-$HCONHSO_2$).

To observe a possible quencher effect of the tolbutamide **(1)** on singlet oxygen ($^1O_2$), tolbutamide **(1)** was also irradiated in presence of photosensitizer rose bengal and maintaining all other experimental conditions the same.

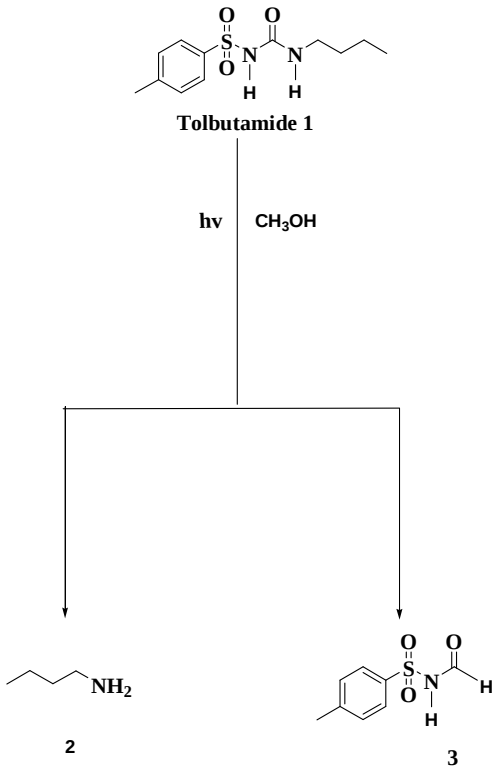
Photosensitized peroxidation of linoleic acid

Phosphate buffered solution of Linoleic acid (1×10^{-3} M) was irradiated in the presence of compound 1 and also in a pre-irradiated solution of 1(1×10^{-5}**)**. The formation of dienic hydroperoxides was monitored by UV–spectra photometry, by the appearance and progressive increases of a new band at λ=233 nm [24] (Fig-1). The lipid peroxidation test was repeated in the presence of reduced glutathione (GSH) as radical scavenger. This test was also carried under argon atmosphere.



[□Linoleic acid+1(hv) 0 Linoleic acid (hv) ▲ Linoleic acid + 1(dark)]

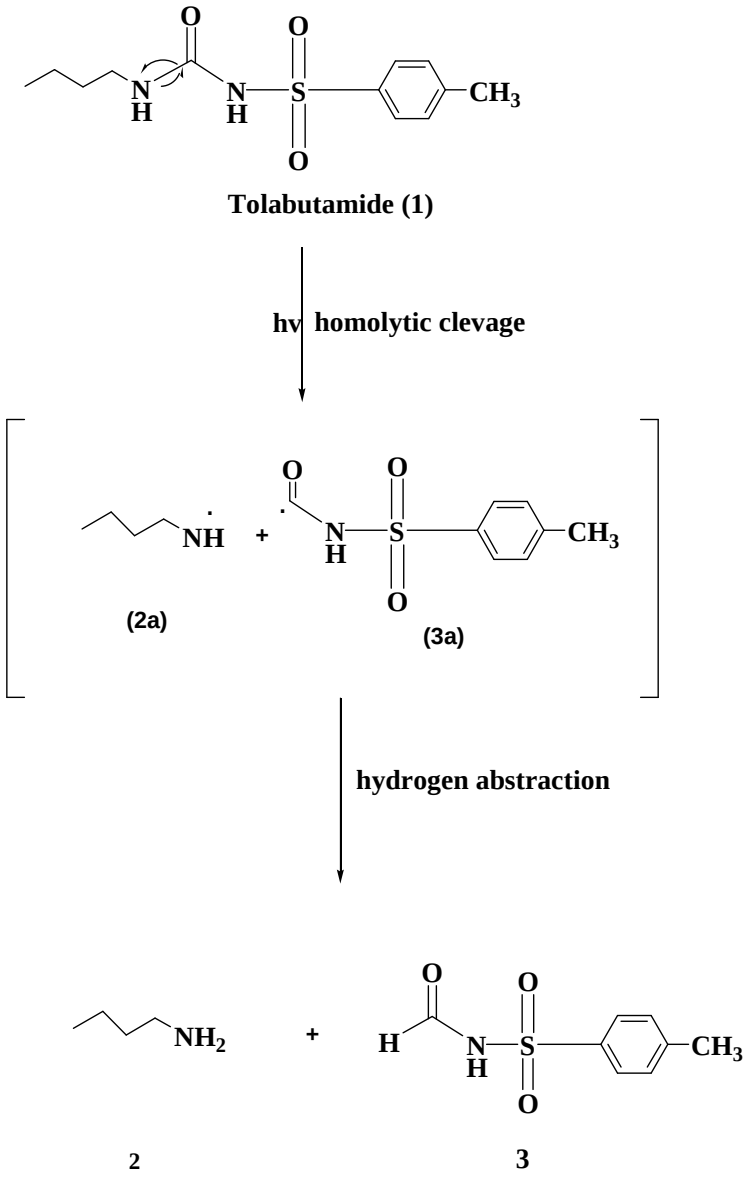
Fig-1- Photoperoxidation of linoleic acid (L, 10^{-3}M) sensitized by tolbutamide (1)



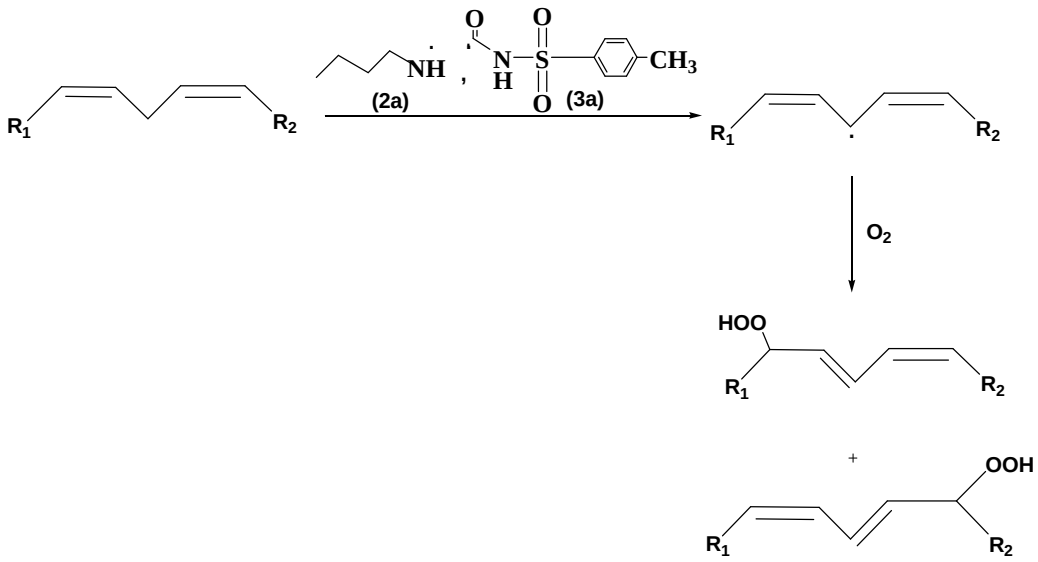
Scheme1: Photoproducts of Tolbutamide

Tolbutamide undergoes homolytic cleavage (rupture of) CO-NH bond resulting in the generation of two intermediates radicals (2a) and (3a) (Scheme2).

Hydrogen abstraction by intermediate radicals generated in tolbutamide photodegradation leads to lipid peroxidation (Scheme-3).The efficient inhibition of lipid peroxidation by well-established radical scavengers GSH, confirmed the involvement of type I mechanism. Lipid peroxidations certainly correlate with damage produced in the cell membranes. The phototoxicity mechanism for tolbutamide most probably involves reaction of free radical intermediates and photoproducts with cellular components. The insignificant decrease in lipid peroxidation test under argon atmosphere indicates that tolbutamide is capable of photosensitizing lipids through a process where oxygen does not play principal role.



Scheme-2
Mechanistic pathways of photodegradation of tolbutamide



Scheme-3

RESULTS AND DISCUSSION

Irradiation of methanolic solution of (1) under oxygen atmosphere with a medium pressure mercury vapour lamp in an immersion well type photo reactor gave Butanamine-1(2), N-tosylformamide (3) as photoproducts (Scheme- 1) which were characterized from their spectral studies. No degradation of tolbutamide was observed when irradiation was carried out in the presence of rose bengal using a potassium chromate solution and maintaining all other experimental conditions the same. Therefore, the interaction with or quenching of singlet oxygen, by tolbutamide was negligible.

The studies of phototoxicity carried out in this work may help to explain the damage produced in protein and organs. The observations in this work may contribute to elucidate the observed accumulations and damaging activity of oxidized proteins during aging and in pathologies such as diabetes, atherosclerosis and neurodegenerative diseases. Lipid photoperoxidation certainly correlates the damage produced in the cell membranes. The phototoxicity mechanism for tolbutamide most probably involves reaction of free radical species than singlet oxygen, super oxide anion or photoproducts with cellular components. The result obtained may be very useful from medical point of view to perform the appropriate screening of phototoxicity in vitro before introducing drugs and chemicals in to chemical therapy.

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