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ORIGINAL ARTICLE

Photodegradation of trimeprazine triggered by self-photogenerated singlet molecular oxygen

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Abstract The antihistaminic drug trimeprazine (**1**, also known as alimemazine) is photolabile under UV-A light in aerobic conditions. Irradiation of a methanol solution of trimeprazine produces two photoproducts which were isolated as N,N2-trimethyl-3-(10*H*-phenothiazin-10-yl sulfoxide) propan-1-amine (**2**) and N,2-dimethyl-3-(10*H*-phenothiazin-10-yl) propan-1-amine (**4**). The formation of products was explained by the oxidative photodegradation of trimeprazine in an irreversible trapping of the self-photogenerated $^1O_2$ by the type II photodynamic action of the drug. The generation of singlet oxygen during photolysis of trimeprazine was confirmed by singlet oxygen scavenger 2,5-dimethylfuran (2,5-DMF).

1. Introduction

Recently, much attention has turned to the problem of biological photosensitization by drugs. Indeed, despite their excellent therapeutic activity, many drugs can induce phototoxic, photoallergic and photomutagenic phenomena, strictly related to the drug's photochemical reactivity (Sortino et al., 2003) Photosensitization reactions leading to phototoxicity are generally considered as belonging to either the type I (radical mediated) or type II (singlet oxygen mediated) (Cosa, 2004; Ouedraogo and Redmond, 2003). There are photosensitizing drugs of varied structural variety and significant variations in the phototoxic mechanisms must be expected depending on the difference in structural features. The variety and number of phototoxic drugs is large and a relationship between structure and the mechanism of chemical reaction that causes the *in vivo* phototoxicity is not available (Vargas and Rivas, 1996) and it is therefore necessary to investigate the photochemistry of every photosensitizing drug.

Phenothiazine derivatives have found a large variety of applications as dyes, antioxidants, and drugs. Accordingly, the antihistaminic and neuroleptic properties of some phenothiazine derivatives are well-known (Asghar and Khan, 2008; Elisei et al., 2002). Moreover, given the phototoxicity of these drugs (Onoue and Tsuda,2006; Miolo et al., 2006) a large number of investigations on the photochemical properties of these substances have been carried out. Several reports also indicate that irradiation of phenothiazines can produce singlet oxygen (Tranchin et al., 1998) but, surprisingly, very few studies have dealt with the chemical reactivity of $^1O_2$ with the phenothiazines themselves.

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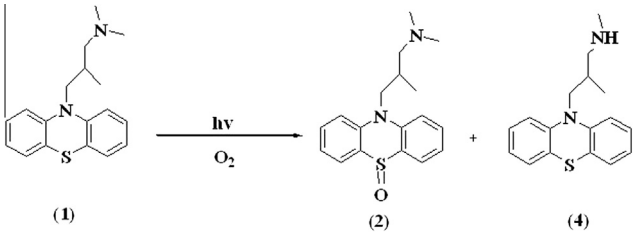

Scheme 1 Oxidative Photodegradation products of trimeprazine.

Trimeprazine (also known as Alimemazine) is a tricyclic Phenothiazine derivative (Lutka and Koziara, 2000). It is in the same class of drugs as chlorpromazine (Thorazine) and trifluoperazine (Stelazine); however, unlike the other drugs in this class, trimeprazine is not used clinically as an anti-psychotic. It acts as anti-histamine, a sedative, and an anti-emetic (anti-nausea) (Bello, 2011). Interest in the photo reactivity of trimeprazine arises from the clinical and pharmacological reports of phototoxic effects demonstrated by this drug (Mio et al., 1999; Quintero and Miranda, 2000).

In pursuance of our interest in the photochemical reactions involved in the phototoxicity of the photosensitizing drugs and their mechanisms, herein we have examined the photo behaviour of the antihistaminic drug trimeprazine (a phenothiazine derivative) under aerobic condition. Photolysis of trimeprazine (**1**) in the presence of oxygen resulted in the formation of two photodegradation products, identified as **2** and **4** from their spectral (IR, ^{1}H NMR, ^{13}C NMR, mass spectra) properties (Scheme 1). The products are formed by oxidative photodegradation of trimeprazine in an irreversible trapping of the self-photogenerated $^1O_2$ in the type II photodynamic action of the drug.

2. Experimental

2.1. Apparatus and chemicals

All chemicals used were of analytical grade. Pure Trimeprazine 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

A solution of Trimeprazine (275 mg, 0.7 mM) in methanol (400 ml) under aerobic condition was irradiated for 1 h in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co; Model RPR-208 equipped with four RUL-350 nm fluorescence lamps) for the complete conversion of reactant. Progress of the reaction was monitored by thin layer chromatography (chloroform–methanol, 98:2). At the end of the reaction formation of two major photoproducts were indicated on TLC and photoproducts were isolated by eluting with dichloromethane–ethyl ether (1:1, v/v) on a silica column. The photoproducts were identified as, N,N2-trimethyl-3-(10H-phenothiazin-10-yl sulfoxide) propan-1-amine (**2**) and N,2-dimethyl-3-(10H-phenothiazin-10-yl) propan-1-amine (**4**) from the following spectral properties:

Table 1 Effect of triplet energies of different sensitizers on the yields of products.

Sensitizer	Triplet energy (kcal /mole)	Yields of product (%) (2 + 4)
Methylene blue	33.5–34.0	60.9 (34.3 + 26.6)
Rose bengal	39.2–42.2	59.5 (32.3 + 27.2)
Riboflavin	57.8	50.4 (26.5 + 23.9)
Benzophenone	68.6–69.1	49.1 (25.1 + 24.0)

2.3. N,N2-trimethyl-3-(10H-phenothiazin-10-yl sulfoxide) propan-1-amine (2)

Yield: 95 mg (34.5%); HRMS calcd. for (M^+) $C_{18}H_{22}N_2OS$ 314.1453. Found 314.1448; IR (KBr, cm^{-1}): 3416, 2965, 1388, 1301, 1270, 1209, 1055 (SO), 978, 763. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.12–6.9 (m, 8 H, arom), 4.60 (d, J = 7.3 Hz, 2 H, H-15), 2.32 (s, 6 H, H-19, H-20), 2.27 (d, J = 7.4 Hz, 2 H, H-17), 2.13 (m, 1 H, H-16), 1.02 (d, J = 6.0 Hz, 3 H, H-21) ppm. ^{13}C NMR (CD_3OD, 300 MHz): 145.1, 131.0, 128.6, 119.3, 118.2, 62.2, 55.3, 36.1, 32.1 16.0 ppm. MS: m/z: 314 (M^+), 298 (M^+-16), 214 (M^+-100).

2.4. N,2-dimethyl-3-(10H-phenothiazin-10-yl) propan-1-amine (4)

Yield: 75 mg (27.2%); HRMS calcd. for (M^+) $C_{17}H_{20}N_2S$ 284.4191. Found 284.4185; IR (KBr, cm^{-1}): 1388, 1301, 1270, 1209, 978, 763. ^{1}H NMR (CD_3OD, 300 MHz): δ 7.12–6.9 (m, 8H, arom), 4.50 (d, J = 7.3 Hz, 2 H, H-15), 2.38 (s, 3 H, H-19), 2.26 (d, J = 7.4 Hz, 2 H, H-17), 2.14 (m, 1 H, H-16), 1.02 (d, J = 6.0 Hz, 3 H, H-20) ppm. ^{13}C NMR (CD_3OD, 300 MHz): δ 145.2, 131.1, 128.7, 119.4, 118.3, 62.3, 55.4, 36.2, 32.2, 15.9 ppm. MS: m/z: 284 (M^+), 198 (M^+-86).

2.5. Singlet oxygen detection

In order to confirm the role of singlet oxygen $^1O_2$ as a trigger of trimeprazine (TMPZ) photodecomposition, photolysis was performed under the same experimental condition but now in the presence of 2,5-dimethylfuran (2,5-DMF) which is normally used as a trap for singlet oxygen ($^1O_2$) (Gollnick and Griesbeck, 1983).

Similar experiment was also carried out by using different sensitizers such as methylene blue, rose bengal, riboflavin, and benzophenone to study the effect of triplet energy of sensitizer on the percentage yields of products (Table 1).

3. Results and discussion

The two major photoproducts, N,N2-trimethyl-3-(10H-phenothiazin-10-yl sulfoxide) propan-1-amine (**2**) and N,2-dimethyl-3-(10H-phenothiazin-10-yl) propan-1-amine (**4**), which were