Journal of Photochemistry and Photobiology A: Chemistry 298 (2015) 55–61

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Comparison of photoreactions of flutamide in acetonitrile and 2-propanol solvents in the absence of cage-forming compounds

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ARTICLE INFO

Article history:
Received 13 July 2014
Received in revised form 2 October 2014
Accepted 10 October 2014
Available online 18 October 2014

ABSTRACT

Flutamide(2-methyl-*N*-[4-nitro-3-(trifluoromethylphenyl)]propanamide) is a widely used anti-cancer drug. It has been reported that photodermatosis is occasionally induced when an individual taking flutamide is exposed to sunlight. In this study, we found that flutamide undergoes different photoreactions in two different solvents: acetonitrile and 2-propanol. The photo-induced nitro–nitrite rearrangement was the predominant reaction when a flutamide solution in acetonitrile was irradiated with UV light, and phenoxy radicals and nitrogen monoxide were generated. The nitrogen monoxide recombined with the phenoxy radical at the *ortho* position and was oxidized by the oxygen dissolved in the acetonitrile. The final product was *o*-nitrophenol derivative. However, the photoreduction of the nitro group followed by solvolysis of the trifluoromethyl group was observed when a flutamide solution in 2-propanol was irradiated with UV light. The three fluorine atoms in the trifluoromethyl group were eliminated by being nucleophilically attacked by a solvent molecule, resulting in an ester bond with 2-propanol being formed.

1. Introduction

Aromatic nitro compounds are known to undergo various photoreactions, such as photosubstitution, photoredox reactions, photodissociation and photo-induced nitro–nitrite rearrangement [1–17]. Photosubstitution and photoredox reactions have been well investigated [1–11], but photodissociation and nitro–nitrite rearrangement have not yet been fully elucidated [10–17]. Nitro–nitrite rearrangement and photodissociation have low reaction efficiencies, and the short-lived intermediates of these reactions are difficult to observe. Chapman et al. proposed a nitro–nitrite rearrangement reaction mechanism [13] in which nitro–nitrite rearrangement arises from an $n\pi^*$ excited state provided by a specific configuration of the nitro group and aromatic ring. This configuration is the nitro group being held almost perpendicular to the plane of the aromatic ring, forming an oxaziridine ring. This three-membered ring immediately collapses and generates a nitrite group, which is converted into a hydroxyl group by the cleavage of the O—N bond.

Flutamide is an aromatic nitro compound that is widely used as a medical treatment [18–20]. Flutamide has been reported to undergo nitro–nitrite rearrangement [21–25]. It is used as an endocrine-system therapy for advanced prostate cancer, and it is converted into the more pharmacologically active metabolite 2-hydroxyflutamide by first pass metabolism in the human liver. The most deleterious side effect of flutamide is its hepatotoxicity, and the pathogenic mechanism related to the enzyme responsible for metabolizing flutamide has been investigated [26,27]. However, it has been reported that when a patient is exposed to sunlight, photodermatosis is a rare side effect of flutamide treatment, with cutaneous symptoms such as erythema, pruritus, and vitiligo appearing [28,29]. This side effect indicates that flutamide is potentially photoreactive within a living organism. Therefore, studying the photochemistry of flutamide is expected to be useful for elucidating the mechanism involved in the pathogenesis of photodermatosis. From a photochemical and photophysical viewpoint, it has been shown in some studies that flutamide photodecomposes at the nitro group when exposed to UV irradiation under various experimental conditions [21–25]. Sortino et al. conducted irradiation experiments in inhomogeneous aqueous solutions using cage-forming products such as β-cyclodextrin. Udagawa et al. also investigated the photochemistry of flutamide using the magnetic field effect and cage-forming compounds [25]. In their studies, irradiation experiments were

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http://dx.doi.org/10.1016/j.jphotochem.2014.10.009
1010-6030/

conducted in aqueous solutions, such as a phosphate buffer, meaning that cage-forming compounds were required to increase the solubility of flutamide in the water. Both Sortino et al. and Udagawa et al. suggested that photoreduction reactions will occur only in inhomogeneous solutions, that is, photoreduction is a bimolecular reaction between flutamide and the cage-forming compound *via* a hydrogen abstraction reaction [23–25]. Moreover, Udagawa et al. found that the photoreduction process occurred in the excited triplet state of flutamide and suggested that only a nitro–nitrite rearrangement product was found when flutamide was irradiated in a phosphate buffer in the absence of a cage-forming compound. Likewise, Sortino et al. suggested that the nitro–nitrite rearrangement of flutamide is the only photoreaction that will occur in a homogeneous solution, such as in methanol or 2-propanol [21]. It is surprising that nitro–nitrite rearrangement occurred as a single photoreaction in a homogeneous solution because there are a wide variety of photoreactions of aromatic nitro compounds, including photoredox reactions, photosubstitution, and photodissociation [1–4]. The occurrences of these reactions of flutamide in different media have been insufficiently investigated; hence, the photoreactions of flutamide need to be further studied to obtain more experimental data. This is especially true for unimolecular photoreactions of flutamide in homogeneous solutions. Therefore, we investigated the photoreactions of flutamide under different experimental conditions than those used in previous studies, which used homogeneous solutions in organic solvents. We attempted to determine if various photoreactions could occur by conducting long hour irradiation experiments in highly reactive solutions.

Some medicines are known to be photoreactive, and some lose their pharmacological effect when exposed to light [30]. The photodecomposition of a photolabile drug can cause, as well as the loss of its pharmacological effect, the *in vivo* generation of free radicals. If a photoreactive drug can generate free radicals, the drug can possibly act as a hapten, causing immunogenicity, inducing photoallergic reactions, when bound to a carrier protein. As well as the nitro group, the trifluoromethyl group can photodecompose. In previous studies, it has been shown that some benzotrifluoride derivatives are photoreactive and that the fluorine atoms can easily be eliminated *via* solvolysis [31–33]. Furthermore, it has been found that fluorobenzene derivatives can undergo photodissociation to release fluorine atoms [34]. This is remarkable because the fluorine atom is generally unreactive in thermal dissociation reactions. The trifluoromethyl group is included in many pharmaceuticals, such as lansoprazole, efavirenz, and bicartamide because of its electron-withdrawing properties. These medicines have not yet been reported to induce photoallergies, but new medicines having benzotrifluoride structure or fluorobenzene structure that may be developed in the future might induce photoallergies. It is, therefore, important to study the photoreactivity of the trifluoromethyl group of flutamide. It would be difficult to study the induction of photodermatosis by flutamide *in vivo* because photodermatosis is a rare side effect, with a very low frequency of onset. Therefore, we attempted to clarify the photosensitivity of flutamide to UV *in vitro* before designing *in vivo* trials. The photoreaction of flutamide was examined in homogeneous solutions, such as methanol, 2-propanol and phosphate buffer, in previous studies. Those studies showed that nitro–nitrite rearrangement was the only route to the formation of photoproducts of flutamide in a homogeneous solution. In this study, we irradiated UV to flutamide in a homogeneous organic solvent, acetonitrile or 2-propanol, in which flutamide was more soluble than in water. The irradiation experiments were conducted under more reactive conditions compared with the preceding studies, the solutions being irradiated with UV for long periods in highly reactive solvents. To investigate the photoreactions of flutamide will allow us to predict the photoreactivity of flutamide *in vivo*.

2. Materials and methods

2.1. Chemicals

Flutamide was purchased from Tokyoukasei and used as-received. Flutamide solutions (at 1.0×10^{-3} M) were prepared in acetonitrile (HPLC grade; Nacalai Tesque) and 2-propanol (HPLC grade; Kantou Chemical). A 1.0×10^{-4} M solution in 2-propanol was also prepared. Deuterated acetonitrile and 2-propanol were prepared so that the origins of hydrogen atoms in the reaction products could be identified. A solution of product 4 (at 1×10^{-3} M) in 2-propanol was prepared so that the mechanism involved in the formation of product 5 could be investigated. Dissolved oxygen was removed from aerated sample solutions using the freeze–thaw method, in which a solution was frozen and thawed three times and then sealed from the atmosphere.

2.2. Irradiation experiments

Flutamide and product 4 were irradiated with UV produced using a super-high pressure mercury lamp (500 W, Ushio Inc.) and filtered through UV-29 (Toshiba) and cylindrical cell filter filled with distilled water to remove infrared light. Irradiation experiments using deuterated solvents were conducted using the same apparatus.

2.2.1. Analytical methods and identification of the photoproducts

The photoproducts were identified by comparing their gas chromatography–mass spectrometry (GC–MS) retention times and fragmentation patterns with those of authentic compounds. The authentic compounds matching products 3–6 were synthesized, and their structures was determinate by GC–MS and NMR spectroscopy. Product 2 was isolated and its structure identified by X-ray crystal structural analysis, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, IR spectroscopy, and GC–MS [35]. IR spectroscopy was used to identify the final compounds that were synthesized. ^{13}C NMR spectroscopy of products 2–4 showed that the carbon atom was coupled with the fluorine atom in each of them, and the coupling constants and chemical shifts were recorded. The IR spectra were obtained using a JASCO FT/IR-400 instrument. The GC–MS analyses were performed using a Hewlett-Packard HP6890/5793MSD instrument, the ^{1}H NMR and ^{13}C NMR spectra were obtained using a JOEL ECS-400 instrument, and the absorption spectra were recorded using a Hitachi U-2310 spectrophotometer.

2.3. Synthesis and characterization of the photoproducts

Photoproducts were produced in the sample solutions during the irradiation experiments. The chemical structures of the photoproducts were confirmed by synthesizing authentic matching compounds using the methods shown below.

2.3.1. Synthesis of 2-methyl-N-[4-hydroxy(3-trifluoromethyl) phenyl] propaneamide (product 1)

Product 1 was synthesized by following a previously published procedure [25].

2.3.2. Synthesis of 2-methyl-N-[3-(trifluoromethyl) phenyl] propaneamide (product 3)

2-Methylpropane chloride (0.08 mL, 0.75 mmol) was added dropwise into 3-aminobenzotrifluoride (0.06 mL, 0.5 mmol) in pyridine and the mixture was stirred for 1 h. 2-Methylpropane chloride (0.08 mL, 0.75 mmol) was then added dropwise to the

solution, which was stirred for another 1 h. The pyridine was removed from the solution by mixing the solution with aqueous cupric sulfate; then the organic phase was extracted using ethyl acetate. The extract was dried using anhydrous sodium sulfate, and the solution was evaporated *in vacuo*. The crude product was purified by performing column chromatography (SiO_2; 2:8 EtOAc/hexane). The purified product was obtained as colorless and transparent crystals (85 mg, 73%). ^{1}H NMR (400 MHz, CD_3Cl) δ: 7.85 (^{1}H, s), 7.72 (^{1}H, d, J = 7.8 Hz), 7.65 (^{1}H, brs), 7.35 (^{2}H, m). ^{13}C NMR (100 MHz, CD_3Cl) δ: 176.60, 138.56, 130.97 (q, J = 32 Hz), 129.15, 123.7 (q, J = 271 Hz), 123.21, 120.50 (q, J = 4 Hz), 116.88 (q, J = 4 Hz), 36.18, 19.23. IR (KBr) cm^{-1}: 3252, 1664, 1448, 1337. MS (EI) m/z 231 (M^+), 212 ($M^+ - F$), 188 ($M^+ - CH(CH_3)_2$), 161 ($MH^+ - COCH(CH_3)_2$, base peak), 71 ($(CH_3)_2CHCO^+$), 43 ($(CH_3)_2CH^+$).

2.3.3. Synthesis of N-[4-amino-3-(trifluoromethyl) phenyl]2-methylpropaneamide (product 4)

Flutamide (0.996 g, 0.36 mmol) and ammonium chloride (1.079 g, 20.2 mmol) were dissolved in 46 mL methanol, and zinc powder (3.56 g, 54.6 mmol) was added. The reaction mixture was stirred for about 1 h at room temperature and filtered. The filtrate was washed with hot water and extracted with ethyl acetate; then the extract was dried using anhydrous sodium sulfate. After evaporation *in vacuo*, brown crystals of the pure product were obtained without any purification. ^{1}H NMR (400 MHz, CD_3Cl) δ: 7.71 (^{1}H, brs), 7.53 (^{1}H, d, J = 2.3 Hz), 7.41 (^{1}H, dd, J = 2.3, 8.6 Hz), 6.65 (^{1}H, d, J = 8.6 Hz), 2.49 (^{1}H, sep, J = 6.9 Hz), 1.20 (^{6}H, d, J = 6.9 Hz). ^{13}C NMR (100 MHz, CD_3Cl) δ: 175.88, 141.22, 128.25, 126.12, 124.40 (q, J = 271 Hz), 118.18 (q, J = 5 Hz), 117.48, 113.51 (q, J = 30 Hz), 36.01, 19.36. IR (KBr) cm^{-1}: 3403, 3273, 1633, 1509, 1102. MS (EI) m/z 246 (M^+), 227 ($M^+ - F$), 176 ($MH^+ - COCH(CH_3)_2$, base peak), 71 ($(CH_3)_2CHCO^+$), 43 ($(CH_3)_2CH^+$).

2.3.4. Synthesis of 1-methylethyl-2-amino-4-(2-methylpropanamido) benzoate (product 5)

The authentic compound matching product **5** was synthesized using the three-stage procedure described below.

Synthesis of 4-(2-methylpropanamido)-2-nitrobenzoic acid: 2-methylpropanoyl chloride (0.70 μL, 6.7 mmol) was added dropwise to 5-amino-2-nitrobenzoic acid (1.01 g, 5.55 mmol) in pyridine, and the mixture was stirred for 24 h. The pyridine was removed by mixing the reaction mixture with aqueous cupric sulfate, and the organic phase was extracted using ethyl acetate. The extract was dried using anhydrous sodium sulfate and evaporated *in vacuo*. The crude product was purified by performing column chromatography, although the target amide was not completely separated from the other products.

Synthesis of 1-methylethyl 2-nitro-4-(2-methylpropanamido) benzoate: the crude 4-(2-methylpropanamido)-2-nitrobenzoic acid (1.73 g), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (2.63 g, 13.7 mmol), and *N,N′*-dimethyl-4-aminopyridine (1.67 g, 13.7 mmol) were dissolved in 15 mL dimethylformamide and 2-propanol (1.6 mL, 21 mmol) was gradually added dropwise to the solution. After a 24 h stirring, the reaction mixture was extracted with ethyl acetate. The extract was dried using anhydrous sodium sulfate and the organic phase was evaporated *in vacuo*. The crude product was purified by performing column chromatography (SiO_2; 4:6 EtOAc/hexane). The target ester was obtained as a brown solid (739 mg, 45%). ^{1}H NMR (400 MHz, CD_3Cl) δ: 8.30 (^{1}H, brs), 7.94 (^{1}H, d, J = 8.8 Hz), 7.83 (^{1}H, dd, J = 2.0, 8.8 Hz), 7.79 (^{1}H, d, J = 2.0 Hz), 5.22 (^{1}H, sep, J = 6.4 Hz), 2.53 (^{1}H, sep, J = 6.8 Hz), 1.31 (^{6}H, d, J = 6.4 Hz), 1.19 (^{6}H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, CD_3Cl) δ: 176.18, 165.87, 143.23, 141.40, 130.53, 125.62, 120.28, 118.76, 70.70, 36.49, 21.20, 19.18. .MS (EI) m/z 294 (M^+), 224 ($MH^+ - COCH(CH_3)_2$, base peak), 71 ($(CH_3)_2CHCO^+$), 43 ($(CH_3)_2CH^+$).

Synthesis of 1-methylethyl 2-amino-4-(2-methylpropanamido) benzoate: 1-methylethyl-2-nitro-4-(2-methylpropanamido) benzoate (739 mg, 2.5 mmol) and ammonium chloride (1.038 g, 19.0 mmol) were dissolved in methanol; then zinc powder (1.65 g, 25 mmol) was added and the mixture was stirred for 19 h. Then the mixture was extracted with ethyl acetate, dried using anhydrous sodium sulfate, and evaporated *in vacuo*. The crude product was purified by performing column chromatography (SiO_2; 4:6 EtOAc/hexane). The target amine was obtained as a brown solid (428.5 mg, 65%). ^{1}H NMR (400 MHz, CD_3Cl) δ: 7.79 (^{1}H, d, J = 2.6 Hz), 7.58 (^{1}H, dd, J = 2.6, 8.6 Hz), 6.97 (^{1}H, brs), 6.65 (^{1}H, d, J = 8.8 Hz), 5.66 (^{1}H, brs), 5.22 (^{1}H, sep, J = 6.2 Hz), 2.48 (^{1}H, sep, J = 6.9 Hz), 1.37 (^{6}H, d, J = 6.2 Hz), 1.20 (^{6}H, d, J = 6.9 Hz). ^{13}C NMR (100 MHz, CD_3Cl) δ: 175.27, 167.12, 147.36, 127.94, 127.07, 122.81, 116.98, 110.92, 67.72, 36.09, 21.81, 19.50. IR (KBr) cm^{-1}: 3363, 3290, 1656, 1574, 1239. MS (EI) m/z 264 (M^+), 221 ($M^+ - CH(CH_3)_2$), 152 ($MH^+ - COCH(CH_3)_2$, base peak).

2.4. Internal irradiation experiment

Isolation of *N*-[4-hydroxy 3-nitro-5-(trifluoromethyl) phenyl]2-methylpropaneamide (product **2**): Flutamide was converted into product **2** when an aerated acetonitrile solution of the starting material (1.8×10^{-3} M) was irradiated with UV light from a high pressure mercury arc (UVL-100HA-100P; Riko). The reaction mixture obtained after photolysis had been performed was evaporated *in vacuo*; then the precipitate was purified by performing column chromatography (SiO_2; 2:8 EtOAc/hexane) to give 43 mg of the photoproduct. ^{1}H NMR (400 MHz, CD_3OD) δ: 10.96 (^{1}H, s), 8.60 (^{1}H, d, J = 2.8 Hz), 8.10 (^{1}H, d, J = 2.8 Hz), 7.82 (^{1}H, s), 2.58 (^{1}H, sep, J = 6.8 Hz) 1.27 (6H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 178.64, 149.52, 135.50, 132.06, 127.18 (q, J = 5 Hz), 123.66 (q, J = 271 Hz), 121.60 (q, J = 31 Hz), 119.76, 36.98, 19.67. IR (KBr) cm^{-1}: 3301, 1671, 1538, 1146. HRMS (FAB$^+$) m/z

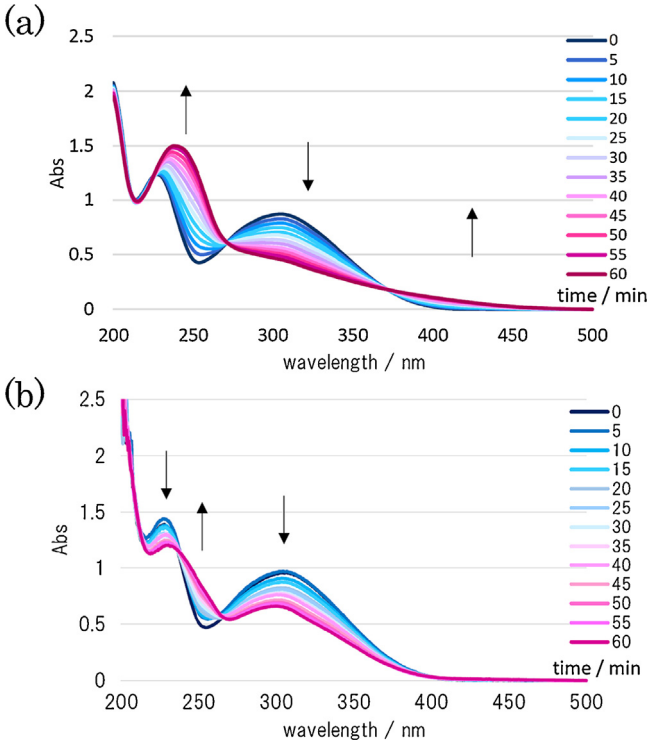


Fig. 1. The time course of absorption spectra for flutamide in (a) aerated acetonitrile and (b) deaerated acetonitrile. The photoreactions were monitored at 5 min intervals. The arrows in each spectrum represent the direction in which the absorption intensity is changing.

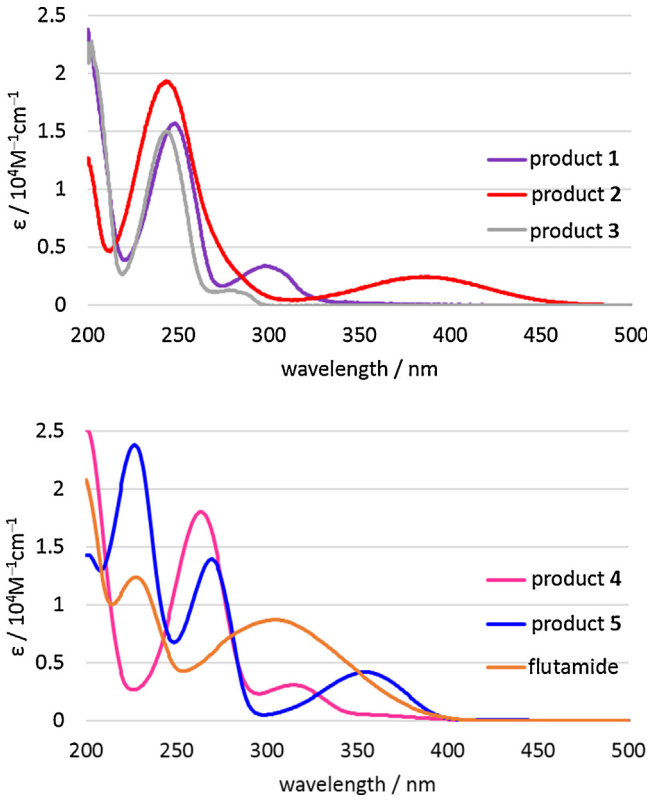


Fig. 2. Absorption spectra of the photoproducts and flutamide in acetonitrile. The maximum absorption wavelengths for products 1–5 and flutamide were 248, 243, 264, 227, 228 and 225 nm, respectively.

$[M+H]^+$ found: 293.0746, calc: 293.0744. MS (EI) *m*/*z* 292 (M^+), 273 ($M^+ - F$), 222 ($MH^+ - COCH(CH_3)_2$, base peak), 71 ($(CH_3)_2CHCO^+$), 43 ($(CH_3)_2CH^+$). The structure of product **2** was determined using X-ray crystal structural analysis [35].

3. Results and discussion

3.1. Photoreactions of flutamide in acetonitrile

The time course of absorption spectra for flutamide in aerated acetonitrile and deaerated acetonitrile solutions are shown in Fig. 1(a) and (b), respectively. Several isosbestic points can clearly be seen in Fig. 1(a), and these imply that the photoreactions did not include successive reactions when the solution was aerated. Moreover, the time courses of absorption spectra were quite different, which indicates that different photoproducts were generated in the aerated and deaerated solutions. For comparison, the absorption spectrum of each photoproduct is shown in Fig. 2.

The predominant photoreaction was nitro–nitrite rearrangement when aerated acetonitrile was used, and the rearrangement products were products **1** and **2**, the main product being product **2**. However, when deaerated acetonitrile was used, the photoproducts were products **1**, **3** and **4**; product **2** was not found. Therefore, it appears that product **2** was generated by the irradiation of flutamide only when the solvent contained dissolved oxygen. The proposed reaction mechanism for the generation of product **2** is shown in Scheme 1.

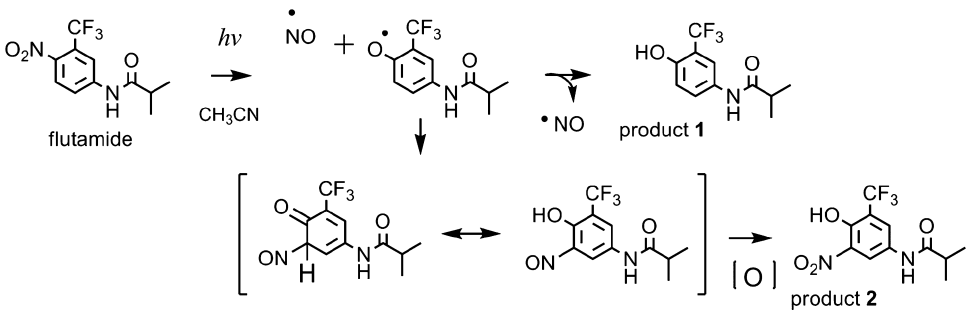
In the proposed mechanism, a nitro–nitrite rearrangement occurs first, producing a phenoxy radical and nitrogen monoxide. The nitrogen monoxide then recombines with the phenoxy radical at the *ortho* position and oxidized by dissolved oxygen. However, during the generation of product **1**, the nitrogen monoxide was expected to dissipate because the side product derived from nitrogen monoxide was not detected. The phenoxy radical that is produced during the generation of product **1** was expected to abstract a hydrogen atom from the reaction system. We conducted an additional irradiation experiment using deuterated acetonitrile as the solvent to identify the origin of the hydrogen atoms of interest in product **1**. Flutamide was converted into products **1** and **2** without deuterium being introduced into the photoproducts. Isotopic peaks for both phenyl–OH and phenyl–OD were observed in our GC–MS analyses even when the deuterated acetonitrile was contaminated with a large excess of water and heavy hydrogen could have been replaced by light hydrogen. The results indicate that the exchange of heavy hydrogen for light hydrogen did not occur in this study because the isotopic peak for heavy hydrogen derived from phenyl–OD was not observed.

3.2. Photoreaction of flutamide in 2-propanol

The time courses of absorption spectra for flutamide in aerated and deaerated 2-propanol solutions are shown in Fig. 3(a) and (b), respectively. No isosbestic points were observed in the spectra, which indicates that the photoreaction was not simple and that several photoreactions occurred. This indicates that substances other than flutamide, such as the photoproducts themselves, participate in the photoreaction.

Three different photoreactions were found to take place when aerated 2-propanol was used as the reaction solvent. The products were a nitro–nitrite rearrangement product (product **1**), a photodissociation product (product **3**), and two photoreduction products (products **4** and **5**), as shown in Scheme 2.

The same photoproducts that were found using the aerated 2-propanol solution were also found when deaerated 2-propanol solution was used. However, the UV spectra indicated that the photoreaction was faster in deaerated 2-propanol than in aerated 2-propanol. In previous studies, the elimination of fluorine atoms in photoreactions is accelerated by the presence of alcohol and water [31–34]. In the case of trifluoromethyl benzene derivatives,



Scheme 1. The generation mechanism of product **1** and **2** from flutamide in acetonitrile solution.

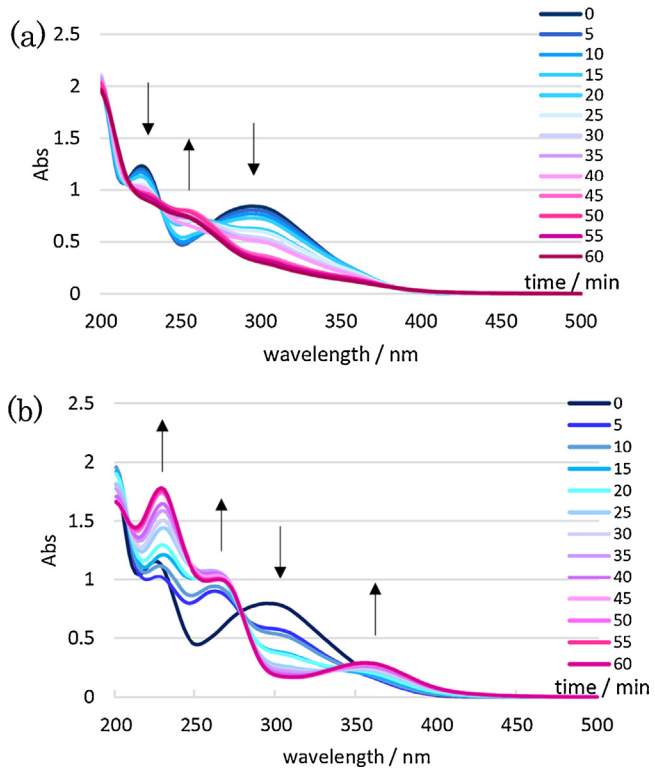
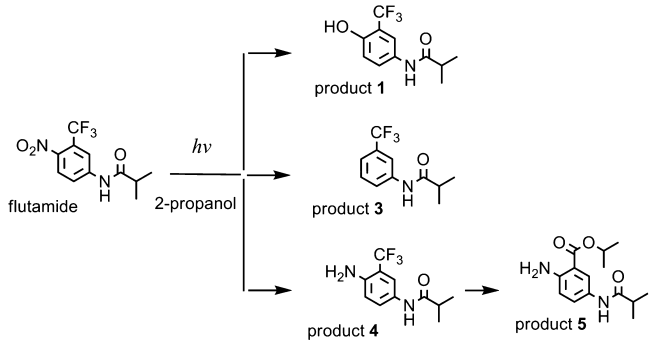


Fig. 3. The time course of absorption spectra for flutamide in (a) aerated 2-propanol and (b) deaerated 2-propanol. The photoreactions were monitored at 5 min intervals. The arrows in each spectrum represent the direction in which the absorption intensity is changing.

an electron donor binding to the phenyl ring likely will induce solvolysis [31,33]. Therefore, product **5** was presumed to be generated from flutamide *via* product **4**. To confirm this, a solution of product **4** in 2-propanol was irradiated under the same conditions as those used to irradiate flutamide. Product **4** in aerated 2-propanol was irradiated for 2 min and the products were analyzed by GC–MS. A GC–MS peak for product **4** was observed at a retention time of 6.24 min, but no photoproduct peaks were observed (Fig. 4(a)). However, a peak for product **4** at a retention time of 6.24 min and a peak for product **5** at a retention time of 7.88 min were found when product **4** in deaerated 2-propanol was irradiated for 2 min (Fig. 4(b)). These results clearly indicate that the yield of product **5** was higher when deaerated 2-propanol was used compared with aerated 2-propanol. That is, dissolved oxygen suppressed the solvolysis of the trifluoromethyl group.



Scheme 2. The photoproducts of flutamide in 2-propanol solution.

In a previous study, it was shown that the photodegradation of 2-hydroxy-4-trifluoromethyl benzoic acid *via* the solvolysis of the trifluoromethyl group is influenced by triplet quenchers such as oxygen, cyclohexadiene and naphthalene [32]. This indicates that the solvolysis of the trifluoromethyl group occurs in the excited triplet state of 2-hydroxy-4-trifluoromethyl benzoic acid. However, in this study, the presence of oxygen in the 2-propanol solution of product **4** caused less solvolysis of the trifluoromethyl group to occur. From these results, the solvolysis of the trifluoromethyl group in a trifluoromethylbenzene derivative might occur in the excited triplet state. Chaignon et al. reported that 3,5-diaminobenzotrifluoride was defluorinated when it was irradiated with UV at 310 nm, although 3,5-dinitrobenzotrifluoride was unchanged when it was irradiated under the same conditions [33]. Using these trifluoromethylbenzene derivatives as an analogy, we concluded that the conversion of the nitro group to an amino group may be necessary for the solvolysis of the trifluoromethyl group to occur.

The expected mechanism for the generation of product **5** from product **4** is shown in Scheme 3.

In the proposed mechanism, the carbon atom in the trifluoromethyl group is first attacked by 2-propanol, and a fluoride ion becomes dissociated. The fluoride ion abstracts a hydrogen atom from the methyl group, which was derived from the 2-propanol added in the previous step. This produces acyl fluoride *via* an E2 dissociation reaction. The acyl fluoride is then nucleophilically attacked by 2-propanol, finally producing product **5**.

We conducted an irradiation experiment using products **1** and **3** under the same conditions as we used for the irradiation experiments on flutamide and product **4** in 2-propanol. Products **1** and **3** both underwent some photoreactions, but the photoproducts generated *via* the solvolysis of the trifluoromethyl group were not detected. Chaignon et al. showed that photosolvolysis of the trifluoromethyl group does not occur in trifluoromethyl benzene derivatives that do not have an electron-donating primary

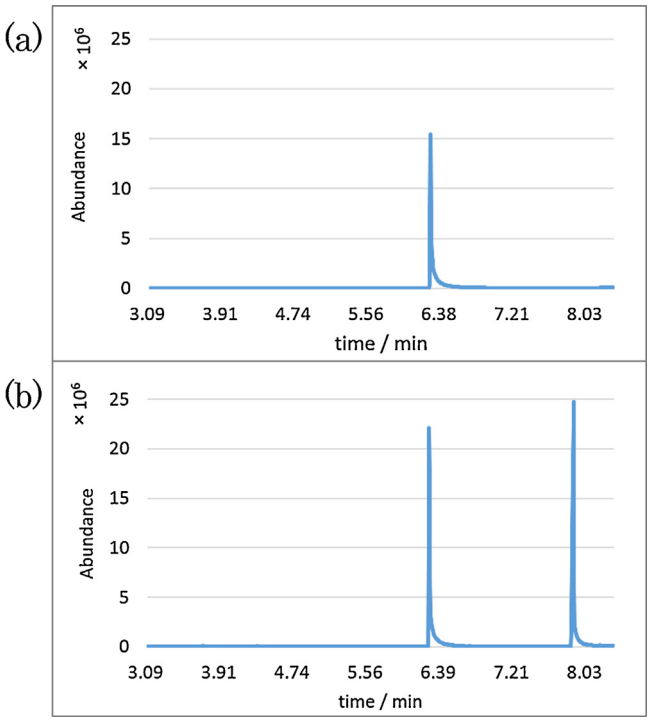
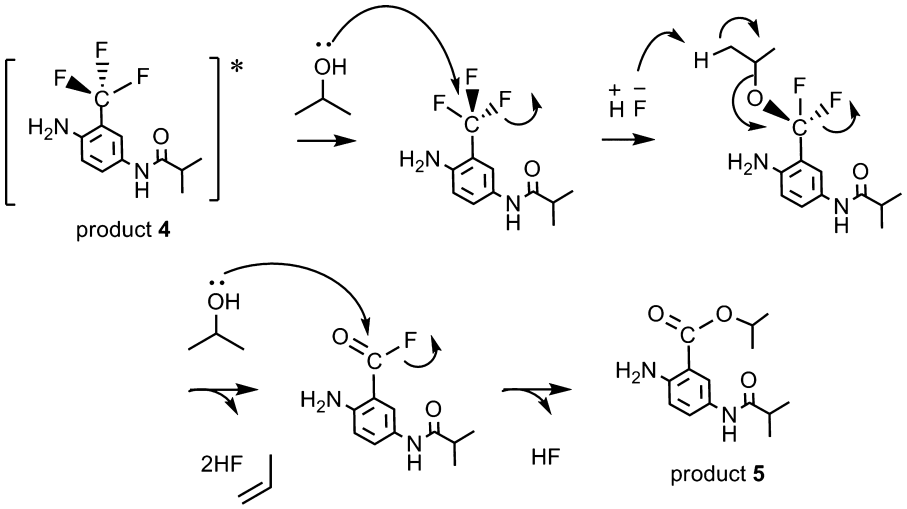


Fig. 4. Gas chromatogram of product 4 in (a) aerated 2-propanol and (b) deaerated 2-propanol after being irradiated with UV. The peaks at retention times of 6.24 min and 7.88 min were identified as products 4 and 5, respectively.



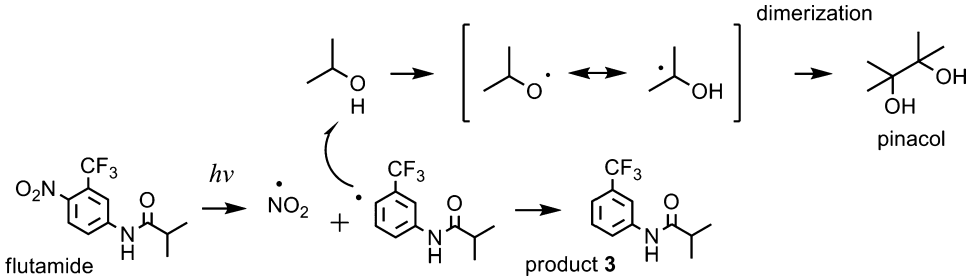
Scheme 3. The generation process of product **5** from product **4** via photosolvolysis.

amine group [33]. Their results are consistent with our experimental results because product **3** did not undergo solvolysis in our experiments. Therefore, we expected that an electron donating substituent is necessary for the reaction to occur. However, we did not observe the solvolysis of the trifluoromethyl group when product **1** was irradiated. The absorption spectra of products **1** and **4** were very similar, and both compounds have electron-donating substituents (a hydroxyl group in product **1** and an amino group in product **4**). These results indicate that the aniline structure is necessary for the solvolysis of the trifluoromethyl group to occur and that the presence of a phenol structure may be insufficient for the reaction to occur. This is why solvolysis of the trifluoromethyl group was only observed in the 2-propanol solution, in which product **4** was produced. 2-Propanol contains a dissociable hydrogen atom in its OH group, and this is preferentially used in the hydrogen abstraction process during the conversion of flutamide to product **4**. This might be the reason that flutamide in 2-propanol tends to undergo photoreduction. Regarding the photoreduction of aromatic nitro compounds, Hurley and Testa investigated the photochemistry of nitrobenzene in 2-propanol at 366 nm and observed hydrogen abstraction from 2-propanol by photoexcited nitrobenzene [2]. They showed, using gas chromatography, that the formation of acetone during the photoreduction reaction was evidence of hydrogen being abstracted from 2-propanol. It has been reported that the photoreduction of aromatic nitro compounds, including the hydrogen abstraction process, occurs in some alcoholic solvents, such as 2-propanol and ethanol [2–4,11].

We conducted additional irradiation experiments using deuterated 2-propanol as the solvent, to examine the reaction between flutamide and 2-propanol. When flutamide was dissolved in 2-propanol-d_8, the exchangeable protons in the amino, hydroxyl, and amide groups became deuterated whether or not the solution had been irradiated with UV. Product **4** could be generated by the abstraction of hydrogen from 2-propanol by the excited flutamide, but we could not clarify the origin of the two hydrogen atoms in the amino group in product **4**. However, we found that, to produce product **3**, the nitro group in flutamide had been substituted with deuterium from the 2-propanol-d_8. This shows that the phenyl radical generated by the photodissociation of flutamide abstracted a hydrogen atom from 2-propanol-d_8, which indicates that the generation of product **3** requires the hydrogen abstraction process to occur. Therefore, product **3** may only have been observed in the reaction in 2-propanol because the hydrogen abstraction process is more likely to occur in 2-propanol than in acetonitrile.

We prepared a more dilute solution of flutamide (at 1×10^{-4} M) in 2-propanol for an additional irradiation experiment. The photoproducts from irradiating this solution were product **3** and pinacol, indicating that photodissociation occurred. Although product **3** was observed when the more concentrated solution of flutamide (1×10^{-3} M) in 2-propanol was irradiated, less pinacol was detected than when the dilute solution of flutamide (1×10^{-4} M) was irradiated. The proposed reaction mechanism for the photoreaction of the dilute solution of flutamide in 2-propanol is shown in Scheme 4.

In the proposed mechanism, a phenyl radical and nitrogen dioxide are first produced by the photodissociation of flutamide, and the phenyl radical abstracts a hydrogen atom from 2-propanol, producing a ketyl radical. The ketyl radical dimerizes, generating pinacol. We could not clearly identify the position in 2-propanol



Scheme 4. The hydrogen abstraction reaction from 2-proapnol in the photoreaction of flutamide.

from which the hydrogen atom is abstracted, although the hydrogen atom from the dissociable OH bond may be abstracted. These results showed that different photoreactions occurred at different flutamide concentrations in 2-propanol, which suggests that the photoreactions of flutamide involve not only reactions between the solute and solvent but also between the solutes.

4. Conclusions

We compared the photoproducts of flutamide in two different solvents and found that using acetonitrile as the solvent caused preferential nitro–nitrite rearrangement of flutamide and using 2-propanol as the solvent caused preferential photoreduction of flutamide. Flutamide is considered to be susceptible to nitro–nitrite rearrangement in a homogeneous solution [21,25]. However, nitro–nitrite rearrangement was the main photoreaction only when the experiments were conducted in acetonitrile in this study. In the photoreaction of flutamide solution in 2-propanol, photoreduction is preferred (rather than nitro–nitrite rearrangement) because the hydrogen abstraction process is facilitated by 2-propanol. Moreover, the solvolysis of the trifluoromethyl group requires the photoreduction product to be formed.

We elucidated the high reactivity of flutamide to UV. Although we could not identify the agent that causes photodermatosis in patients being treated with flutamide, our results clearly indicate that flutamide is highly photosensitive to UV of sunlight. The photoreaction of flutamide generates radical species as reaction intermediates and these can react with biopolymers *in vivo*. Reactions between radicals and biopolymers might generate immunologically active substances. The identification of the agent that causes photodermatosis will be an objective of future studies.

Acknowledgment

The authors express their appreciation to the late Prof. Ryoichi Nakagaki, whose contribution to this work was of great significance.

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