# Photodegradation behaviour of fluticasone propionate under different irradiation conditions

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**Abstract - In the present study we investigated the photochemical behaviour of the anti-inflammatory drug fluticasone propionate (1) under aerobic as well as in anaerobic condition with different irradiation wavelengths (254 nm and 310 nm) in acetonitrile and propanol. Photoproducts obtained were isolated and characterized on the basis of IR, $^{1}$H NMR, $^{13}$C NMR spectroscopy and elemental analysis. The products were: 6,9 Difluro-11-Hydroxy-16 Methyl-3-oxo-17-(1oxopropoxy) 5cycloandrosata-3ene-2,-17-Carbothioic acid- S-(fluro methyl)ester 2 (254 nm), 6,9 Difluro-11-hydroxy-16-Methyl -3oxo-17-(1oxopropoxy)-18,20-Cycloandrosta -1-4 diene-17-carbothioic acid-S-(fluromethyl) ester 3 (310 nm/ propanol, anaerobic), 6, 9 Difluro-17-hydroperoxy-16-methyl-3-oxo-17-(1oxopropoxy) pregn-1,4-diene-3-one 4 (310 nm/aerobic/ Propanol). Due to U.V light interaction Cyclohexadienone moiety in ring A and keto group at C-17 were found to be deeply modified and therefore loss of biological activity during storage and *in vivo* cannot be ruled out.**

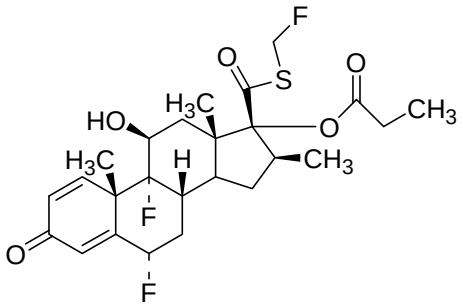
**Keywords**: Photochemistry, fluticasone propionate, anti-inflammatory drug.

## Introduction

A detailed knowledge of the photochemical properties of a photosensitizing drug is an essential to understand its mechanism of action. Photochemical processes have severe pharmaceutical and medicinal consequences.[1,2] Photodegradation, an important photochemical process should not be implicit only as a decomposition process but it also involves in the generation of free radicals or transfer of energy. Such phenomena contribute to formation of diverse photoproducts showing various physicochemical features. In recent years drugs photostability become a significant problem in pharmaceutical research because the photochemical decomposition of drugs may lead to a decrease in their therapeutic effectiveness or even to the appearance of toxic products.[3-5] The loss of pharmaceutical activity is usually unavoidable. The photoproducts can also react with endogenous substances and thus be a source of many dangerous side-effects, including phototoxicity, photoallergy or carcinogenic activity.[5, 6]

Gluco-corticosteroids are a class of steroid hormone produced by the adrenal cortex that enable the body to cope with stress or by increasing concentration in the blood of glucose fatty acid and amino acid and by raising blood pressure.[7-9] Both natural and semi synthetic glucocorticosteroids are readily decompose when irradiated with UV-A or UV-B light in organic solvents, either through rearrangement of the cyclohexadienone moiety or a mechanism involving radicals, respectively.[10-12]

Fluticasone propionate (FP, 1) is a synthetic trifluorinated corticosteroid based on the androstane nucleus with potent anti-inflammatory action.[13] It is also used for the treatment of Eczema, Psoriasis and Neurodermatoses.[14] It has been used intranasally, as therapy for seasonal and allergic perennial rhinitis. [15, 16] Fluticasone propionate is a subject of fascinating photochemistry because it bears two spatially separated chromophore ie cyclohexadienone moity in ring A and carbonyl group at $C_{20.}$ [17]




Fluticasone propionate

Many steroidal drugs bearing two spatially separated chromophore have long been subject of investigation in photochemistry of particular interest is establishing correlation between mechanism of drug photodegradation and drug phototoxicity. [18-20] With this interest here in we have investigated the photochemistry of fluticasone propionate under different combinations of solvent and irradiation wavelength.

## Experimental Section

### Apparatus and chemicals

Pure fluticasone was obtained from ZYG Pharma Pvt. Ltd., (India). The solvents used in the photoreactions were of spectroscopic grade. Irradiations at 254 nm were carried out in an immersion well type photoreactor (quartz) equipped with 20 W low-pressure mercury arc lamp. For irradiations at 310 nm the solutions were irradiated with15 W phosphorus coated lamps. IR spectra were recorded in KBr discs on a Perkin Elmer model spectrum RX1. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DRX-300 spectrometer using $SiMe_4$ as internal standard and DMSO as solvent. High-resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 eV ionization voltages. Merck silica gel 60 $F_{254}$ plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (70-230 mesh).

### Photoirradiation procedure

The solution of fluticasone in different solvent was stirred for 1 h before irradiation and was kept bubbling during the irradiations. The course of reaction was monitored by thin layer chromatography on pre-coated silica gel TLC plates using chloroform- acetone (10:2) mixture. After the completion of reaction (when desired conversions have reached) the solvent was removed in a rotary evaporator and products were purified by silica gel column chromatography.

### Irradiation of fluticasone under anaerobic condition in acetonitrile

When the Solution of **FP (1)** (264 mg, 0.52 mmol) in acetonitrile (500 ml) under anaerobic condition was irradiated for 2.5 h at 254 nm. After following the steps described in the photoirradiation procedure, **2** (125 mg) was obtained as the product.

### 6,9Difluro-11-Hydroxy-16 Methyl-3-oxo-17-(1oxopropoxy) 5cycloandrosata-3ene-2,-17-Carbothioic acid-S-(fluromethyl)ester (2).

Yield: 125 mg (47.3%); UV λmax (MeOH) 251 nm **;**IR (KBr) 3410, 1678 (C=O), 1575 (C=C), 1352, 1160, 1031 $cm^{-1}$ (cyclopropyl); $^{1}$H-NMR (DMSO, δ, ppm) 6.68 (d,1H,H-4), 5.69(d,1H,J=6.2Hz,H-3) 5.67 (s, 2H, H-22), 3.15 (t, 1H, H-11), 2.29 (m, 2H, H-24), 2.0 (brs, exch., OH),1.89 (t, 1H, H-16), 1.63 (d,2H, H-12), 1.59 (t, 1H, H-6), 1.55 (m, 1H,H-15), 1.16(6H,2×$CH_3$),1.06 (S, 1H, H-1); $^{13}$C-NMR (DMSO, δ, ppm) 198.3 (C-20), 193.3(C-2),173.2(C-22), 161.1 (C-4), 132.5 (C-3), 112.6 (C-9), 96.2 (C-17), 93.0 (C-6), 81.1 (C-23), 70.1 (C-11), 41.6 (C-21), 40.6 (C-14), 40.6 (C-1), 35.8 (C-16), 33.3 (C-12), 32.8 (C-15), 28.7(C-7), 27.3 (C-10), 25.3 (C-5), 14.5 (C-18), 9.3 (C-19); HRMS calcd. for (M+) $C_{26}H_{35}F_30_5S$ 516.2157, found 516.6133.

When the solution of **FP (1)** (264 mg, 0.52 mM) under anaerobic condition in acetonitrile (500 ml) was irradiated for 2 h at 310 nm. After following the steps described in general photo irradiation procedure, **3** (98 mg) was obtained as main product with a trace amount of **2**, as detected on TLC.

### 6,9 Difluro-11-hydroxy-16-Methyl -3oxo-17-(1oxopropoxy)-18,20-Cycloandrosta -1-4 diene-17-carbothioic acid-S-(fluromethyl)ester (3).

Yield: 98 mg (37.12%); UV λmax (MeOH) 240 nm **;** IR (KBr) 3415, 1675, 1628, 1618; $^{1}$HNMR(DMSO, δ, ppm) 6.34 (d, J=9 Hz, 1H, H-2), 6.33 (s, J=9 Hz, 1H, H-1), 6.12 (s, 1H, H-4), 5.24(s, 2H, H-22), 4.0 (t, 1H, H-6), 3.43(t, 1H, H-11), 2.48 (s, 2H, H-18), 2.29 (m, 2H, H-24), 2.0 (brs, exch., OH), 1.68(m, 1H, H8), 1.66 (m,1H,H-16), 1.63 (d, 2H, H-12), 1.58 (m, 2H, H-7), 1.55 (m, 2H, H-15), 1.36 (3H, $CH_3$), 1.14 (3H, $CH_3$), ; $^{13}$C-NMR (DMSO, δ, ppm) 185.8 (C-3),173.1 (COOR), 163.1 (C-5), 155.4 (C-1), 124.2 (C-4), 110.2 (C-17), 100.3 (C-9), 87. 8 (C-6), 79.2 (C-20), 76.3 (C-22), 70.8 (C-11), 47.9 (C-10), 40.9 (C-14), 39.9 (C-18), 37.9 (C-13), 33.7 (C-7), 33.6 (C-12), 32.9 (C-15), 32.2 (C-8),29.1 (C-16), 28.2 (C-24), 18.9 ($CH_3$), 12.7 ($CH_3$), 9.4 ($CH_3$); HRMS calcd. for (M+) $C_{25}H_{31}F_3O_5S$ 500.5708, found 500. 1844

### Irradiation of fluticasone under aerobic condition in acetonitrile

When the solution of FP (**1)** (264 mg, 0.52 mM) under aerobic condition in acetonitrile (500 ml) was irradiated for 2.5 h at 254 nm and 310 nm. After following the steps described in the general photo irradiation procedure, compound **2** (130 mg, 49.2%) was obtained as the product at 254 nm; whereas a complex mixture of the products was obtained at 310 nm.

### Irradiation of fluticasone under anaerobic condition in propanol

When the solution of FP (**1)** (264 mg, 0.52 mM) under anaerobic condition in propanol (500 ml) was irradiated for 2 h at 254 nm and at 310 nm. After following the steps described in the general photo irradiation procedure, compound **2** (140 mg, 53%) was obtained as the product at 254 nm. Whereas at 310 nm both the compounds **2** (45 mg, 17%) and **3** (96 mg, 36.3%) were obtained as the products.

**Irradiation of fluticasone under aerobic condition in propanol**

A solution of **1** (264 mg, 0.52 mM) in oxygen-saturated propanol (500 ml) was irradiated for 2.5 h at 254 nm and 310 nm. After following the steps described in the general photoirradiation procedure, compound **2** (152 mg, 57.5%) was obtained as the product at 254 nm. At 310 nm **2** (52 mg, 19.6%) and **4** (134 mg, 50.7%) were obtained as the products.

**6, 9 Difluro-17-hydroperoxy-16-methyl-3-oxo-17-(1oxopropoxy) pregn-1, 4-diene-3-one (4)**

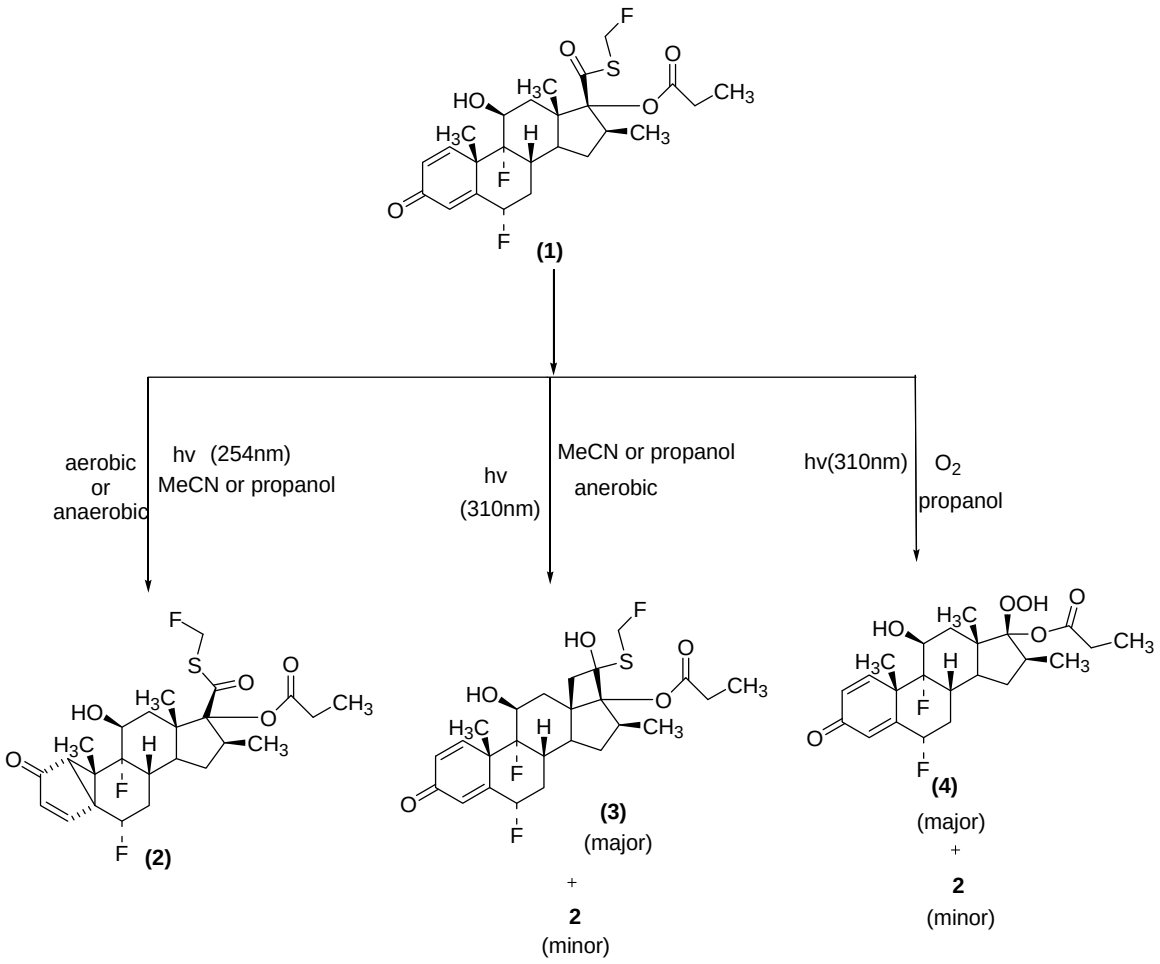
Yield:134mg (50.7%); UV λmax (MeOH) 241 nm IR (KBr) 3410, 1660, 1615, 1610; 1H-NMR (DMSO, δ, ppm) 8.8 (brs, exch., OOH), 6.34 (d, 1H, J=9 Hz, H-2), 6.33 (s, 1H, H-4), 6.28 (d, 1H, H-1), 4.00 (t, 1H, H- 6), 3.43 ( (t, 1H, H-11), 2.35 (m, 1H, H-16), 2.O (brs, exch., OH),1.68 (d, 1H, H-8,), 1.63 (d, 1H, H-12), 1.58 (m, 2H, H-7), 1.55 (m, 2H, H-16), 1.40(t, 1H, H-14), 1.36 (3H, $CH_3$), 1.06 (3H, $CH_3$); $^{13}$C-NMR 185.8 (C-3), 173.1(-$OCOCH_2CH_3$), 163.1 (C-5), 155.4 (C-1), 128.4 (C-2), 124.8 (C-17), 124.2 (C-4), 100.3 (C-9), 87.8(C-6),70.8(C-11) 47.9 (C-10), 43.6 (C-16), 37.6 (C-14), 33.7 (C-7), 32.2(C-8), 30.3 (C-12), 29.6 (C-15), 28.2 (-$OCOCH_2CH_3$), 25.2 (C-7), 18.9 ($CH_3$), 11.3 ($CH_3$), 9.4 (-$OCOCH_2CH_3$); HRMS calcd. for ($M^+$) $C_{23}H_{30}F_2O_6$ 440.4775, found 440.2014.

## Results and Discussion

When fluticasone in acetonitrile was irradiated at 254 nm under aerobic and anaerobic condition it gave compound **2** as a major photoproduct. The fluticasone in propanol at 254 nm show a similar course of reaction under aerobic as well as under anaerobic conditions. Irradiation of FP under anaerobic condition at 310 nm in acetonitrile or propanol gave photoproduct **2** along with a new compound **3**. At the same irradiation wavelength (310 nm) under aerobic condition affected the product distribution: in propanol compound **3** was not formed and a hydroperoxide compound **4** was obtained as main product along with compound **2**. In acetonitrile a complex mixture of products was obtained (Scheme 1). The comparative yields of the photoproducts (**2**, **3** and **4**) under different reaction conditions are given in Table 1.

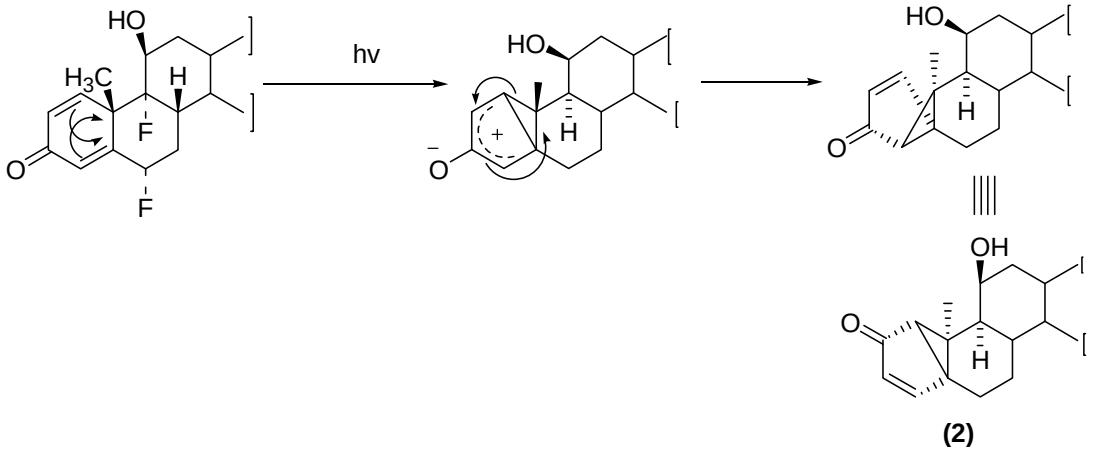
Table 1. Yields of the reaction products, in photochemical reaction of (1) under different reaction conditions.

| Solvent condition | Wavelengths | Photoproduct (s) | Yield of the product (%) |
|---|---|---|---|
| $CH_3CN$/anaerobic | 254 | 2 | 47.3% |
| $CH_3CN$/anaerobic | 310 | 3+2 | 3 (37.12%), 2 (trace on TLC) |
| $CH_3CN$/aerobic | 254 | 2 | 49.2% |
| $CH_3CN$/aerobic | 310 | A complex mixture of products | - |
| Propanol/anaerobic | 254 | 2 | 53% |
| Propanol/anaerobic | 310 | 3+2 | 3(36.3%), 2 (17%) |
| Propanol/aerobic | 254 | 2 | 57.5% |
| Propanol/aerobic | 310 | 4+2 | 4 (50.7%), 2 (19.6%) |



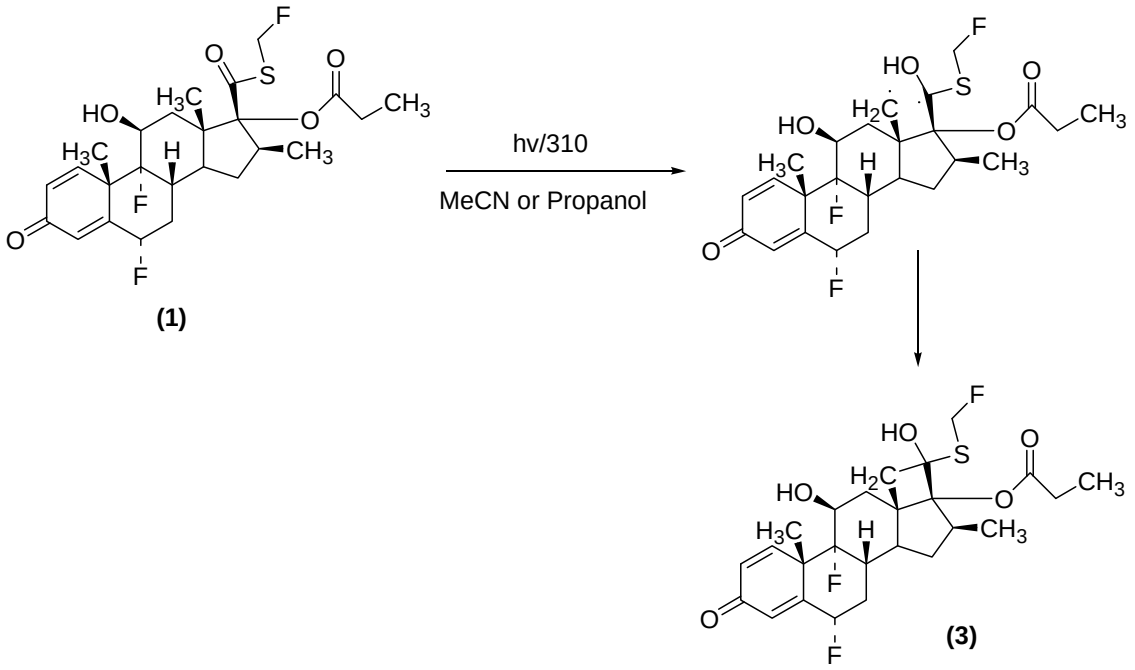

**Scheme 1**

The formation of these photoproducts can be explained on the basis of different photochemical reaction mechanism of the two-separated chromophores present in this drug. At 254 nm compound 2 was obtained and their formation can be explained by well lumiketone rearrangement. The rearrangement involve in the formation of compound **2** is a concerted process and therefore, not affected by the solvent medium.

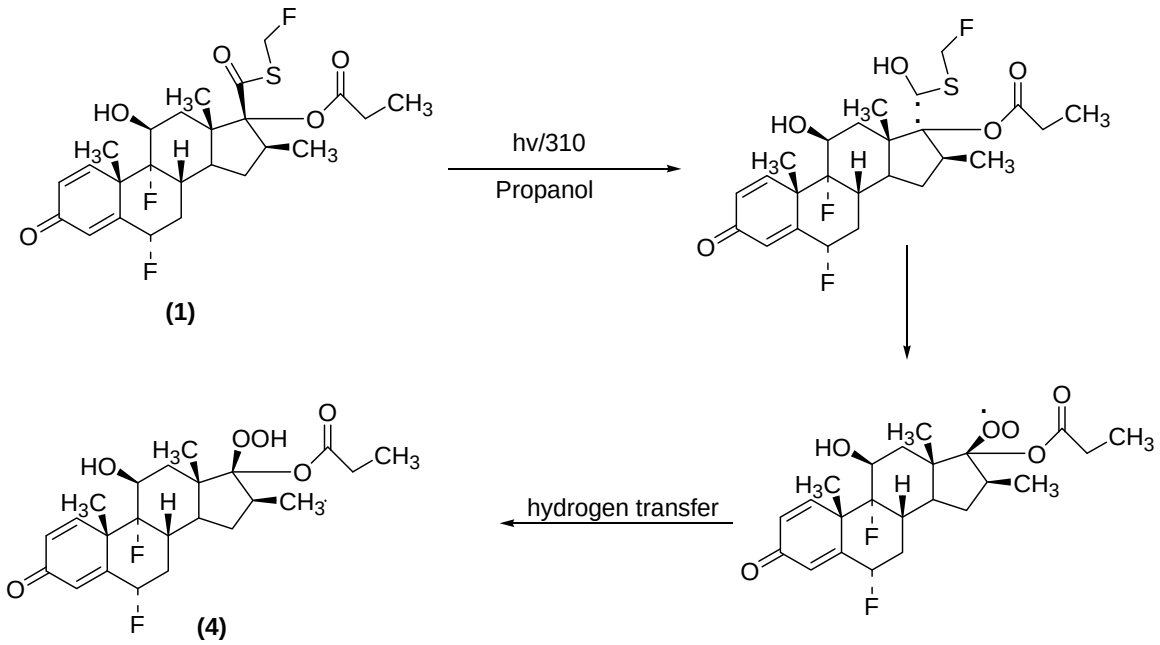



**Scheme2**

On the other hand at 310 nm major fraction of light was absorb by isolated ketone at $C_{20}$ and compound 3 was obtained as photoproduct, which was formed via hydrogen atom abstraction from the close lying 18-methyl group followed by cyclization (Scheme 3). In aerobic condition trapping of alkyl radicals by oxygen is quite efficient to yield peroxy radicals. This peroxy radical abstracts hydrogen from hydrogen donating solvent (propanol) and gives the isolated hydroperoxy derivative **4** (Scheme 4).




**Scheme 3**




**Scheme 4**

All the photoproducts obtained were characterized and identified on the basis of the following spectral evidence. The IR spectra of compound **2** showed absorption bands at 1352, 1160, 1031 (cyclopropyl), 1575 (C=C), 1678 (C=O) and the NMR spectrum of compound 2 show doublet at δ 6.68 and 5.69. The $^{1}$H-NMR spectrum and the IR band values indicated the presence of an α, β-unsaturated ketone in ring A. The NMR spectrum of compound 2 indicate that the ring B, C and D were found to be unaffected while signals due to ring A were strongly modified. $^{13}$C-NMR spectrum of compound 2 show signals at 40.6, 25.3 and 27.3 indicate the presence of a cyclopropyl carbonyl system in ring A. The NMR spectra of compound **3** indicated that the steroidal skeleton was unaffected but both the C-20 ketone and 18-methyl signals were missing. The presence of three olefinic protons at δ 6.34, 6.33, and 6. 12 confirmed that the dienone system was intact. These data along with the appearance of a new methylene carbon and the IR absorption bands at 3415 (OH), 1675 (α, β-un saturated C=O), 1628, 1618 (C=C) cm-1, supported the assigned structure of compound **3**. The NMR spectra of compound **4** suggested that rings A, B and C were found to be unaffected, In addition a strongly deshielded signal at δ 8.8 (brs, exch., 1H) in the $^{1}$H-NMR and a new signal at δ 124.8 (C-17) in$^{13}$C-NMR suggested the

presence of a hydroperoxy group in **4**. The spectroscopic indications (in the experimental section) allowed assignment of the hydroperoxide structure to compound **4**.

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