Photochemistry of Desonide, a Non-fluorinated Steroidal Anti-inflammatory Drug

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The photochemistry of anti-inflammatory drug desonide (De, 1) was studied in aerobic as well as in anaerobic condition with different irradiation wavelengths (254, 310 nm) in acetonitrile and 2-propanol. All photoproducts obtained were isolated and characterized on the basis of IR, ^{1}H-, ^{13}C-NMR spectroscopy and elemental analysis study. The products were: 11β,21-dihydroxy-16α,17α-(1-methylethylidenedioxy)-1,5-cyclopregn-3-ene-2,20-dione 2 (254 nm), 11β-hydroxy-16α,17α-(1-methylethylidenedioxy)androsta-1,4-diene-3-one 3 (310 nm/2-propanol), 17β-hydroperoxy-11β-hydroxy-16α,17α-(1-methylethylidenedioxy)androsta-1,4-diene-3-one 4 (310 nm/O_2/2-propanol). Cyclohexadienone moiety in ring A and keto group at C_{17} were found to be deeply modified by UV light therefore, loss of biological activity both during storage and *in vivo* can not be ruled out.

Key words photochemistry; desonide; anti-inflammatory drug

Polyfunctional molecules in which different photochemically reactive chromophores are connected by rigid hydrocarbon framework are a subject of fascinating photochemistry.[1—3] The intramolecular energy transfer (both singlet–singlet and triplet–triplet) may occur from an 'antenna' group to other chromophore leading to chemistry different from that observed by direct excitation of that chromophore.[4—7] In the photochemistry of such multichromophoric molecules the evaluation of interaction between the chromophores, the mode and extent of local reaction at any chromophore after electronic excitation and possible role of energy transfer is of high mechanistic significance.

Morrison established, through a series of elegant papers,[4—7] that intramolecular energy transfer (both singlet–singlet and triplet–triplet) occurred from the phenyl 'antenna' to C_{17} keto group in the steroids by the way of through-bond mechanism. This lead to a different photochemistry observed by the direct excitation of ketone chromophore. Albini *et al.*[8,9] have demonstrated non-communicating reaction paths in some pregna-1,4-diene-3,20-dione. Since many steroidal drugs are commonly used and several reports on their phototoxic effects have been reported,[10—13] it was of interest to extensively study the aspect of competition between chemical reactions of the separated excited moieties incorporated in the rigid skeleton of the steroids. It was expected that such photochemical mechanisms might have some relevance for the mechanism of phototoxicity.

Glucocorticosteroids are natural hormones with a steroidal structure derived from 5α-pregnane. These steroidal hormones with powerful anti-inflammatory effects are secreted by the cortex of adrenal gland. Semisynthetic derivatives of these hormones are widely used as drugs to treat inflammatory illness, including arthritis and asthma, and many of them are effective by topical use in dermatoses and other dermatological disease.

Desonide (**De**,**1**) is a synthetic nonfluorinated corticosteroid for topical dermatological use. It is used to treat inflammation caused by a number of conditions such as allergic reactions, asthma and psoriasis.[14,15] Desonide is very interesting from photochemical point of view because it bear two spatially separated chromophores *i.e.* cross conjugated dienone moiety in ring A and an isolated ketone at C_{20}. A number of photochemical studies have been carried out on these steroidal ketones, both in solution and in solid state.[16—22] The photochemistry of cross-conjugated cyclohexadienone has been intensively studied because of their facile and fascinatingly complex photochemical reactions. Williams *et al.*[23] carried out photolysis of prednisolone, a molecule structurally related to **De**, at 254 nm and observed that only photoprocess occurring in dioxane solution was the "lumiketone" rearrangement of the cyclohexadienone moiety. With this interest, herein we have investigated the photochemistry of desonide under different combinations of solvents and irradiation wavelengths.

Experimental

Chemicals and Instrumentation All chemicals used were of analytical grade and were used as such without any further purification. Pure desonide was obtained from Galderma Pvt. Ltd. (Mumbai, India). 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 with 15 W phosphor coated lamps. IR spectra were recorded as KBr discs on a Perkin Elmer model spectrum RX1. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 spectrometer using $SiMe_4$ as internal standard and $CDCl_3$ as solvent. Circular dichroism spectra were measured on a Jasco-J 41A spectropolarimeter. 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 (70—230 mesh).

Photoirradiation Procedure **De** solution (in acetonitrile or 2-propanol) was stirred and flushed with argon or oxygen (as desired) for 1 h before irradiation and was kept bubbling during the irradiations. The course of reaction was monitored by thin layer chromatography on precoated silica gel TLC plates using chloroform–acetone mixtures. 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 De in Argon-Saturated Acetonitrile A solution of **De** (210 mg, 0.5 mM) in argon-saturated acetonitrile (400 ml) was irradiated for 2.5 h at 254 nm. After following the steps described in general photoirradiation procedure and column chromatography (cyclohexane–ethyl acetate), compound **2** was obtained as product.

11β,21-Dihydroxy-16α,17α-(1-methylethylidenedioxy)-1,5-cyclopregn-3-ene-2,20-dione (**2**): Yield: 115 mg (55%); HR-MS Calcd for (M^+) $C_{24}H_{32}O_6$ 416.5073, Found 416.5065; IR (KBr) 3410, 1680 (C=O), 1565 (C=C), 1355, 1160, 1022 cm^{-1} (cyclopropyl); ^{1}H-NMR (DMSO-d_6) δ: 7.24 (d,1H, J=6 Hz, H-4), 5.98 (d, 1H, J=6 Hz, H-3), 4.87 (br s, 1H, exch., OH), 4.69

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(s, 2H, H-21), 4.10 (t, 1H, H-16), 3.98 (br s, exch., OH), 3.16 (dd, 1H, J= 11,5 Hz, H-11), 1.82 (s, $OC(CH_3)_2$, 6H), 1.6—1.8 (m, 5H), 1.2—1.5 (m, 6H), 1.16 (s, 3H, H-19), 1.08 (s, 1H, H-1), 0.95 (s, 3H, H-18); ^{13}C-NMR (DMSO-d_6) δ: 211.4 (C-20), 193.2 (C-2), 132.5 (C-3), 158.1 (C-4), 109.2 ($O\underline{C}(CH_3)_2$), 98.7 (C-17), 81.4 (C-16), 65.2 (C-11), 64.6 (C-21), 58.2 (C-9), 47.4 (C-1), 48.2 (C-14), 40.4 (C-12), 36.6 (C-13), 35.1 (C-6), 32.1 (C-5), 29.9 (C-10), 27.4 (C-8), 26.0 (C-15), 25.3 (C-7), 20.8 (C-19), 14.4 (C-18).

A solution of **De** (210 mg, 0.5 mM) in argon-saturated acetonitrile (400 ml) was irradiated for 2 h at 310 nm. After following the steps described in general photoirradiation procedure and column chromatography (cyclohexane–ethyl acetate), compound **3** was obtained as the main product along with a trace amount of **2** as detected on TLC.

11β-Hydroxy-16α,17α-(1-methylethylidenedioxy)androsta-1,4-diene-3-one (**3**): Yield: 105 mg (50%); HR-MS Calcd for (M^+) $C_{22}H_{30}O_4$ 358.4712, Found 358.4718; IR (KBr) 3500, 1670, 1625, 1610; ^{1}H-NMR (DMSO-d_6) δ: 7.52 (d, J=8 Hz, 1H, H-1), 6.14 (d, 1H, J=8 Hz, H-2), 6.03 (s, 1H, H-4), 3.92 (m, 1H, H-16), 3.87 (d, J=5 Hz, 1H, H-17), 3.40 (br s, 1H, exch., OH), 3.26 (m, 1H, H-11), 1.6—2.0 (m, 6H), 1.4—1.6 (m, 5H), 1.37 (s, 3H, H-19), 1.31 (s, 6H), 1.16 (s, 3H, H-18); ^{13}C-NMR (DMSO-d_6) δ: 185.8 (C-3), 168.3 (C-5), 155.4 (C-1), 128.4 (C-2), 124.2 (C-4), 113.3 ($O\underline{C}(CH_3)_2$), 80.4 (C-16), 103.3 (C-17), 66.7 (C-11), 59.0 (C-9), 46.7 (C-14), 43.1 (C-12), 34.4 (C-10), 33.6 (C-6), 32.0 (C-7), 31.6 (C-13), 29.9 (C-8), 28.7 (C-15), 26.6 ($OC(\underline{C}H_3)_2$), 25.7 (C-19), 17.3 (C-18).

Irradiation of De in Oxygen Saturated Acetonitrile A solution of **De** (210 mg, 0.5 mM) in oxygen-saturated acetonitrile (400 ml) was irradiated for 2.5 h at 254 and 310 nm. After following the steps described in general photoirradiation procedure and column chromatography (cyclohexane–ethyl acetate), compound **2** (140 mg, 67%) was obtained as product at 254 nm whereas a complex mixtures of products was obtained at 310 nm.

Irradiation of De in Argon-Saturated 2-Propanol A solution of **De** (210 mg, 0.5 mM) in argon-saturated 2-propanol (400 ml) was irradiated for 2 h at 254 and 310 nm. After following the steps described in general photoirradiation procedure and column chromatography (cyclohexane–ethyl acetate), compound **2** (130 mg, 62%) was obtained as major product at 254 nm. Whereas at 310 nm both the compounds **2** and **3** were obtained as products.

Irradiation of De in Oxygen-Saturated 2-Propanol A solution of **De** (210 mg, 0.5 mM) in acetonitrile (400 ml) was irradiated for 2.5 h at 254 and 310 nm. After following the steps described in general photoirradiation procedure and column chromatography (cyclohexane–ethyl acetate), compound **2** (135 mg, 64%) was obtained as product at 254 nm. At 310 nm **2** (55 mg, 26%) and **4** (110 mg, 52%) were obtained as products.

17β-Hydroperoxy-11β-hydroxy-16α,17α-(1-methylethylidenedioxy)androsta-1,4-diene-3-one (**4**): Yield: 110 mg (52%); HR-MS Calcd for (M^+) $C_{22}H_{30}O_6$ 390.4700, Found 390.4694; IR (KBr) 3400, 1655, 1620, 1600; ^{1}H-NMR (DMSO-d_6) δ: 8.9 (br s, exch., OOH), 7.56 (d, J=8 Hz, 1H, H-1), 6.18 (d, 1H, J=8 Hz, H-2), 6.08 (s, 1H, H-4), 4.12 (m, 1H, H-16), 4.82 (br s, 1H, exch., OH), 2.2—2.6 (m, 4H), 1.2—1.9 (m, 6H), 1.4 (s, 3H), 1.3 (s, 3H), 1.2 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ: 192.0 (C-3), 167.1 (C-5), 156.4 (C-1), 125.7 (C-2), 124.4 (C-4), 121.5 (C-17), 105.4 ($O\underline{C}(CH_3)_2$), 73.8 (C-16), 67.1 (C-11), 58.6 (C-9), 40.8 (C-14), 37.1 (C-10), 36.2 (C-12), 33.1 (C-6), 31.9 (C-7), 30.4 (C-13), 29.6 (C-8), 22.8 (C-15), 26.4 ($OC(\underline{C}H_3)_2$), 25.4 (C-19), 17.5 (C-18).

Triphenylphosphine (26 mg) was added to a solution of hydroperoxide **4** (20 mg) in dichloromethane (20 ml) and stirring was pursued for 2 h, when the starting material was consumed, extraction with water and evaporation gave 15 mg of Compound **5**.

11β,16α-Dihydroxyandrosta-1,4-diene-3,17-dione (**5**): HR-MS Calcd for (M^+) $C_{19}H_{24}O_4$ 316.3915, Found 316.3920; IR (KBr) 3450, 1745, 1660, 1600; ^{1}H-NMR (DMSO-d_6) δ: 7.31 (d, J=8 Hz, 1H, H-1), 6.42 (d, 1H, J= 8 Hz, H-2), 6.01 (s, 1H, H-4), 4.98 (br s, 1H, exch., OH), 4.10 (m, 1H, H-16), 4.01 (br s, 1H, exch., OH), 2.5 2.8 (m, 3H), 1.7 2.4 (m, 5H), 1.3 1.7 (m, 4H), 1.41 (s, 3H), 0.98 (s, 3H); ^{13}C-NMR (DMSO-d_6) δ: 205.4 (C-17), 181.3 (C-3), 165.2 (C-5), 152.5 (C-1), 130.1 (C-2), 127.2 (C-4), 75.2 (C-16), 67.4 (C-11), 58.3 (C-9), 40.8 (C-10), 40.4 (C-19), 39.7 (C-13), 36.7 (C-14), 32.0 (C-6), 31.5 (C-8), 30.5 (C-12), 29.6 (C-7), 27.7 (C-15), 21.2 (C-18).

Results and Discussion

Irradiation of **De** at 254 nm in argon flushed acetonitrile or in oxygen-saturated solution gave compound **2** as product. The photoreaction of **De** in 2-propanol at 254 nm followed a similar course of reaction under aerobic as well as anaerobic conditions. When argon flushed **De** solution (acetonitrile or 2-propanol) was irradiated at 310 nm two products were obtained in both the solvents, which were identified as **2** and **3**. At the same irradiation wavelength (310 nm) saturation of the solution with oxygen affected the product distribution: in 2-propanol **3** was not formed; instead hydroperoxide **4** was obtained as main product along with trace amount of **2**. Whereas in acetonitrile a complex mixture of products was obtained (Chart 1).

These results can be rationalized on the basis of different mechanism of photochemical reaction of the two-separated chromophores present in this drug. At 254 nm, cross-conjugated ketone absorbs predominantly or exclusively, which causes the well known lumiketone rearrangement[24,25] of this chromophore and leads to the formation of compound **2** (Chart 2). The rearrangement leading to **2** is a concerted process and therefore not affected by the medium. On the contrary at 310 nm, where isolated ketone at C_{20} absorbs a large fraction of light, compound **3** was obtained as product which arises *via* Norrish Type I homolytic photocleavage of

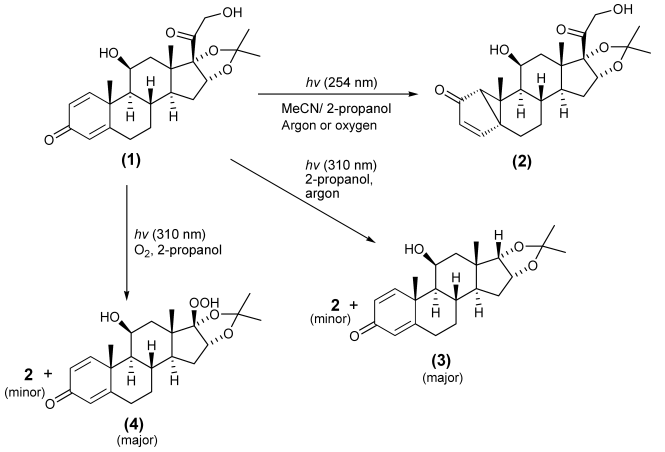

Chart 1

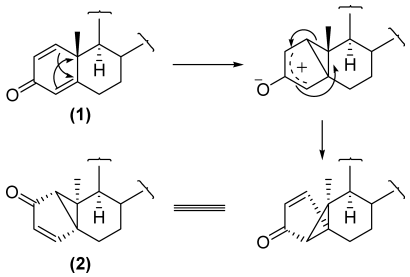

Chart 2

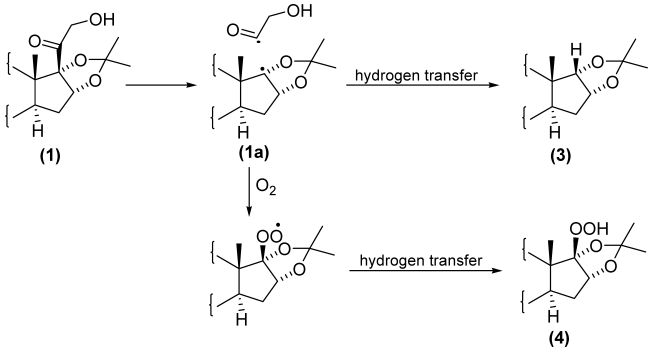

Chart 3

Table 1. Circular Dichroism Spectra of **2** and Other Related Lumiproducts

Compd.	λ_{max} ($\Delta\varepsilon$)	λ_{max} ($\Delta\varepsilon$)	Crossover λ	λ_{max} ($\Delta\varepsilon$)	Crossover λ	λ_{max} ($\Delta\varepsilon$)
2		343 (−4.71)	313	278 (+12.22)	253	225 (−11.71)
Related lumiproducts[a)]	357 (−3.71)	344.5 (−3.77)	309	272 (+10.3)	250	Short wavelength –ve CD

a) See refs. 26, 27.

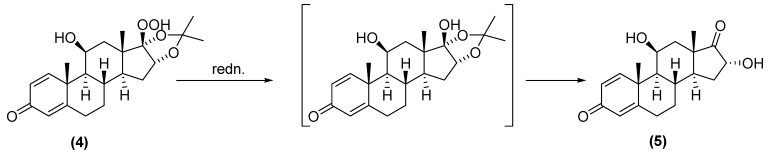

Chart 4

C_{17}–C_{20} bond followed by hydrogen atom abstraction by alkyl radical from solvent or from $HOCH_2CO$ radical. In oxygen saturated solution trapping of alkyl radical by oxygen is quite efficient to yield peroxy radical. This peroxy radical abstracts hydrogen from 2-propanol to give the isolated hydroperoxy derivative **4** (Chart 3).

All the products obtained were characterized on the basis of the following spectral evidences. The IR spectrum of **2** showed absorption bands at 1355, 1160, 1022 (cyclopropyl), 1565 (C=C), 1680 (C=O). In the NMR spectrum of **2**, signals due to the rings B, C and D were found to be unaffected while signals due to ring A was strongly modified since only two of the olefinic CH were conserved and third was substituted by a sp^3 carbon. In addition two doublets centered at δ 7.24 and 5.98 with J=6.0 Hz in the ^{1}H-NMR spectrum and the IR band values indicated the presence of an α,β-unsaturated ketone in ring A. A proton singlet at δ 1.08 and ^{13}C-NMR signals at 47.4, 32.1 and 29.9 indicated a cyclopropyl carbonyl system in ring A. Proof of the stereochemistry came from a comparison of its circular dichroism spectra with those of other lumiketones that showed positive and negative cotton effects of similar magnitude and position to those reported in literature[26,27] (Table 1).

Spectroscopic study of compound **3**, particularly NMR data indicated that the steroidal skeleton was unaffected while the side chain at C_{17} has been lost. In the ^{1}H-NMR spectrum of **3** the three deshielded olefinic protons at δ 7.52 (d, J=8 Hz, 1H), 6.14 (d, J=8 Hz, 1H) and 6.03 (s, 1H) confirmed that the dienone system was intact, and on the basis of chemical shifts and spin–spin coupling constants these signals were assigned to the C-1, C-2 and C-4 protons respectively. Signals due to ring B, C and D were also unaffected while no signal was observed due to side chain at C_{17} in its NMR spectrum. Its IR spectrum with absorption bands at 3500 (OH), 1670 (α,β-C=O), 1625, 1610 (C=C) cm^{-1}, further support the assigned structure **3** for this compound.

The NMR spectra of **4** suggested that the structural features in ring A, B and C were again conserved while side chain at C_{17} had been lost. In addition a strongly deshielded signal at δ 8.9 (br s, exch., 1H) in the ^{1}H-NMR and a new signal at δ 121.5 (C-17) in ^{13}C-NMR suggested the presence of hydroperoxy group in **4**. This compound could be reduced by triphenylphosphine and gave 16-hydroxy-17-keto derivative **5** as product (Chart 4). This chemical evidence along with the spectroscopic indications (in Experimental) allowed assignment of the hydroperoxide structure **4** for the product.

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