JOC Article

General Patterns in the Photochemistry of Pregna-1,4-dien-3,20-diones

Andrea Ricci, Elisa Fasani, Mariella Mella, and Angelo Albini*

Dep. Organic Chemistry, University of Pavia, Via Taramelli 10, 27100 Pavia, Italy

albini@chifis.unipv.it.

Received January 21, 2003

The photochemistry of six pregna-1,4-dien-3,20-diones has been compared and found to involve both the cyclohexadienone moiety in ring A and the isolated ketone at C-20. The two reactions take place proportionally to the fraction of light absorbed by each chromophore. The cross-conjugated ketone absorbs predominantly or exclusively at both 254 and 366 nm and undergoes the "lumi" rearrangement to bicyclo[3.1.0]hex-3-en-2-one. The quantum yield of the reaction diminished somewhat with increasing λ_{exc}, e.g., for prednisolone $\Phi_{254\ nm} = 0.42$, $\Phi_{366\ nm} = 0.3$. A much stronger lowering is caused by halogen substitution in position 9 (by a factor of 3 for F, >50 for Cl), apparently due to a shortened triplet lifetime caused by heavy atom effect. At 310 nm, both chromophores absorb to a comparable degree and both may react. The reaction at C_{20} ketone involves either quite efficient α-cleavage ($C_{17}-C_{20}$) for compounds bearing an acetal or hydroxyl function at C_{17} or less effective (by a factor of ca. 10) hydrogen abstraction from the 18-methyl group in the other cases (finally resulting in Norrish II fragmentation or Yang cyclization). The results allow generalizing how the substitution pattern surrounding each chromophore affects the photoreactivity at that site and the competition between the two modes, allowing predicting the photochemistry of this family of antiinflammatory drugs.

Introduction

Pregna-1,4-diene-3,20-diones are largely used as topic antiinflammatory drugs, e.g., against solar light induced erythema.[1] However, these compounds may also be *phototoxic*.[2] From the photochemical point of view, these steroid derivatives are interesting because they bear two spatially separated chromophores, viz., the cross-conjugated cyclohexadienone moiety in ring A and an isolated ketone functionality in C_{20}. Photochemical work on these compounds includes a number of studies in the solid state[3] and in solution.[4,5] Williams and co-workers[5] found that the only photoprocess occurring upon irradiation at 254 nm of prednisolone (11β,17α,21-trihydroxy-pregna-1,4-dien-3,20-dione, **1**, and similarly of prednisone, with a third ketone functionality at C_{11} replacing the C_{11}-β-hydroxy group, as well of their 21-acetates) in dioxane solution was the "lumiketone" rearrangement[6] of the cyclohexadienone moiety to yield products such as **5**, characterized by the bicyclo[3.1.0]hex-3-en-2-one structure (Scheme 1).

In a recent study on some fluorinated pregna-1,4-diene-3,20-diones (**2**−**4**, Scheme 2), we found,[7] however, a 2-fold photochemistry. Irradiation at 254 or 366 nm, where the cross-conjugated hexadienone moiety absorbs predominantly or exclusively, the incident light caused the "lumirearrangement" of ring A. On the contrary, irradiation at 310 nm, where the absorption by the two chromophores is similar, caused the Norrish I photocleavage of the C_{20} ketone. Apparently, no intramolecular energy transfer occurred between the two chromophores.

Establishing whether such a wavelength-dependent photobehavior is common to all of the pregna-1,4-diene-3,20-diones and to what extent it could be directed by means of a judicious choice of the substituents is a target

* To whom correspondence should be addressed. Phone: +39-0382-507316. Fax: +39-0382-507323.

(1) Ortel, B.; Sivayathorn, A.; Honigsmann, H. *Dermatology (Basel)* **1989**, *178*, 39.

(2) (a) Suzuki, T.; Kato, T.; Kitagachi, T.; Ono, M.; Shirawaka, K.; Nagata, M.; Konishi, R. *J. Toxicol. Sci.* **1996**, *21*, 475. (b) Keknes, A.; Jahn, P.; Lange, L. *J. Am. Acad. Dermatol.* **1993**, *28*, 786. (c)Uchiyama, H.; Tanaka, T.; Uehara, N.; Nakamura, M.; Tsuji, M.; Shinomiya, M.; Tanaka, H. *J. Toxicol. Sci.* **1996**, *21*, 475.

(3) (a) Reisch, J.; Enkel, G.; Ekiz-Guecer, N.; Nolte, G. *Liebigs Ann. Chem.* **1992**, 63. (b) Reisch, J.; Topaloglu, Y.; Henkel, G. *Acta Pharm. Tech.* **1986**, *32*, 115. (c) Takàcs, M.; Ekiz-Guecer, N.; Reisch, J.; Gergely-Zobin, A. *Pharm. Acta Helv.* **1991**, *66*, 137. (d) Ekiz-Guecer, N.; Reisch, J.; Nolte, G. *J. Pharm. Biopharm.* **1991**, *37*, 234.

(4) (a) Arakawa, Y.; Fukaja, C.; Yamanouchi, K.; Yokoyama, K. *Yakagaku Zasshi* **1985**, *105*, 1029. (b) Hidaka, T.; Huruumi, S.; Tamaki, S.; Shiraishi, M.; Minato, H. *Yakagaku Zasshi* **1980**, *100*, 72. (c) Thoma, K.; Kerker, R.; Weissbach, C. *Pharm. Ind.* **1987**, *49*, 961. (d) Ogata, M.; Noro, Y.; Yamada M.; Tahara, T.; Nishimura, T. *J. Pharm. Sci.* **1998**, *87*, 91.

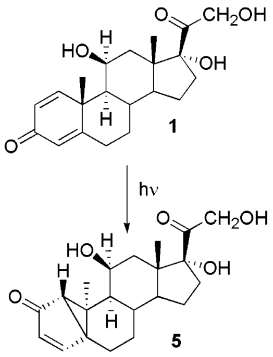
(5) (a) Williams, J. R.; Moore, R. H.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *15*, 5019. (b) Williams, J. R.; Moore, R. H.; Li, R.; Weeks, C. M. *J. Org. Chem.* **1980**, *45*, 2324.

(6) (a) Schuster, D. I. *Acc. Chem. Res.* **1978**, *11*, 65. (b) Shaffner, K.; Demuth, M. In *Rearrangements in the Ground and Excited State*; De Mayo, P., Ed., Academic Press: New York, 1980; Vol. 3, p 281. (c) Barton, D. H. R. *Helv. Chim. Acta* **1959**, *42*, 1604. (d) Caine, D. In *CRC Handbook of Photochemistry and Photobiology*; Horspool, W. M.; Song, P. S., Eds.; CRC Press: Boca Raton, FL, 1995; p 701. (e) Schultz, A. G. In *CRC Handbook of Photochemistry and Photobiology*; Horspool, W. M.; Song, P. S., Eds.; CRC Press: Boca Raton, FL, 1995; p 716.

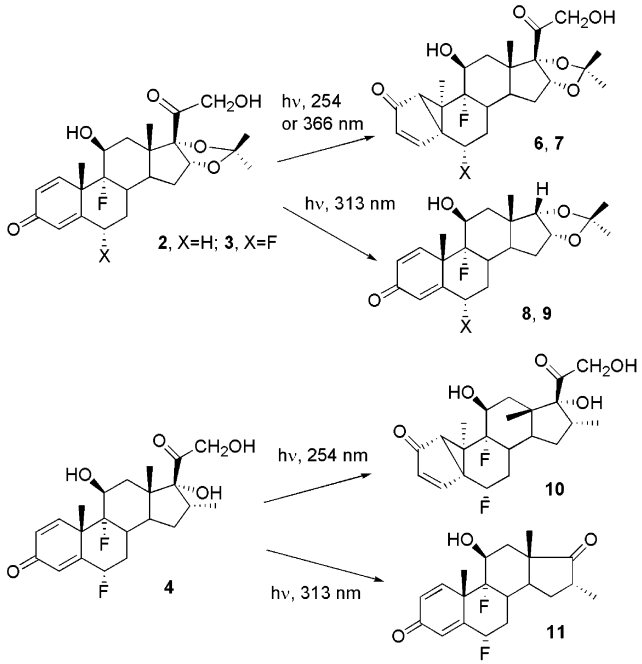
(7) Ricci, A.; Fasani, E.; Mella, M.; Albini, A. *J. Org. Chem.* **2001**, *66*, 8086.

10.1021/jo034070a CCC: $25.00
Published on Web 05/03/2003

SCHEME 1



SCHEME 2



not only for basic research but also for practical application in view of predicting and controlling the photolability and phototoxicity of such semisynthetic drugs on the basis of their structure. Therefore, we presently report a product and quantum yield study on prednisolone **1** and some of its derivatives with strategic changes in the substitution pattern adjacent to *both* chromophores, the cross-conjugated ketone in ring A, and the isolated ketone at position C_{20}.

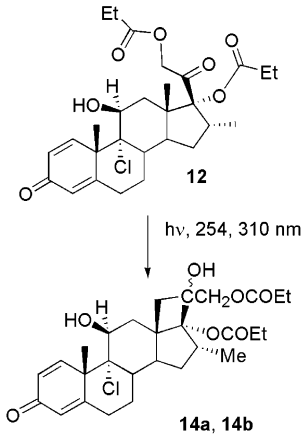
Results

As mentioned in the Introduction, the photochemistry of prednisolone **1** has already been reported[5] to form the lumiderivative **5** at 254 nm, although the quantum yield of the reaction has not been measured. We repeated the irradiation in argon-flushed acetonitrile and confirmed that compound **5** is essentially the only product (70% isolated yield). Separate experiments at low (≤20%) conversion, to avoid secondary photolysis, allowed measuring a quantum yield of 0.42. When the irradiation was carried out at 310 and 366 nm, representative of the UV−B and, respectively, the UV-A component of UV light, rearrangement to **5** was again essentially the only photoprocess, though with a somewhat lower quantum yield (Φ 0.3) and isolated yield in the preparative irradiations (60%).

TABLE 1. Quantum Yield for the Photochemical Reactions of Pregnadiendiones

steroid	irradiation wavelength	overall quantum yield (Φ_r)	reaction at the cross-conjugated dienone (Φ)	reaction at C20-ketone (Φ)
1	254 nm	0.423	**5** (0.296)	
1	310 nm	0.305	**5** (0.183)	
1	366 nm	0.302	**5** (0.181)	
2	254 nm	0.181	**6** (0.135)	**8** (0.005)
2	310 nm	0.450	**6** (0.049)	**8** (0.293)
2	366 nm	0.060	**6** (0.030)	
3	254 nm	0.051	**7** (0.043)	**9** (0.005)
3	310 nm	0.310	**7** (0.015)	**9** (0.263)
3	366 nm	0.031	**7** (0.015)	
4	254 nm	0.052	**10** (0.041)	**11** (0.005)
4	310 nm	0.110	**10** (0.011)	**11** (0.071)
12	254 nm	0.008		**14a**, **b** (0.001)
12	310 nm	0.083		**14a**, **b** (0.042)
12	366 nm	≤0.0001		
13	254 nm	0.052	**15** (0.039)	
13	310 nm	0.073	**15** (0.015)	**16**+**17** (0.033)
13	366 nm	0.029	**15** (0.014)	

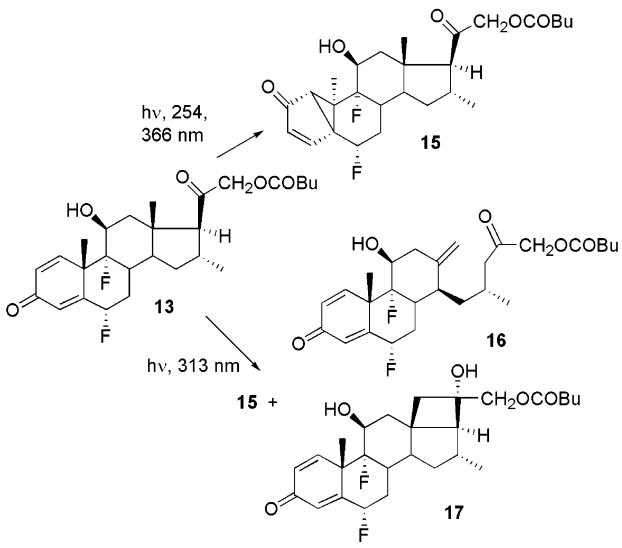
SCHEME 3



The quantum yields at the three λ_{irr} are reported in Table 1, where these are compared with the data for the previously considered fluorinated glucocorticosteroids, **2** (triamcinolone acetonide), **3** (fluocinolone acetonide), and **4** (flumethasone) with the characteristic wavelength-dependent photochemistry.

We then explored the effect of a different halogen by studying the photochemistry of 9-chloro-11β,17α,21-trihydroxy-16α-methyl-pregna-1,4-dien-3,20-dione-17,21-dipropionate (beclomethasone 17,21-dipropionate **12**), that bore a chlorine atom (rather than a fluorine as in compounds **2**−**4**) in position 9 and further had the hydroxyl groups in C_{17} and C_{21} protected as the propionate ester. The photodegradation of compound **12** at 254 or 310 nm occurred with different quantum yields (0.008 and 0.08 respectively) but afforded the same mixture of two photoproducts (in 1:4 ratio at both wavelengths, Scheme 3). Spectroscopic analysis, in particular NMR data, indicated that the steroid skeleton was unaffected, but both the C_{20} ketone and the 18-methyl signals were lacking. These data, along with the appearance of a new methylene carbon (see the Experimental Section for details and further information) supported the structure

SCHEME 4



of the diastereoisomeric 20-hydroxy-18,20-cyclopregna-1,4-dien-3-ones **14a** and **14b** for these products. The (cumulative) isolated yield in preparative experiments was 50% at 310 nm and 10% at 254 nm. Surprisingly, no trace of the expected "lumiproduct" was detected at either 254 or 310 nm, or indeed at 366 nm, where compound **12** showed to be virtually photostable ($\Phi < 1 \times 10^{-3}$).

A further variation was explored with 6α,9-difluoro-21-hydroxy-16α-methyl-pregna-1,4-diene-3,20-dione-21-valerate (**13**, diflucortolone 21-valerate). This pregnadiendione has the same fluorination pattern as compounds **3** and **4** but differed by lacking an oxygenated functionality at C_{17}, while maintaining the one at the C_{21} (hydroxyl group esterified as valerate). This compound showed again a wavelength-dependent photoreactivity (Scheme 4). Thus, irradiation at 254 nm in argon-flushed acetonitrile ($\Phi = 0.05$) afforded in high yield a single product isomeric with the starting material, which was recognized as the lumiderivative **15** (75%, see the Experimental Section for the structural attribution). When the irradiation was effected at 366 nm, the quantum yield of the reaction was somewhat lower (0.03) and **15** was again the main product (70%), although it underwent further photoreaction at a longer irradiation time.

On the other hand, irradiation of **13** at 310 nm ($\Phi =$ 0.07) gave, besides a certain amount of "lumiketone" **15** (30%), two new compounds, which were separated and characterized by analytical and spectroscopic methods. Key evidence from the NMR spectra was the fact that rings A−C and the valerate chain were unaffected, whereas the 18-methyl signal was missing in both of them. The major one (30%) maintained the ketone at C_{20} unaffected and showed an olefin methylene signal, whereas the minor one (5%) lacked the carbonyl C_{20} signal and showed the presence of an aliphatic methylene group. These data, along with further evidence (see the Experimental Section for details) allowed the assignment of the structure **16** to the major product and **17** to the minor one.

The quantum yields data for derivative **12** and **13**, obtained at low conversion at the three wavelengths, are likewise reported in Table 1.

Discussion

In our previous study[7] of pregnadiendiones **2**−**4**, we showed that both of the separated chromophores on these derivatives, the cross conjugated dienone in ring A and the ketone at C20, react independently from the respective triplet states, and intramolecular T−T energy transfer does not compete with fast local reaction, as expected from theory. As a result, it is the fraction of light absorbed by each chromophore at each wavelength that determines the site of the reaction. For derivative **2**, it has been measured[7] that the fraction of light absorbed by the cyclohexadienone is 0.992 at 254 and 1 at 366 nm, whereas at 310 nm, it is only 0.57. A substantial amount of the incident light is thus absorbed by the isolated ketone at this wavelength (0.43). This essentially holds also for the present derivatives and one would expect the rearrangement at 254 and 366, with some degree of competition by reaction at the ketone functionality at C20 at 310 nm. The aim of the present investigation was to explore the structural effects on the efficiency of the photoreactions at each chromophore and to rationalize the overall chemical path followed as a result of their competition. This would also allow arriving at predicting the photoreactivity (and indirectly the phototoxicity) or these family of compounds, all of which are used as drugs.

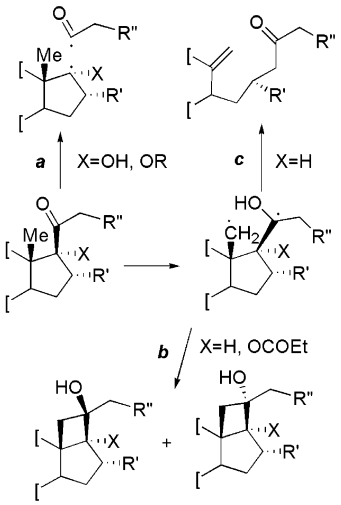
"Lumiketone" Rearrangement. This rearrangement and its role in the photochemistry of steroids has been largely investigated in the previous literature.[6] On monocyclic cyclohexa-2,5-dienones, it occurs with quantum yields close to unitary (0.75−1),[8] although it has been reported that some substituents affect the efficiency of the photoprocess, a fact mainly attributed to a change in the stability of the suggested zwitterionic intermediates of the rearrangement.[8−10] In polycyclic derivatives, and in particular with steroid cyclohexadienones, the quantum yield is slightly lower. A value of 0.58 has been reported for Δ^1-dehydrotestosterone,[11] a compound strictly related to the presently studied ketones.

In keeping with this result, we measured a quantum yield value of 0.42 for the reaction of prednisolone **1** in argon flushed acetonitrile at 254 nm, and the only process occurring was the "lumi" rearrangement. A conspicuous substituent effect was observed. Thus, under the same conditions, the quantum yield of this rearrangement decreased to 0.18 with **2** (a 9-monofluoro derivative) and to ca. 0.05 with **3**, **4**, and **13** (6α,9-difluoro derivatives). With the 9-choro derivative **12**, the overall quantum yield of reaction was only 0.008 at 254 nm. The main contribution to the reaction, however, was fragmentation of the ketone in position 20, as shown by the formation of products **14a**,**b** even at this wavelength, and rearrangement to the nondetected lumiketone must have a still lower Φ value.

The simplest rationalization of this remarkable decrease induced by halogens is a heavy atom effect that

(8) Schuster, D. I.; Patel, D. I. *J. Am. Chem. Soc.* **1968**, *90*, 5145.
(9) (a) Schuster, D. I.; Abraitis, Y. Y. *Chem. Commun.* **1969**, 419. (b) Schuster, D. I.; Patel, D. I. *J. Am. Chem. Soc.* **1968**, *90*, 5137.
(10) (a) Caine, D.; Brake, P. F.; de Bartdeleben, J. F.; Dawson, J. B. *J. Org. Chem.* **1973**, *38*, 967. (b) Broca, C. A. *J. Org. Chem.* **1988**, *53*, 575. (c) Stille, C. J. K.; Retting, T. A.; Kneunerle, E. W. *J. Org. Chem.* **1976**, *41*, 2950. (d) Zimmerman, H. E.; Pasteris, R. J. *J. Org. Chem.* **1980**, *45*, 4864.
(11) Schuster, D. I.; Barringer, W. C. *J. Am. Chem. Soc.* **1971**, *93*, 73.

SCHEME 5



shortens the triplet lifetime by increasing the rate of ISC to S_0 (by a factor of 3 with a 9-F, 9 with 6α,9-F_2, of >50 with 9-Cl). Inspection of MM2 models shows that the C−X bond in **9** is collinear with the π system of the cyclohexadienone and ideally suited for exerting such an effect. Dramatic effects of halogens on T_1-S_0 ISC rate have been well documented with aromatics,[12] and although there is no close precedent for dienones, it appears reasonable that the favorable geometric position makes halogen induced k_{ISC} competitive with k_r (for 4,4-dimethylcyclohexa-2,5-dienone the rate of rearrangement has been estimated $k_r = 7 \times 10^8$ mol^{-1} s^{-1} by quenching experiments).[8] The further decrease in quantum yield caused by introducing a second fluorine in position 6 may be due to the same reason or to a destabilization of the zwitterionic intermediate caused by the electron-withdrawing ability of the halogen.

The second trend that has been noted is a decrease by a factor of 2 from 254 to 366 nm in the rearrangement quantum yield upon increasing λ_{irr}. That occurs with all of the steroids examined. We are not aware of previous systematic investigations of the effect of adsorbed radiation on the lumirearrangement, but the present data suggest that either ISC (S_n-T_1) changes significantly for higher-lying singlets or that rearrangement from T_1 encounters a significant energy barrier, at least when the cyclohexadienone moiety is incorporated in a rigid skeleton as in the present case.

Reaction at the Isolated Ketone. Reaction at C_{20} ketone occurs for most of the examined pregnadiendiones upon irradiation at 310 nm and also in this case there is a strong dependence on the substitution close to the moiety involved. As previously found with compounds **2** and **3**, both of which bear an acetalic function at $C_{16}-C_{17}$, the main process at 310 nm is the Norrish type I cleavage of the $C_{17}-C_{20}$ bond (path *a* in Scheme 5) with $\Phi = 0.41$ and 0.3, respectively. With **4**, bearing a hydroxyl group at C_{17}, Φ is lower (0.11), reasonably because the less rigid structure diminishes the optimal alignment of the C−O bond with the fragmentable C−C bond. It should be noted that a hydroxyl group at freely rotating C_{21} is present in most of these compounds, but the alternative $C_{20}-C_{21}$ Norrish I cleavage is never observed, a fact that can be similarly attributed to the lack of the favorable alignment.

The determining role of a rigid acetal or, to a lower degree, of a hydroxyl or alkoxy function in promoting the Norrish type I cleavage at C_{17} can be appreciated by the fact that such a fragmentation does not occur with **12** (which has a propionyloxy group, apparently unable to reach the correct configuration and/or a poorer electron-donor) and with **13** which has no oxygenated functions at C_{17}. Different reactions of the nπ* ketone take place with this compounds, viz., hydrogen abstraction from the close-lying 18-methyl group followed by cyclization (Yang reaction, path *b* in Scheme 5) with the first, and to a lesser degree, with the latter ketone, or by fragmentation of the $C_{13}-C_{18}$ bond (path *c*, main process with the latter ketone). The initial abstraction is facilitated in both compounds by the fact that C_{20} ketone and 18-methyl groups, both with β orientation, are held in a suitable conformation by the rigid skeleton. Cyclization of the biradical to hydroxycyclobutane has been reported by Shaffner et al.[13] for some pregnan-20-ones lacking further photoreactive moieties in the structure and bearing a hydrogen atom in position 17α. Alternatively, β-scission of the 1,4-biradical (Norrish type II photoreaction) leads to the open chain alkene **16**, the major process from ketone **13** (also in this case, there is a precedent for a simpler steroid).[14]

Summing up, a hydroxyl or acetal function in **17** (but not in **21**) exerts a bias toward α-fragmentation. In the other cases, intramolecular hydrogen abstraction from the γ-position leading to Norrish type II fragmentation or cyclization results. The first process is more efficient and occurs with a quantum yield of ∼0.3 (for acetals **2** and **3**) and ∼0.07 (for alcohol **4**) at 310 nm, which, taking into account that the absorption by the ketone at this wavelength is around 40%, indicates an intrinsic efficiency of cleavage of 0.8 and 0.2, respectively. On the contrary, hydrogen abstraction is characterized by a quantum yield of ∼0.04 at this wavelength and, thus, an intrinsic efficiency of ∼0.1

Competition between the Two Photoprocesses. The competition between the two photoprocesses is determined by the absorption by each chromophore and the efficiency of the reaction at each site. The cyclohexadienone moiety absorbs all of the light at 366 and >99% of it at 254, and 50% or more at 310 nm. Thus, with a halogen-free pregnadiendione such as **1**, the lumirearrangement occurs efficiently with no measurable competition by reaction at the isolated ketone (here not particularly favored, because there is an OH group, not an acetal at C_{17}). A wavelength-independent photochemistry thus results, with some decrease in the quantum yield with decreasing excitation energy.

(12) (a) Ermolaev, V. L.; Svitashev, K. K. *Opt. Spectr.* **1959**, *7*, 399. (b) Castro, G.; Hochstrasser, R. M. *J. Chem. Phys.* **1966**, *44*, 412. (c) McGlynn, S. P. *Chem. Rev.* **1958**, *58*, 1113. (d) McGlynn, S. P.; Azumi, T.; Kinoshita, M. *Molecular Spectroscopy of the Triplet State*; Prentice Hall: Engelwood Cliffs, New Jersey, 1969. Birks, J. B. *Photophysics of Aromatic Molecules*, Wiley-Interscience: London, 1970.

(13) (a) Buchschacher, P.; Cereghetti, M., Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2122. (b) Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1960**, *43*, 354. (c) Wehrli, H.; Cereghetti, M.; Schaffner, K.; Urech, J.; Vischer, E. *Helv. Chim. Acta* **1961**, *44*, 1927.

(14) Suginome, H.; Nakayama, Y. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1843.

Compound **12** represent the opposite case. In this instance, the 9-chloro atom so effectively suppresses the lumirearrangement that the photochemistry is again wavelength-independent, but this time it is the one of the isolated ketone. Consistently with the proposed mechanism, the quantum yield is much higher at 310 nm than at 254 nm, because the reactive chromophore absorbs a much larger fraction of light at the former wavelength (and indeed, no reaction takes place at 366 nm where the isolated ketone is transparent). In all of the other cases (**2**−**4** and **13**) a wavelength-dependent photochemistry takes place, with reaction at both of the photolabile moieties proportional to the relative absorptions by each chromophore.

For the studied pregandiendiones, the overall quantum yield at 254 nm is consistently larger than Φ_{366}, because at both of the wavelengths it is the cross conjugated ketone that absorbs almost exclusively the light and the efficiency decreases by shifting λ_{irr} to the red (except for ketone **12** that does not react at this moiety). On the contrary, Φ_{310} may be lower or higher than Φ_{254} according to the efficiency of the reaction of the isolated ketone that contributes significantly in this case.

Conclusions

The main finding in this work is the dramatic decrease of the quantum yield of the lumiketone rearrangement by the effect of suitably situated fluorine or chlorine atoms through heavy atom effect (dropping to $<^1/_{50}$ with chlorine in position 9). This removes from the pregnadiendiones most part of the photoreactivity. As for the isolate ketone at C_{20}, this is protected from photoreaction by the strong absorption by the cross-conjugated chromophore through an inner filter effect, because it has a much lower absorption over a large part of the spectrum. When it shows up (irradiation at 310 nm), reaction at this site is again substituent-dependent. An acetal or hydroxyl function in position 17 induces α-cleavage (intrinsic efficiency 0.2−0.8), whereas hydrogen abstraction from the methyl in position 18 occurs with a lower intrinsic efficiency, ∼0.1, when no oxygenated function is present and assists the previous reaction.

The conclusions presented here allow to predict the type and efficiency of the photoreaction(s) occurring in a steroid of this family on the basis of the above-discussed key structural features in the vicinity of the two chromophores. This should allow us to propose hypotheses on the mechanism of the phototoxic behavior of these drugs. When a concerted process such as the lumiketone rearrangement takes place, toxicity, if any, must be related to the formation of toxic end-photoproducts. When a process involving homolytic fragmentation such as the Norrish type I cleavage or hydrogen atom abstraction occurs, the phototoxicity may be related not only to the formation of toxic photoproducts but also to the role of alkyl radicals formed as transients or of hydroperoxyl radicals formed from them by oxygen addition (such radicals have been demonstrate to damage DNA).[15]

The substituent effect on the photobehavior of the chromophores should be considered along with other factors when planning the improvement of pharmacological effect and the lessening of undesirable side effects in semisynthetic glucocorticosteroids. Thus, a halogen atom in position 9, found to increase the antiinflammatory activity,[16] also reduces the possible phototoxic effects due to the cyclohexadienone photoreactivity, as it partially quenches the rearrangement of this moiety. On the contrary, introduction of an oxygenated function in position 17, found to reduce mineralcorticoid activity, an undesired side effect, unfortunately enhances the C_{20} ketone photoreaction and, thus, the formation of the radical, which may induce a specific phototoxicity (though relevant only upon UV−B irradiation).

Experimental Section

Diflucortolone-21-valerate (**13**) and beclomethasone-17,21-dipropionate (**12**) were kindly supplied by Farmabios, Gropello Cairoli, Italy. Their purity was checked by HPLC and NMR spectroscopy. Prednisolone (**1**) was a commercial sample. Spectroscopic grade solvents were used for irradiations.

Preparative Photochemical Reactions. Irradiation at 254 nm was performed in an immersion well apparatus fitted with a quartz filtered 20 W low-pressure mercury arc lamp. Before irradiation, purified argon was flushed under stirring for 2 h, and a low gas flux was maintained during the reaction. For the irradiations at 310 and 366 nm, the solution was distributed in a series of serum-capped quartz tubes, nitrogen flushed, and then externally irradiated in a multilamp apparatus fitted with eight 15 W phosphor coated lamps with the required emission band.

The reactions were monitored by means of HPLC (Hypersil ODS-2, 4,6 × 250 mm, 5 μm column, eluting with acetonitrile/water mixtures) and TLC (eluting with cyclohexane−ethyl acetate mixtures).

When the desired conversion was reached, the solvent was rotary evaporated and the products were purified by recrystallization or by preparative chromatographic separation with a 0.04−0.063 silica gel column eluting with the above solvent mixtures.

The characterization of the new compounds was based on analytical and spectroscopic techniques. [α_D] were measured at 20 °C in MeOH (5 mg/mL), and NMR spectra were recorded on a 300 MHz spectrometer.

Photolysis of Prednisolone (1) at 254 nm. A solution of compound **1** (0.4 g, 1.1 mmol) was irradiated in acetonitrile (220 mL) for 1 h and a 90% conversion was reached. Recrystallization from ethyl acetate of the residue gave 250 mg of the previously reported[5] 11β,17α,21-trihydroxy-1,5-ciclopregn-3-ene-2,20-dione **5**. Colorless crystals; mp 233−234 °C (AcOEt); $[\alpha]_D = -73{,}2°$; IR: 3461, 2929, 2846, 1710, 1670, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, Me-18), 1.28 (s, 3H, Me-19), 2.3 (bs, 1H, H-1), 1.0−2.8 (m, 15H); 4.46 (m, 1H, H-11), 4.32 and 4.67 (AB system, J = 20 Hz, 2H, H-21), 5.9 (d, J = 6 Hz, 1H, H-3), 7.28 (d, J = 6 Hz, H-4).

Photolysis of Beclomethasone-17,21-dipropionate (12) at 310 nm. A solution of compound **12** (1 g, 1.9 mmol) was irradiated at 310 nm in acetonitrile (384 mL) for 10 h until a 50% conversion was reached. Chromatographic separation gave a mixture of two isomers (247 mg, 50%). These were identified as the two isomeric cyclobutanols **14a** and **14b**, mainly on the basis of NMR (no carbonyl group, presence of a hydroxyl group a new methylene replacing a methyl group). Signals superimposition discouraged investigating the C-20 configuration in this case, and the stereochemistry was assigned by comparing the NMR with the analoguous derivative **18** (see below) which was isolated as pure compound. IR: 3300, 1730, 1650 cm^{-1}.

(15) Adam, W.; Arnold, M. A.; Saha-Möller, C. R. *J. Org. Chem.* **2001**, *66*, 597.

(16) Foye, W. O.; Lemke, L.; Williams, T. *Principles of Medicinal Chemistry*; Lea&Febiger Books: Philadelphia, PA, 1995.

9-Chloro-16α-methyl-11*β*,17α,20,21-tetrahydroxy-18,20-cyclopregna-1,4-dien-3-one 17,21-dipropionate (14a). ^{1}H NMR($CDCl_3$): δ 1.15 (t, $J = 7$, 3H, Me), 1.2 (t, $J = 7$, 3H, CH_3), 1.25 (d, $J = 7$, 3H, CH_3), 1.6 (s, 3H, Me), 2.3−2.4 (m, 4H, CH_2), 1.2−2.8 (m, 15H), 4.55 (m, 1H, H-11), 4.5 and 4.7 (m, 2H, AB system, $J = 18$, CH_2-21), 6.05 (bt, $J = 1.5$, 1H, H-4), 6.4 (dd, $J = 10$, 1.5, 1H, H-2), 7.2 (d, $J = 10$, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 8.9 (CH_3), 9.1 (CH_3), 18.9 (CH_3), 24.2 (CH_2), 24.2 (CH_3), 26.6 (CH_2), 27.5 (CH_2), 30.4 (CH_2), 31.1 (CH_2), 34.3 (CH), 37.7 (CH_2), 39.2 (CH_2), 40.3 (CH), 46.5, 48.4 (CH), 49.6 (C-10), 67.9 (CH_2-21), 75.3 (CH-11), 77.7 (C-9), 82.2 (C-20), 94.4 (C-17), 124.8 (CH-4), 129.3 (CH-2), 151.7 (CH-1), 165.5 (C-5), 174.7 (COOR), 174.9 (COOR), 186.3 (C-3).

9-Chloro-16α-methyl-11*β*,17α,20,21-tetrahydroxy-18,20-cyclopregna-1,4-dien-3-one 17,21-dipropionate (14b). ^{1}H NMR ($CDCl_3$): δ 1.18 (t, $J = 7$, 3H, Me), 1.22 (s, 3H, CH_3), 1.25 (d, $J = 7$, 3H, Me), 1.65 (s, 3H, Me), 2.3−2.4 (m, 4H, CH_2), 1.2−2.8 (m, 15H), 4.4 (m, 1H, H-11), 4.3 and 5.1 (m, 2H, AB system, $J = 18$, CH_2-21), 6.05 (bt, $J = 1.5$, 1H, H-4), 6.42 (dd, $J = 10$, 1.5, 1H, H-2), 7.22 (d, $J = 10$, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 8.5 (CH_3), 8,7 (CH_3), 18.6 (CH_3), 24.2 (CH_3), 27.2 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 31.2 (CH_2), 34.3 (CH), 37.4 (CH_2), 39.2 (CH_2), 40.3 (CH), 45.2, 48.0 (CH), 49.8, 63.6 (CH_2-21), 75.6 (CH-11), 77.9 (C-9), 86.3 (C-20), 87.0 (C-17), 124.8 (CH-4), 129.3 (CH-2), 151.9 (CH-1), 165.6 (C-5), 173.3 (COOR), 174.7 (COOR), 186.3 (C-3).

Photolysis of Diflucortolone-21-valerate (13) at 254 nm. A solution of compound **13** (1 g, 2.1 mmol) in acetonitrile (420 mL) was irradiated for 7 h, and 60% conversion was reached. Chromatographic separation of the residue (eluting with a cyclohexane−ethyl acetate, 80/20 mixture) gave 300 mg (50%) of compound **15**.

6α,9-Difluoro-16α-methyl-11*β*,21-dihydroxy-1,5-cyclopregna-3-en-2,20-dione 21-valerate (15). Colorless crystals; mp 220 °C (AcOEt); $[\alpha]_D$ +8°. IR: 3490, 2954, 1721, 1685, 1172, 968 cm^{-1}. Anal. Calcd for $C_{27}H_{36}F_2O_5$ C, 67.76; H, 7.58. Found: C, 67.88; H, 7.31. ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, Me-18), 0.93 (d, $J = 7$, 3H), 0.98 (t, $J = 7$, 3H), 1.3 (s, 3H, Me-19), 1.6 (m, 2H, CH_2), 2.45 (t, $J = 7$, 2H, CH_2−CO), 2.75 (m, 1H, H-16), 4.33 (m, 1H, H-11), 4.45 and 4.7 (AB system, $J = 17$, 2H, H-21), 5.2 (dt, $J = 53$, 7.5, 1H, H-6), 6.1 (d, $J = 5.5$, 1H, H-3), 7.67 (d, $J = 5.5$, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 7.89 (CH_3), 13.4 (CH_3), 15.5 (CH_3), 21.6 (CH_3), 21.9 (CH_2), 26.6 (CH_2), 27.6 (d, $J = 23$, CH_2-7), 29.1 (dd, $J = 18.8$, CH-8), 30.9 (CH), 32.6 (CH_2), 33.2 (CH_2), 36.0 (t, $J = 7$, CH-1), 41.6 (CH_2), 44.8, 46.8 (CH), 52.3 (d, $J = 27$, C-10), 68.8 (d, $J = 35$, CH-11), 69.1 (CH_2-21), 86.5 (d, $J = 175$, CH-6), 94.8 (d, $J = 175$, C-9), 133.6 (CH-3), 159.8 (d, $J = 10$, CH-4), 172.9 (COOR), 202.8 (C-2), 203.6 (C-20).

Photolysis of Diflucortolone-21-valerate at 310 nm. A solution of compound **13** (1 g, 2.1 mmol) in acetonitrile (420 mL) was irradiated for 4 h, when 50% conversion was reached. Column chromatography (eluting with cyclohexane/ethyl acetate 80/20) afforded the following photoproducts: **15**, 20 mg (20%); **16**, 125 mg (30%) and a cyclobutanol derivative identified as **17**, 20 mg (5%).

6α,9-Difluoro-16α-methyl-11*β*,21-dihydroxy-13-methylene-18-nor-13,17-seco-pregna-1,4-dien-3,20-dione 21-valerate (16). Colorless crystals; mp 190 °C (AcOEt); $[\alpha]_D$ +10°. IR: 3300, 2960, 1725, 1660, 1620, 1075, 900 cm^{-1}. Anal. Calcd for $C_{27}H_{36}F_2O_5$: C, 67.76; H, 7.58. Found: C, 67, 8; H, 7.61. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, $J = 7$ Hz, CH_3), 0.98 (d, 3H, $J = 7$ Hz, CH_3), 1.45 (s, 3H, CH_3, Me-19), 1.4 (m, 2H), 1.65 (m, 2H, $J = 7$ Hz), 2.46 (t, 2H, $J = 7$ Hz), 4.3 (m, 1H, H-11), 4.62 (AB system, 2H, H-21), 5.0 and 5.05 (bs, 2H, CH_2-18), 5.3 (dddd, $J = 50$, 13, 8, 2 Hz, 1H, H-6), 6.4 (d, $J = 10$ Hz, 1H, H-2), 6.45 (bs, 1H, H-4), 7.14 (d, $J = 10$ Hz, 1H, H-1), 1.3−2.8 (m, 11H + OH). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3), 20.9 (CH_3), 21.9 (CH_2), 23.05 (d, $J = 5$ Hz, CH_3 Me-19), 26.7 (CH_2), 27.0 (CH), 33.3 (CH_2), 33.4 (d, $J = 23$ Hz, CH_2-7), 35.1 (CH_2), 39.4 (dd, $J = 18$, 8 Hz, CH-8), 40.5 (CH_2), 40.8 (CH), 44.6 (CH_2), 47.3 (d, $J = 10$ Hz, C-10), 68.0 (CH_2), 68.9 (d, $J = 35$ Hz, CH-11), 86.3 (d, $J = 175$ Hz, CH-6), 98.0 (d, $J = 175$ Hz, C-9), 112.3 (CH_2-18), 120.9 (d, $J = 10$ Hz, CH-4), 130.0 (CH-2), 149.7 (C-13), 149.7 (CH-1), 160.2 (C-5), 172.9 (COOR), 184.9 (C-3), 203.1 (CO).

6α,9-Difluoro-16α-methyl-11*β*,20,21-trihydroxy-18,20-cyclopregna-1,4-dien-3-one 21-valerate (17). Colorless crystals; mp 105 °C; $[\alpha]_D$ +42°. IR: 3250, 2690, 1660, 1620, 900 cm^{-1}. Anal. Cald for $C_{27}H_{36}F_2O_5$: C, 67.76; H, 7.58. Found: C, 676.72; H, 7.63. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, $J = 7$ Hz, 3H), 0.94 (d, $J = 7$ Hz, 3H), 1.37 (ses, 2H, butyl methylene), 1.48 (s, 3H, Me-19), 1.65 (qui, 2H, butyl methylene), 1.9 (d, $J = 4$ Hz, 1H, H-17), 2.1 (exch, 2H, OH), 2.0 (m, 1H, H-16), 2.0 and 2.4 (m, 2H, H-12), 2.35 (t, $J = 7$ Hz, 2H, buthyl methylene), 1.5−2.2 (m, 8H), 4.0 (AB system, 2H), 4.4 (m, 1H), 5.4 (dddd, $J = 50$, 13, 8, 2 Hz, 1H), 6.35 (dd, $J = 10$, 2 Hz, 1H), 6.43 (bs, $J = 2$ Hz, 1H), 7.1 (d, $J = 10$ Hz, 1H). The C-20 configuration was attributed on the basis of NOESY experiment: a cross-peak between H-21 (4.0 ppm) and the hydrogen at 2.02 ppm (attributed to H-18) was apparent, whereas no correlations with H-17 (1.9 ppm) and with the methyl group in position 16 were found. A cross-peak between H-17 and the methyl in 16 position was apparent, confirming their spatial closeness. Thus, in the cyclobutane ring the hydroxy group was cis to H-17, whereas the chain was at the opposite side.

^{13}C NMR ($CDCl_3$): δ 13.5 (CH_3), 22.0 (CH_2), 22.5 (CH_3), 23.0 (d, $J_{C-F} = 5$ Hz, CH_3), 26.9 (CH_2), 32.3 (dd, $J_{C-F} = 18$, 8 Hz, CH-8), 32.8 (CH_2), 33.8 (CH), 33.9 (d, $J_{C-F} = 23$ Hz, CH_2-7), 33.9 (CH_2), 34.2 (CH_2), 35.8 (CH_2), 41.2 (CH_2), 43.7, 43.9 (CH), 48.1 (d, $J_{C-F} = 27$ Hz, C-10), 60.1 (CH-17), 66.9 (CH_2), 72.5 (C-20), 72.5 (d, $J_{C-F} = 36$ Hz, CH-11), 86.4 (d, $J_{C-F} = 175$ Hz, CH-6), 99.1 (d, $J_{C-F} = 175$ Hz, C-9), 120.9 (d, $J_{C-F} = 13$ Hz, CH-4), 129.9 (CH-2), 150.7 (CH-1), 161.3 (d, $J_{C-F} = 10$ Hz, C-5), 174.0 (COOR), 185.5 (C-3).

Quantum Yields Measurements. A total of 3 mL of an acetonitrile solution (2.5×10^{-3} M for all of the steroids, but 2×10^{-4} M for beclomethasone base) of the pregnane derivatives were irradiated in spectrophotometric sealed cuvettes. The light source was a low-pressure mercury arc lamp for 254 nm and a focalized high-pressure mercury arc lamp with the appropriate interference filter for 313 and 366 nm. The fraction of light absorbed was measured by means of a photon counter placed behind the cuvette. The steroids conversion was determined by HPLC analyses. The light flux was measured by ferrioxalate actinometry.

Acknowledgment. Partial support of this work by MIUR, Rome, and ISS, Rome, is gratefully aknowledged.

JO034070A