Noncommunicating Photoreaction Paths in Some Pregna-1,4-diene-3,20-diones

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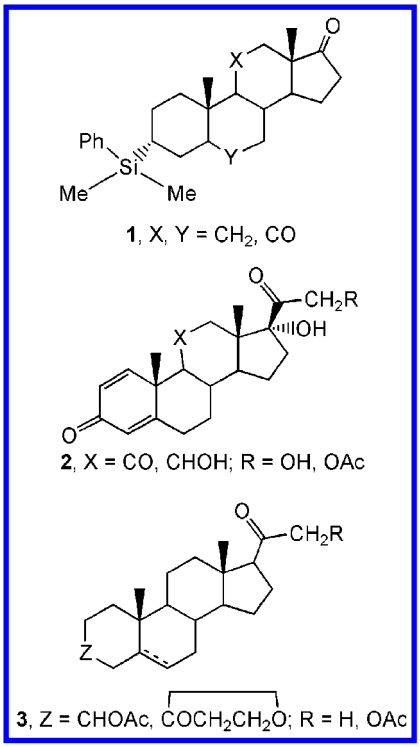
The photochemistry of three pregna-1,4-diene-3,20-diones bearing a hydroxy or alkoxy group at C_{17} (**4**−**6**) has been examined. Irradiation at 254 or 366 nm, where absorption by the cross-conjugated ketone moiety in ring A is predominant or exclusive, causes the 'lumiketone' rearrangement of this chromophore in low to medium quantum yield (Φ_r 0.05 to 0.31). On the contrary, irradiation at 310 nm, where the isolated ketone at C_{20} absorbs a large portion of light causes Norrish-I fragmentation of that chromophore with a higher Φ_r (0.11−0.83). This leads to end-products arising from the conversion of the C_{17} alkyl radical, in a way depending on the structure and the medium (reduction by hydrogen donating solvent, addition of oxygen when present). No intramolecular T−T energy transfer between the separated chromophores occurs. The 'lumiketone' rearrangement occurs independently from the irradiation wavelength (Φ_r 0.06−0.18) with the strictly related androsta-1,4-dien-3-one **8** lacking the C_{20} ketone function.

Polyfunctional molecules have long been a subject of investigation in photochemistry. Of particular interest is establishing the mechanisms for delocalizing and transmitting electronic excitation in molecules in which the chromophores are connected by a rigid hydrocarbon framework.[1] A considerable part of this work made use of steroid derivatives, from which a variety of models with unambiguous geometry can be prepared.[2,3] As an example, Morrison established through a series of elegant papers[2] that intramolecular energy transfer (both singlet−singlet and triplet−triplet) occurred from the phenyl 'antenna' to the C_{17} keto group in steroids **1** (see Scheme 1) by way of a through-bond mechanism. This led to a chemistry different from that observed by direct excitation of the ketone chromophore. Additional keto groups in **6** or in **11** increased the efficiency of the through-bond energy transfer.

Further photochemical work on steroidal ketones has been extensively carried out, both in solution[4−8] and in the solid state,[8,9] and is a classical chapter of organic photochemistry. There is also a pharmacological motiva-

Scheme 1



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tion for such studies, since many steroids are used as topical drugs and absorb in the near UV, and phototoxic effects have been reported.[10,11]

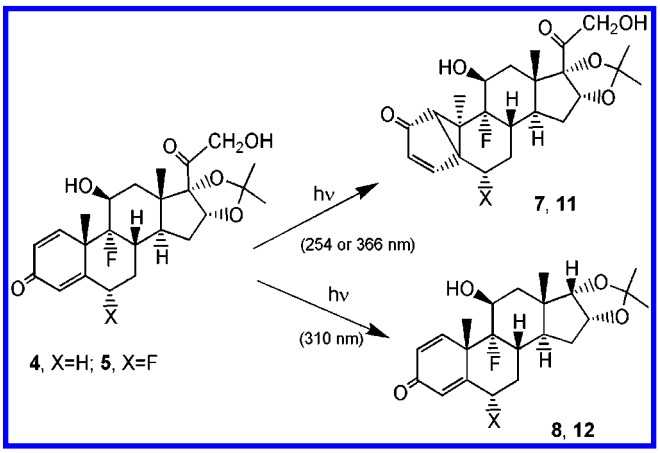
In particular, we like to point out the work on prednisone and prednisolone (**2**), which contain two separated carbonyl chromophores, the conjugated ketone in ring A, and the isolated ketone function at C_{20}. Williams,[4] following pioneering work by Barton,[5] showed that irradiation at 254 nm of these molecules caused the characteristic[12] rearrangement of cross-conjugated cyclohexadienone chromophore to a bicyclo[3.1.0]hexenone, just as it happens in analogues lacking the C_{20} ketone,[6] while the latter function was unaffected. Reaction at C_{20} ketone occurred when no other photoactive function was present, as shown by Shaffner,[7] (e.g., in the case of monoketones of structure **3**).

In contrast, the irradiation *in the solid state* of several steroids strictly related to **2** was reported to leave intact the cross-conjugated chromophore in ring A and rather involve the side chain with the keto group at C_{20}. This different course of the photoreaction in the solid state may have resulted from lattice control, and at any rate the reported isolated yields after irradiation in the solid state were quite low, thus making it difficult to arrive at mechanistic conclusions. However, the difference was intriguing and suggested the question whether there was any interaction between the two chromophores present in these diketones. It appeared to us that bichromophoric systems similar to **2** were worth further investigation, since both chromophores were expected to be highly photochemically reactive, and it was useful to assess the mode and extent of local reaction at either chromophore after electronic excitation and the possible role of energy transfer.

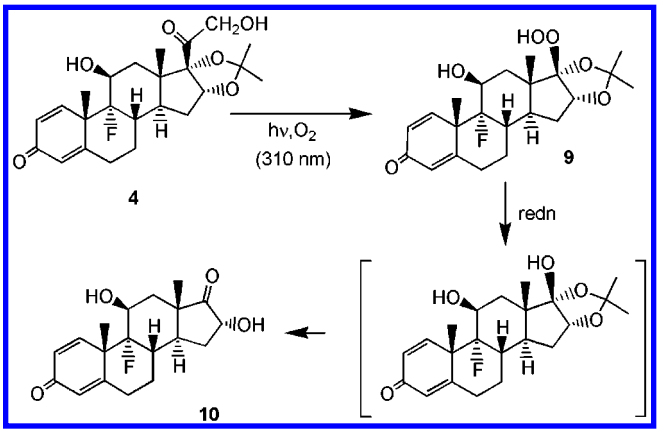
Results

Various pregna-1,4-diene-3,20-diones were considered. As discussed in the Introduction, the subject of the study was the competition between chemical reactions of separated excited moieties incorporated in a rigid skeleton. To make the ketone function in position 20 a sensitive probe of energy transfer, maximal unimolecular reactivity was desired. This led to the choice of steroid derivatives bearing hydroxy or alkoxy substituents at both C_{17} and C_{21}. Thus, two 11,21-dihydroxy-16,17-acetonylpregnadiendiones, the 9-fluoro (**4**), and the 6,9-difluoro derivative (**5**) (Scheme 2) were studied, along with the 11,17,21-trihydroxypregnadienone **6** (see Scheme 4 below). All of these compounds are used in therapy as antiinflammatory agents, and thus a photochemical study may have some relevance for the mechanism of phototoxicity. As it will be showed in the following, the photochemistry of a related androstadienone lacking the C-20 keto group was also studied for the sake of comparison.

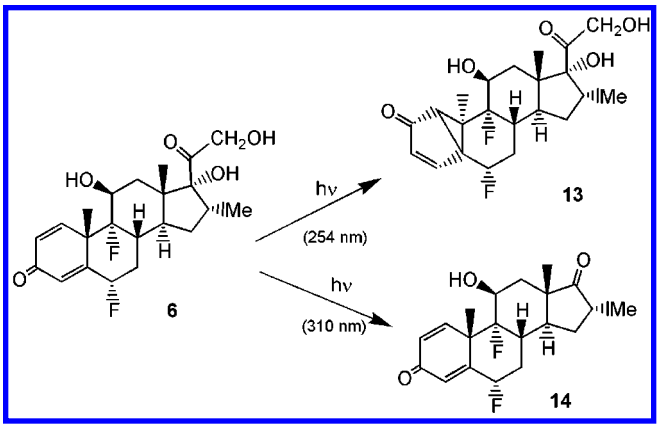
Scheme 2



Scheme 3



Scheme 4



The absorption spectrum of all of the steroids studied showed a maximum at 235 nm (log ϵ ca. 4.2) and a longer-wavelength absorption with a shoulder or maximum at 290−295 nm (log ϵ ca. 2) extending to 375 nm (see Figure 1).

Photochemistry of Pregnadiendione 4. Irradiation at 254 nm of the 3,20-dione **4** (1×10^{-3} M) in argon-flushed acetonitrile gave a main product in 75% yield along with a minor one in ca. 3% yield (yields in low conversion experiments are reported in Table 1 for comparison with quantum yield data, see below; isolated yields from preparative reactions are reported in the Experimental Section). The NMR spectrum of the main

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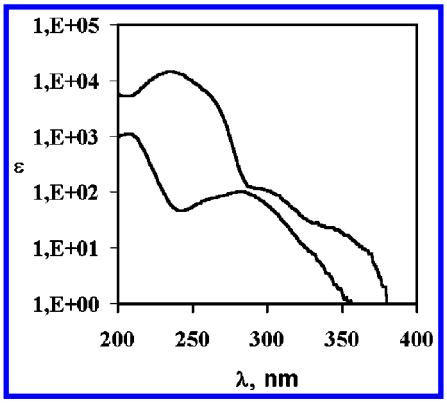


Figure 1. UV absorption spectra of pregna-1,4-diene-3,20-dione **4** (upper curve) and of pregnan-20-one **18** (lower curve) in acetonitrile.

Table 1. Photochemical Reactions of Steroids 4, 5, and 6

steroid	solvent	conditions	Φ_r	products (% yield)[a]
4	MeCN	254 nm, Ar satd	0.18	**7** (75), **8** (3)
4		254 nm, O_2 satd	0.13	**7** (85)
4	*i*-PrOH	254 nm, Ar satd	0.29	**7** (80), **8** (3)
4		254 nm, O_2 satd	0.23	**7** (82)
4	MeCN	310 nm, Ar satd	0.45	**7** (11), **8** (65)
4		310 nm, O_2 satd	0.31	**7** (9)
4		310 nm, O_2 satd[b]	0.32	**7** (10), **8** (38), **9** (40)
4	*i*-PrOH	310 nm, Ar satd	0.83	**7** (17), **8** (24)
4		310 nm, O_2 satd	0.35	**7** (31), **9** (52)
4	MeCN	366 nm Ar satd	0.06	**7** (50)
5	MeCN	254 nm, Ar satd	0.05	**11** (85), **12** (10)
5	MeCN	310 nm, Ar satd	0.31	**11** (5), **12** (85)
5	MeCN	366 nm, Ar satd	0.04	**11** (50)
6	MeCN	254 nm, Ar satd	0.05	**13** (80), **14** (10)
6	MeCN	310 nm, Ar satd	0.11	**13** (10), **14** (65)
8	MeCN	254 nm, Ar satd	0.18	**15** (90)
8	MeCN	254 nm, O_2 satd	0.13	**15** (90)
8	MeCN	310 nm, Ar satd	0.08	**15** (90)
8	MeCN	310 nm, O_2 satd	0.055	**15** (90)

[a] At ca. 30% conversion (20% for the irradiations at 366 nm). [b] In the presence of 0.1 M dodecanthiol.

compound showed that rings B−D were unaffected, while ring A was strongly modified since only two of the olefinic CH were conserved, and the third was substituted by a sp^3 carbon. This, along with further evidence (see Experimental Section, in particular as far as the stereochemistry is concerned) allowed the assignment of the structure, as that of the acetonide of the pentacyclic enone **7** (see Scheme 2). The quantum yield of reaction was 0.18.

The photoreaction of substrate **4** in 2-propanol followed a similar course, with a somewhat higher quantum yield (0.29). Quantum yield values along with product distributions, measured at ca. 30% conversion in order to minimize secondary reactions, are reported in Table 1. In both of the solvents tested, the pentacyclic derivative **7** remained the main product also in oxygen-equilibrated solution, though the quantum yield was moderately decreased (by 20 and 28%, respectively, in the two solvents) under these conditions.

When diketone **4** was irradiated at 310 nm in acetonitrile, however, the product distribution was reversed. The yield of rearranged ketone **7** was reduced to 11%, while the compound observed in a low amount at 254 nm was now the main product with 60% yield. The NMR spectrum of this compound showed that it had conserved the cross-conjugated dienone moiety and in general that the whole skeleton was hardly affected, while the side-chain in C-17 had been lost. All of the other properties supported the structure of androstanedienone **8** for this compound. The reaction quantum yield in MeCN was higher (0.45) than at 254 nm and still higher (0.83) in 2-propanol, where ketone **8** was again the main product, though with a somewhat lower yield (see Scheme 2, Table 1).

At this irradiation wavelength saturation of the solution with oxygen affected not only the quantum yield (with a stronger decrease than at 254 nm, by 31 and 58% in the two solvents) but also the product distribution. In *i*-PrOH dienone **8** was not formed and was substituted as the main product by a different compound, again maintaining the starting structure in rings A−C and having lost the C_{17} chain. This showed a strongly deshielded O−H signal. This compound could be reduced by sodium sulfite or triphenylphosphine. The latter reaction was studied in more detail and gave a further product recognized 16-hydroxy-17-keto derivative **10**. This chemical evidence along with spectroscopic indications (see Experimental Section) allowed assignment of the structure of semiacetalic hydroperoxide **9** to the initial photolysis product (Scheme 3, Table 1). In acetonitrile a more complex products mixture was obtained. This contained a not fully identified steroidic carboxylic acidic, but, significantly, compound **8** was not formed also in this case. Furthermore, when the a similar experiment was carried out in the presence of 0.1 M dodecanthiol, isolated yields were high again, with androstanone **8** and androstanhydroperoxide **9** as the main products.

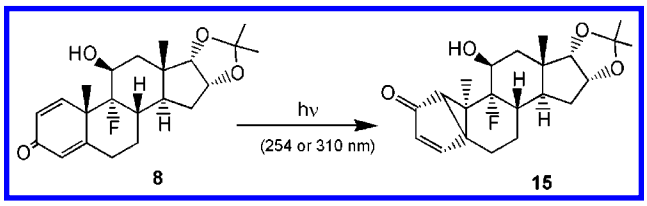
When the irradiation wavelength was further changed to 366 nm, the main process returned to be rearrangement to **7**, even though the yield of this compound was lower because of an efficient secondary photoreaction occurring under this condition. Compound **8** was not formed at all.

In view of the difference observed upon direct irradiation, sensitization and quenching experiments were carried out. Irradiation of a 1×10^{-2} M benzophenone solution containing 1×10^{-3} M **4** at 366 nm caused decomposition of the latter, but none of the above compounds was formed in an appreciable extent, nor indeed was any product isolated. The same observations applied to the irradiation at 310 nm of an acetone solution of **4** (light absorption by the solvent). In the presence of piperylene the photoreaction (λ_{irr} 310 nm) was quenched to some extent (K 2.5 M^{-1}).

Photochemistry of Further Pregnadienediones. The steroidal diketone **5**, differing from **4** for a further fluorination in position 6, was next examined (see Scheme 2). The photochemistry observed was similar to the case of **4** in that a closely related wavelength-dependent product distribution was demonstrated, though the quantum yields were somewhat lower. Thus, rearrangement to pentacyclic dione **11** took place by irradiation at 254 nm and Φ_r was 1/3rd with respect to **4**, and the same product predominated at 366 nm. On the other hand, irradiation at 310 nm induced loss of the C_{17} chain to give monoketone **12** with a quantum yield 2/3rd of that of **4**.

The further pregnadiendione **6** had the same substitution pattern as **5**, but differed for bearing a single hydroxy group in position 17 instead of the 16, 17-acetonyl functionality characteristic of both of the previously considered substrates. Similarly to the previous cases, this substance rearranged by irradiation at 254 nm to give a pentacyclic derivative, dione **13** (Scheme 4). By

Scheme 5



irradiation at 310 nm the yield of **13** was reduced to 10% and a different compound, present in a low amount at 254 nm, was now the main product.

Spectroscopic examination showed that this was the 17-keto-16-methyl derivative **14** resulting from the loss of the C_{17} chain and oxidation of the hydroxyl group at that position, while the other stereocenters in ring D were unchanged. The yield of this product was 65% at 50% conversion, though it decreased at more extensive reaction.

Photochemistry of Androstadienone 8. Finally, the photochemistry of androstadiene ketone **8** (obtained from the photocleavage of **4** as reported above) was examined. This was chosen as model since the structure was identical to that of **4** but lacked the side-chain ketone function. The photoreaction gave a single photoproduct, identified as the rearranged pentacyclic ketone **15** (Scheme 5) on the basis of the analytical and spectroscopic properties (see Experimental Section). This was formed in ca. 90% yield irrespectively of the irradiation wavelength and on the presence of oxygen, though these factors induced some change in the quantum yield.

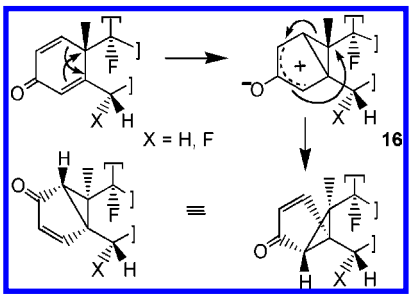
Discussion

All of the examined pregna-1,4-diene-3,20-diones (**4**, **5**, **6**) exhibit a wavelength dependent photochemistry. Reaction at the dienone chromophore predominates by irradiation at 254 and is the exclusive process at 366 nm, while reaction at the 20-keto function is the main path at 310 nm. The two kinds of chemistry observed are both largely precedented in related systems.

'Lumiketone Photorearrangement'. The first reaction corresponds to the well-known 'lumiketone' rearrangement of cross-conjugated cyclohexadienones[12] and occurs in the same way with the androsta-1,4-dien-3-one **8**, lacking the second ketone functionality. It occurs stereoselectively (with configuration inversion at C_{10}) and with the same regiochemistry observed with other steroidal dienones.[4−8] There is a large consensus that this rearrangement occurs from the low-lying nπ* triplet via a zwitterionic intermediate (**16** in Scheme 6).[12,13]

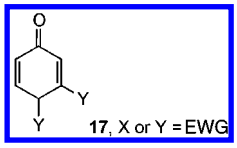
The reaction occurs with a low to moderate quantum yield and is somewhat more efficient in 2-propanol, possibly due to the increased energy of the nπ* triplet. With simpler cyclohexadienone models quantum yields are larger than observed here (0.75 to 1),[14a] and this holds also for the strictly related Δ^1-dehydrotestosterone, where the rearrangement quantum yield is 0.58, though the value is lower with some 4-alkyl derivatives.[14b] Thus, the

Scheme 6



low Φ_r with the present steroidal ketones is probably linked to the fluorine substitution. Notably, introduction of a second fluorine atom in position 6 (X = F in Scheme 6) leads to a strong decrease of Φ_r (compare **5** and **4** in Table 1).

With model 2,5-cyclohexadienones, it has been previously reported that an electron-withdrawing substituent (trichloromethyl,[15a] carbonyl, carboxyl)[15b,c] in position 4 (see formula **17**) affects the course of the 'lumi'-rearrangement[15a] and may lead to different products.[15b,c]



This is possibly because the substituent disfavors the positive charge in the zwitterionic intermediate (the same holds when the same groups are present in position 2).[15b,c] A group (carboxyl, cyano) in position 3 has been reported not to change the regioselectivity, though it is not known whether it affects the efficiency.[16] As for the presently considered dienones, compound **4** bears a CR_2F group in position 4 (with respect to the ketone function in ring A, see formula **17** and Scheme 6) and compound **5** a further CR_2F group in position 3. The reaction is clean, the 'lumi' rearrangement being virtually the only photoprocess involving this moiety, but, as mentioned above, the quantum yield is low. According to Scheme 6, the unfavorable effect of the added fluorines may be understood as an effect of the electron-withdrawing groups which disfavor the formation of the zwitterion.

In turn, the lumiketones **7** and **11** (as well as **15**), undergo secondary photorearrangements, that we have not examined beyond the fact that these are quite efficient by irradiation at 366 nm, limiting the amount of lumiketones obtainable under such conditions. The easy occurrence of secondary photoreactions by irradiation at long wavelength has been documented in the previous literature.[17]

Norrish I Photocleavage. The second reaction observed with the pregnadiendiones is Norrish I cleavage involving the C_{17} side chain, which contains an α-alkoxy (or hydroxy in the case of dione **6**)-α′-hydroxy ketone. The reaction is the most efficient photoprocess in these steroids (see further below for the comparison of Φ values). The cleavage is regioselective, involving the C_{17}−

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Scheme 7

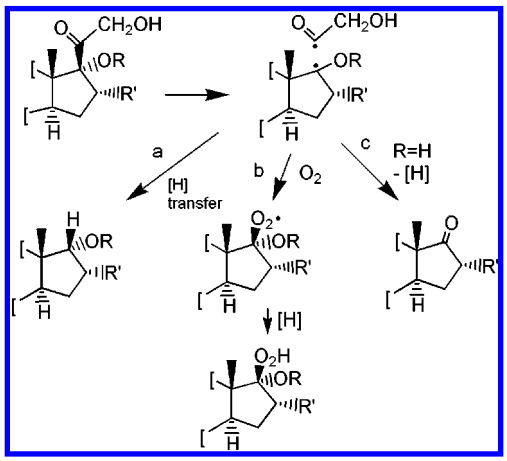


Table 2. Spectroscopic Data for Steroids 4 and 18

steroid	λ (log ϵ)	ϵ_{254}	ϵ_{310}	ϵ_{366}
4	240 (4.15), 300 (1.95)	8200	70	10
18	208 (3.04), 282 (2.01)	63	30	0

C_{20} rather than the $C_{20}-C_{21}$ bond, despite the fact that there is an oxygen-bonded substituent at both C_{17} and C_{21}. This is reasonably due to the optimal alignment of the nonbonding orbital of the acetonyl oxygen atom with the cleaving bond in the rigid system of the two fused five-membered rings (for **4** and **5**) or simply in the polysubstituted cyclopentane ring (in **6**). This favors the observed reaction more that does the hydroxyl on freely rotating C_{21}. Efficient Norrish I cleavage of the $C-C_\alpha$ had been previously reported for some α,β-acetonylcyclohexanones, which have a partially analogous geometric arrangement.[18,19]

The C_{17} alkyl radical formed abstracts hydrogen from the solvent (see increased Φ in *i*-PrOH) or from the caged $HOCH_2CO^\bullet$ radical (path a, Scheme 7) yielding monoketones **8** from **4** and **12** from **5** (Scheme 2).

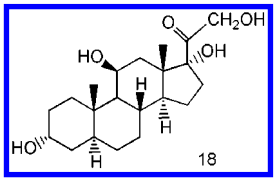
Trapping by oxygen is quite efficient, and in oxygen-saturated solution the alkyl radicals are intercepted (path b). In a hydrogen donating solvent such as *i*-PrOH the thus-formed peroxyl radical abstracts a hydrogen and gives the isolated hydroperoxy derivative (**9**, Table 1 and Scheme 3). In acetonitrile, hydrogen transfer from the solvent is slow, and some rearrangement takes place forming a not fully identified carboxylic acid arising from the cleavage of ring D. On the other hand, adding a strong reducing agent ($C_{12}H_{25}SH$, 0.1 M) leads to competition for the alkyl radical, which in part abstracts hydrogen (giving **8**), in part adds oxygen, giving the peroxy radical that in this case is smoothly reduced to hydroperoxide **9** (Table 1). The 'lumi' rearrangement, a minor path under these conditions, is unaffected, as one may expect (Table 1). Finally, when a hydroxy rather than an alkoxy group is present at C_{17}, as in dione **6**, hydrogen transfer takes place and leads to ketone **14** (path c in Scheme 7).

Wavelength-Dependent Photochemistry. The wavelength-dependent chemistry observed can be rationalized with reference to the absorption by the two separated chromophores in these diketones. In Table 2 and Figure 1 the absorption spectra of dione **4** and that of a related steroid derivative bearing only the ketone function at C_{20} (tetrahydroxypregnan-20-one **18**) are compared.

Table 3. Fractional Absorption of the Two Chromophores and Quantum Yield for Steroid 4 in Acetonitrile

λ_{irr}	F_D[a]	F_K[a]	Φ_r[b]	Φ_D[c]	Φ_K[c]
254	0.992	0.008	0.18	0.173	0.007
310	0.57	0.43	0.45	0.065	0.385
366	1	0.00	0.06	0.06	0.00

[a] From Table 2. [b] From Table 1. Φ_r times the ratio. Yield of products of dienone rearrangement (or respectively of ketone fragmentation)/total yield.



From these data, the fraction of light absorbed by the isolated ketone (F_K) and by the dienone chromophore (F_D) are obtained for bichromophoric **4** in acetonitrile (Table 3). If each chromophore reacts independently, the overall quantum yield of reaction (Φ_r, Table 1) is the sum of the efficiencies of reaction at each moiety (η, see eq 1)

$$\Phi_r = F_K\eta_K + F_D\eta_D \qquad (1)$$

The quantum yields ($\Phi_r \times$ yield of the product, see Table 1) of each of the two photoprocesses, the Norrish I fragmentation (Φ_K) and the dienone rearrangement (Φ_D) are compared in Table 3. One can see that $\Phi_K \cong F_K$ both at 254 and at 310, thus $\eta_K \cong 1$. The localized triplet at the saturated ketone chromophore reacts with unitary efficiency. This state is short-lived, but measurably quenched, and both the experiments in oxygenated solution and those in the presence of piperylene indicate a lifetime of a few nanoseconds. The reaction at the dienone chromophore is much less efficient. For **4**, η_D ($= \Phi_D/F_D$) is 0.17 in the strongly allowed first absorption band (λ_{ir} 254 nm) and drops to 011 and 0.06 in the long wavelength absorption bands (λ_{ir} 310 and 366 nm). Similar values are obtained with **8**, which bears only the dienone chromophore. The diminishing efficiency of the dienone rearrangement upon decreasing excitation energy is not accompanied by increasing reaction at the isolated ketone, thus does not involve intramolecular energy transfer. Literature data suggest that dienone triplets are also short-lived (they have not been detected by flash photolysis).[20] Intramolecular triplet−triplet energy transfer over such a distance (ca. 7.5 Å) is expected to be slow from theory,[21] although this fact has been rarely documented experimentally.[22] Thus, while T−T energy transfer from the long-lived benzene triplet in the

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(19) For a discussion of the Norrish I photoprocess see Weiss, D. S. *Org. Photochem.* **1981**, *5*, 347. Bohne, C. in ref 12d, p 416.

(20) Schuster, D. I.; Lam, K. *Mol. Photochem.* **1969**, *1*, 415.

(21) (a) Dexter, D. L. *J. Chem. Phys.* **1953**, *21*, 836. (b) Wagner, P. J.; Kochevar, I. *J. Am. Chem. Soc.* **1968**, *90*, 2232. (c) Birks, J. B. *Organic Molecular Photophysics*; *Wiley: New York: 1973.*

(22) (a) Ren, Y.; Wang, Z.; Zhu, H.; Weininger, S. J.; McGimpsey, W. G. *J. Am. Chem. Soc.* **1995**, *117*, 4367. (b) Toledano, E.; Rubin, M. B.; Speiser, S. *J. Photochem. Photobiol. A: Chem.* **1996**, *94*, 93. (c) Becker, H. D.; Burgdorff, C.; Loehmannsroeben, H. B. *J. Phootochem. Photobiol. A: Chem.* **1995**, *86*, 133.

antenna has been documented to occur over a somewhat larger distance in the case of ketone **1** (X = CH_2),[2] the short lifetime of the dienone triplet precludes such transfer with ketones **4**−**6**. At the low concentration attainable with these steroids (1×10^{-3}), intermolecular energy transfer is inefficient, and attempted sensitization by acetone or benzophenone (in the latter case potentially involving only the conjugated ketone) leads to no clean result, with considerable destruction of the substrate via paths different from the previous ones, reasonably involving radical processes initiated by hydrogen abstraction.

Conclusion

The intriguing difference between solid-state and solution photochemistry reported for some pregnadiendiones in solution and in the solid state is presumably due to the different light source used.[23] Although absorption by the dienone chromophore is more intensive and extends more to the red than that by the isolated ketone moiety, there is window in the region 280−320 nm where absorption and reaction (Norrish I fragmentation, Φ = 1) by the latter chromophore predominates. In the other regions of the spectrum, reaction at this moiety is proportional to the (in most cases marginal) fraction of light absorbed, and no T−T energy transfer intervenes. Reaction at the excited cross-conjugated chromophore is less efficient and is dependent on structure and conditions. From the phototoxicological point of view, it is noteworthy that both UV-A and UV-C cause a concerted rearrangement at ring A, whereas UV-B causes a homolytic cleavage. Thus, two different phototoxic mechanisms may operate, the latter one via radicals (acyl, alkyl, and, in the presence of oxygen, peroxyl radicals) and the photobiological action spectrum of these compounds does not simply coincide with the overall photoreactivity spectrum.

Experimental Section

Samples of pregnadienediones **4**, **5**, and **6** were kindly supplied by Farmabios, Gropello Cairoli, Italy. Their purity was checked by HPLC and NMR spectroscopy. Tetrahydroxypregnanone **18** was of commercial origin (Sigma-Aldrich). The solvents used in the photoreactions were spectroscopic grade.

Preparative Photochemical Reactions. Irradiations at 254 nm were carried out in an immersion well apparatus fitted with a 20 W low-pressure mercury arc. In the argon-equilibrated reactions, the solutions was stirred and flushed with purified argon for 2 h before irradiating, and a low gas flux was maintained during the reactions. In the oxygen-equilibrated reactions, it proceeded analogously. For the irradiations at 310 or 366 nm, the solution was distributed in a series of serum-capped quartz tubes which were flushed with argon or oxygen and irradiated in a multilamp apparatus fitted with eight 15 W phosphor-coated lamps with the appropriate emission band.

The course of the reactions was followed by HPLC (Hypersil ODS2, 4.6 × 25 mm, 5 μm column, eluting with acetonitrile − water mixtures) and TLC (eluting with cyclohexane−ethyl acetate or chloroform−acetone mixtures).

When the desired conversion was reached, the solvent was rotary evaporated and the products were purified by recrystallization or by preparative chromatographic separations by means of 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. $[\alpha]_D$ were measured at 20 °C in MeOH (5 mg/mL), and NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported relative to TMS as internal standard. The details of the structure were deduced from ^{1}H, ^{13}C, DEPT-135, and 2D-correlation experiments (H,H-COSY, HSQC for all of the products, HMBC, and/or NOESY when appropriate).

Photolysis of Pregnadienedione 4 in Argon-Equilibrated Acetonitrile at 254 nm. A solution of compound **4** (1 g, 2.3 mmol) in acetonitrile (2.3 L) was irradiated for 2 h, and a 80% conversion was reached. Crystallization of the residue from ethyl acetate gave 560 mg (70% yield) of 11β,21-dihydroxy-16α,17α-(1-methylethylidenedioxy)-9α-fluoro-1,5-cyclopregn-3-ene-2,20-dione (**7**). Mp 227 °C (AcOEt); $[\alpha]_D$ −2.2. Anal. Calcd for $C_{24}H_{31}O_6F$: C, 65.54; H, 7.17. Found: C, 65.7; H, 7.3. IR (KBr) 3500, 1700 cm^{-1}. ^{1}H NMR (CD_3COCD_3) δ 0.8 (s, 3H), 1.2 (s, 3H), 1.3 (s, 3H), 1.5 (s, 3H), 1.4−1.8 (m, 6H), 2.0−2.4 (m, 5H), 3.2 (br, exch, 1H), 3.5 (t, J = 5 Hz, exch, 1H), 4.3 (dd, J = 20, 5 Hz, 1H), 4.4 (m, 1H), 4.6 (dd, J = 20, 5 Hz, 1H), 5.1 (d, J = 5. Hz, 1H), 6.0 (d, J = 5, 1H), 7.3 (d, J = 5 Hz, 1H). ^{13}C NMR (CD_3COCD_3) δ 8.1 (d, J_{C-F} = 3 Hz, CH_3), 16.4 (CH_3), 19.9 (CH_2), 22.9 (CH_2), 25.4 (CH_2), 26.3 (CH_3), 32.4 (d, J_{C-F} = 21 Hz, CH), 33.4 (CH_2), 34.7 (CH_2), 38.1, 39.0 (d, J_{C-F} = 6 Hz, CH), 41.6 (CH), 45.3, 52.8 (d, J_{C-F} = 27 Hz), 67.0 (CH_2), 69.2 (d, J_{C-F} = 30 Hz, CH), 81.5 (CH), 95.4 (d, J_{C-F} = 175 Hz), 97.2, 111.1, 132.1 (CH), 165.2 (CH), 205.7, 210.3. The detailed structure assignment was obtained by combined HSQC, HMBC, and NOESY experiments. The presence of the C_1−C_5 bond was evidenced by the long-range correlations observed in the HMBC spectrum: C-1 (39.0 ppm) correlated with H-19 (1.29 ppm), H-3 (5.95 ppm), and H-4 (7.31 ppm); the last one was absent in the starting steroid **4**, so confirming the presence of the bond between C-1 and C-5. The orientation of 19-Me and ring A was defined considering the characteristic cross-peak in the NOESY spectrum: H-19 (1.29 ppm) with H-11 (4.35 ppm), H-3 and H-4, thus proving their spatial proximity. Thus the stereochemistry deducted from NMR data was completely consistent with previous assignments on related 'lumiketones' mainly based upon circular dichroism measurements.[24]

Photolysis of Pregnadienedione 4 in Argon-Equilibrated Acetonitrile at 310 nm. A solution of compound **4** (0.434 g, 1 mmol) in acetonitrile (1 L) was irradiated for 40 min, and a 80% conversion was reached. Chromatography of the residue (eluting with a cyclohexane−ethyl acetate 70/30 mixture) gave 34 mg (11%) of compound **7** and 180 mg (60%) of 9α-fluoro-11β-hydroxy-16α, 17α-(1-methylethylidenedioxy)-androsta-1,4-dien-3-one (**8**). Mp 255 °C (cyclohexane); $[\alpha]_D$ +10.5. Anal. Calcd for $C_{22}H_{29}O_4F$: C, 70.19; H, 7.76. Found: C, 70.2; H, 7.8. IR (KBr) 3410, 1664, 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 0.9 (s, 3H), 1.2 (s, 3H), 1.3 (s, 3H), 1.5 (s, 3H), 1.2−1.9 (m, 5H), 2.2−2.6 (m, 4H), 4.0 (d, J = 5 Hz,1H), 4.2 (m, 1H), 4.7 (m, 1H), 5.1 (d, J = 5. Hz, 1H), 5.4 (bs, exch, 1H), 6.0 (d, J = 1.5 Hz, 1H), 6.2 (dd, J = 10, 1.5 Hz, 1H), 7.3 (d, J = 10 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 22.9 (CH_3), 26.8 (d, J_{C-F} = 5 Hz,CH_3), 27.8 (CH_3), 30.0 (CH_3), 31.6 (CH_2), 34.1 (CH), 36.6 (d, J_{C-F} = 20 Hz, CH), 37.2 (CH_2), 40.7 (CH_2), 44.5 (CH_2), 46.0, 51.8 (d, J_{C-F} = 23 Hz), 74.4 (d, J_{C-F} = 30 Hz, CH), 89.8 (CH), 90.7 (CH), 105.1(d, J_{C-F} = 175 Hz), 112.7, 128.1 (CH), 132.9 (CH); 156.6 (CH); 170.8, 189.2.

Photolysis of Pregnadienedione 4 in Oxygen-Equilibrated 2-Propanol at 310 nm. A solution of compound **4** (1 g, 2.3 mmol) in 2-propanol (2.3 L) was irradiated for 55 min, and a 77% conversion was reached. Column chromatography eluting with a 40/60 cyclohexane−ethyl acetate mixture followed by recrystallization of the main fraction afforded 432 mg (60%) of 9α-fluoro-17β-hydroperoxy-11β-hydroxy-16α,17α-(1-methylethylidenedioxy)androsta-1,4-dien-3-one (**9**). Mp 175 °C (AcOEt); $[\alpha]_D$ +41.9. Anal. Calcd for $C_{22}H_{29}O_6F$: C, 64.69;

(23) Either a high-pressure or a low-pressure mercury arc have been used as the light source in the various photochemical studies of crystalline steroid ketones, ref 8 and 9. It is not clear whether there is a wavelength effect.

(24) Schaffner, K.; Snatzke, G. *Helv. Chim. Acta* **1965**, *48*, 347.

H, 7.16. Found: C, 64.3; H, 7.2. IR (KBr) 3400, 1680, 1620 cm^{-1}. ^1H NMR (CD_3COCD_3) δ 1.2 (s, 3H), 1.3 (s, 3H), 1.4 (s, 3H), 1.6 (s, 3H), 1.2−1.7 (m, 2H), 1.8−2.2 (m, 5H), 2.2−2.8 (m, 3H), 4.2 (m, 1H), 4.3 (d, J = 5.5 Hz, 1H), 4.4 (br, exch, 1H), 6.0 (br t, J = 1.5 Hz, 1H), 6.2 (dd, J = 10, 1.5 Hz, 1H), 7.3 (d, J = 10 Hz, 1H), 11.1 (br s, exch, 1H). ^{13}C NMR (CD_3COCD_3) δ 15.4 (CH_3), 22.7 (d, J_{C-F} = 5 Hz, CH_3), 25.9 (CH_3), 26.5 (CH_3), 27.1 (CH_2), 30.4 (CH_2), 32.5 (CH_2), 33.1 (d, J_{C-F} = 20 Hz, CH), 38.3 (CH_2), 43.0 (d, J_{C-F} = 2 Hz, CH), 46.1, 48.1 (d, J_{C-F} = 22 Hz), 71.2 (d, J_{C-F} = 33 Hz, CH), 82.7 (CH), 100.7 (d, J_{C-F} = 175 Hz), 111.8, 120.6, 124.4 (d, J_{C-F} = 2 Hz, CH), 129.2 (CH); 151.8 (CH); 165.8 (d, J_{C-F} = 2 Hz), 185.0. Triphenylphosphine (26.2 mg) was added to a solution of hydroperoxide **9** (20 mg) in dichloromethane (15 mL), and stirring was pursued for 2 h, when the starting material was consumed (TL). Extraction with water (3 × 20 mL) and evaporation gave 18 mg (94%) of 9α-fluoro-11β,16α-dihydroxyandrosta-1,4-diene-3,17-dione (**10**). Anal. Calcd for $C_{19}H_{23}O_4F$: C, 68.25; H, 6.93. Found: C, 68.0; H, 7.0. IR (KBr) 3400, 1740, 1660, 1600 cm^{-1}. ^1H NMR (DMSO) δ 1.1 (s, 3H), 1.5 (s, 3H), 1.3−1.7 (m, 2H), 1.7−2.3 (m, 5H), 2.4−2.7 (m, 3H), 4.2 (m, 1H), 4.3 (m, 1H), 5.3 (d, J = 6 Hz, exch, 1H), 5.6 (d, J = 3 Hz, exch, 1H), 6.0 (d, J = 1.5 Hz, 1H), 6.3 (dd, J = 10, 1.5 Hz, 1H), 7.3 (d, J = 10 Hz, 1H). ^{13}C NMR (DMSO) δ 16.0 (CH_3), 23.3 (d, J_{C-F} = 5 Hz, CH_3), 26.3 (CH_2), 30.3 (CH_2), 31.6 (CH_2), 33.2 (d, J_{C-F} = 20 Hz, CH), 36.6 (CH_2), 42.2 (CH), 46.4, 48.2 (d, J_{C-F} = 22 Hz), 70.2 (CH), 70.4 (d, J_{C-F} = 36 Hz, CH), 101.5 (d, J_{C-F} = 175 Hz), 124.6 (d, J_{C-F} = 2 Hz, CH), 129.3 (CH); 152.8 (CH), 166.9 (d, J_{C-F} = 2 Hz), 185.5, 217.5.

Photolysis of Pregnadienedione 5 in Argon-Equilibrated Acetonitrile at 254 nm. A solution of compound **5** (1 g, 2.2 mmol) in acetonitrile (440 mL) was irradiated for 2.5 h, and a 50% conversion was reached. Column chromatography (eluting with cyclohexane−ethyl acetate 40−40 mixture), and recrystallization of the main fraction afforded 497 mg (50%) of 6α,9α-difluoro-11β,21-dihydroxy-16α,17α -(1-methylethylidenedioxy)-1,5-cyclopregn-3-ene-2,20-dione(**11**). Mp 247 °C (AcOEt); $[\alpha]_D$ −20.8. Anal. Calcd for $C_{24}H_{30}O_6F_2$: C, 63.71; H, 6.68. Found: C, 63.8; H, 6.7. IR (KBr) 3500, 1700, 1580 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.7 (s, 3H), 1.1 (s, 3H), 1.2 (s, 3H), 1.4 (s, 3H), 1.5 (m, 2H), 1.9 (m, 1H), 2.2 and 2.6 (m, 2H), 2.1 (m, 2H), 2.2 (m, 1H), 2.4 (br s, 1H), 4.0 (d, J = 19 Hz, 1H), 4.1 (m, 1H), 4.5 (d, J = 19 Hz, 1H), 4.9 (d, J = 5 Hz, 1H), 5.1 (br, exch, 1H), 5.2 (d, J = 5 Hz, exch, 1H), 5.3 (dt, J = 50, 7.5 Hz, 1H), 6.1 (d, J = 5.5 Hz, 1H), 7.7 (d, J = 5.5 Hz, 1H). ^{13}C NMR (DMSO) δ 7.9 (d, J_{C-F} = 3 Hz, CH_3), 16.8 (CH_3), 25.5 (CH_3), 26.7 (CH_3), 28.3 (dd, J_{C-F} = 18, 8 Hz, CH), 28.5 (d, J_{C-F} = 21 Hz, CH_2), 33.0 (CH_2), 35.4 (CH_2), 36.2 (t, J_{C-F} = 6 Hz, CH), 41.2 (d, J_{C-F} = 26 Hz), 42.0 (CH), 45.0, 52.0 (d, J_{C-F} = 27 Hz), 66.3 (CH_2), 68.2 (d, J_{C-F} = 37 Hz, CH), 81.0 (CH), 87.5 (d, J_{C-F} = 175 Hz), 95.9 (d, J_{C-F} = 175 Hz), 97.3, 110.7, 134.0 (CH), 160 (d, J_{C-F} = 9 Hz, CH), 203.3, 210.1. As for the case of compound **7**, the detailed structural attribution was based upon NMR evidence. A similar correlation was found in the HMBC spectrum: C-1 (36.1 ppm) with H-4 (7.7 ppm), H-19 (1.2 ppm) with C-1, C-10 (52.0 ppm) and C-5 (41.2 ppm), H-1 (2.4 ppm) with C-9 (95.9 ppm). In the NOESY spectrum, H-1 gave NOE correlation with H-6 (5.25 ppm) and H-8 (1.9 ppm); H-19 (1.2 ppm) with H-4, H-3 (6.1 ppm) and H-11 (4.1 ppm).

Photolysis of Pregnadienedione 5 in Argon-Equilibrated Acetonitrile at 310 nm. A solution of compound **5** (0.3 g, 0.663 mmol) in acetonitrile (290 mL) was irradiated for 2 h, and a 90% conversion was reached. Column chromatography (eluting with cyclohexane−ethyl acetate 60/40 mixture) gave 5 mg (5%) of compound **11** and 188 mg (80%) of 6α,9α-difluoro-11β-hydroxy-16α,17α-(1-methylethylidenedioxy)-androsta-1,4-dien-3-one (**12**). Mp 245 °C (cyclohexane); $[\alpha]_D$ +12.4. Anal. Calcd for $C_{22}H_{28}O_4F_2$: C, 66.99; H, 7.15. Found: C, 67.2; H 7.2. IR (KBr) 3450, 1660, 1640 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.0 (s, 3H), 1.2 (s, 3H), 1.3 (s, 3H), 1.5 (s, 3H), 1.2−1.6 (m, 4 H), 1.7−1.8 (m, 2H), 2.3 (m, 1H), 2.4−2.6 (m, 1H), 4.0 (d, J = 5 Hz, 1H), 4.2 (m, 1H), 4.6 (m, 1H), 5.5 (dd,, exch, 1H), 5.7 (dddd, J = 50, 13, 7.5 Hz, 1H), 6.1 (br t, J = 1.5 Hz, 1H), 6.3 (dd, J = 10, 1.5 Hz, 1H), 7.3 (d, J = 10 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 23.1 (CH_3), 26.9 (d, J_{C-F} = 3 Hz,.CH_3), 28.0 (CH_3), 30.2 (CH_3), 35.2 (dd, J_{C-F} = 19, 11 Hz, CH), 37.3 (CH_2), 38.5 (d, J_{C-F} = 11 Hz,CH_2), 40.8 (CH_2), 44.7 (CH), 46.5, 52.4 (d, J_{C-F} = 23 Hz), 74.5 (d, J_{C-F} = 36 Hz, CH), 85.1 (CH), 90.1 (CH), 91.1 (d, J_{C-F} = 175 Hz), 104.5 (d, J_{C-F} = 175 Hz), 113.1, 123.5 (d, J_{C-F} = 3 Hz, CH), 133.2 (CH), 158.5 (CH), 167.4 (d, J_{C-F} = 15 Hz, CH), 188.9.

Photolysis of Pregnadienedione 6 in Argon-Equilibrated Acetonitrile at 254 nm. A solution of compound **6** (0.52 g, 1.27 mmol) in acetonitrile (260 mL) was irradiated for 2.5 h, and a 50% conversion was reached. Column chromatography (eluting with chloroform−acetone 98/2 mixture), and recrystallization of the main fraction gave 154 mg (60%) of 6α,9α-difluoro-16α-methyl-11β,17α,21-trihydroxy-1,5-cyclopregn-3-ene-2,20-dione (**13**). Mp 251 °C (AcOEt); $[\alpha]_D$ −20.8. Anal. Calcd for $C_{22}H_{28}O_5F_2$: C, 64.38; H, 6.88. Found: C, 64.3; H, 7.0. IR (KBr) 3500, 1700 cm^{-1}. ^1H NMR (DMSO) δ 0.8 (d, J = 7 Hz, 3H), 0.9 (s, 3H), 1.2 (s, 3H), 1.1 and 1.5 (m, 2H), 1.7−1.8 (m, 1H), 1.4 and 1.9 (m, 2H), 1.4 and 2.2 (m, 2H), 2.2 (m, 1H), 2.3 (m, 1H), 2.9 (m, 1H), 4.0 (dd, J = 19, 5.5 Hz, 1H), 4.1 (m, 1H), 4.5 (dd, J = 19, 5.5 Hz, 1H), 4.7 (t, J = 5.5 Hz, exch, 1H), 5.0 (br s, exch, 1H), 5.1 (d, J = 4.5 Hz, exch, 1H), 5.3 (dt, J = 50, 7.5, 1H), 6.1 (d, J = 5.5 Hz, 1H), 7.7 (d, J = 5.5 Hz, 1H). ^{13}C NMR (DMSO) δ 8.0 (d, J_{C-F} = 3 Hz, CH_3), 15.6 (CH_3), 17.1 (CH_3), 28.5 (d, J_{C-F} = 23 Hz, CH_2), 29.3 (dd, J_{C-F} = 18, 8 Hz, CH), 32.0 (CH_2), 35.1 (CH_2), 35.2 (CH), 36.4 (t, J_{C-F} = 7 Hz, CH), 41.3 (d, J_{C-F} = 26 Hz), 42.4 (CH), 47.7, 52.3 (d, J_{C-F} = 27 Hz), 66.6 (CH_2), 68.5 (d, J_{C-F} = 35 Hz, CH), 87.5 (d, J_{C-F} = 175 Hz), 90.4, 96.5 (d, J_{C-F} = 175 Hz), 134.0 (CH), 160.1 (d, J_{C-F} = 10 Hz, CH), 203.4, 211.4. The following long-range correlations in HMBC experiment supported the structure attribution: H-1 (2.32 ppm) with C-3 (134.0 ppm), C-4 (160.1 ppm) and C-9 (96.5); C-1 (36.4 ppm) with H-3 (6.1 ppm), H-4 (7.65 ppm) and H-19 (1.2 ppm). The relative stereochemistry was confirmed with NOESY experiment: H-1 gave NOE correlation with H-6 (5.3 ppm), H-19 with H-3, H-4 and H-11 (4.1 ppm).

Photolysis of Pregnadienedione 6 in Argon-Equilibrated Acetonitrile at 310 nm. A solution of compound **6** (1 g, 2.44 mmol) in acetonitrile (490 mL) was irradiated for 1 h, and a 20% conversion was reached. Column chromatography (eluting with chloroform) and recrystallization of the main photoproduct gave 84 mg (50%) of 6a,9α-difluoro-16α-methyl-11β-hydroxy-androsta-1,4-dien-3-one (**14**). Mp 249 °C (cyclohexane); $[\alpha]_D$ +18.4. Anal. Calcd for $C_{20}H_{24}O_3F_2$: C, 68.55; H, 6.90. Found: C, 68.6; H, 6.9. IR (KBr) 3400, 1740, 1680, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.2 (d, J = 7 Hz, 3H), 1.3 (s, 3H), 1.6 (s, 3H), 1.7−1.9 (m, 3H), 1.6 and 2.1 (m, 2H), 1.8 and 2.4 (m, 2H), 2.5−2.8 (m, 2H), 4.4 (m, 1H), 5.5 (dddd, J = 50, 13, 7.2 Hz, 1H), 6.4 (dd, J = 10, 1.5 Hz, 1H), 6.5 (bt, J = 1.5 Hz, 1H), 7.1 (d, J = 10 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3), 16.9 (CH_3), 23.5 (d, J_{C-F} = 5 Hz, CH_3), 30.2 (CH_2), 32.8 (d, J_{C-F} = 28 Hz, CH), 33.1 (d, J_{C-F} = 21 Hz, CH_2), 37.9 (CH_2), 39.1 (CH), 42.3 (CH), 47.4, 48.5 (d, J_{C-F} = 26 Hz), 71.9 (d, J_{C-F} = 36 Hz, CH), 86.8 (d, J_{C-F} = 175 Hz), 99.7 (d, J_{C-F} = 175 Hz), 121.6 (d, J_{C-F} = 5 Hz, CH_3), 130.6 (CH), 150.9 (CH), 161.6 (d, J_{C-F} = 9 Hz, CH), 186.0, 220.2.

Photolysis of Androstadienone 8 in Argon-Equilibrated Acetonitrile at 254 nm. A solution of compound **8** (1 g, 2.44 mmol) in acetonitrile (490 mL) was irradiated for 1 h, and a 20% conversion was reached. Column chromatography eluting with chloroform gave 84 mg (43% yield) of 9α-fluoro-11β-hydroxy-16α,17α-(1-methylethylidenedioxy)-1,5-cycloandrost-3-en-2-one (**15**). Mp 150 (AcOEt); $[\alpha]_D$ −69.8. Anal. Calcd for $C_{22}H_{29}O_4F$: C, 66.82; H, 7.39. Found: C, 66.7; H, 7.5. IR (KBr) 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (s, 3H), 1.3 (s, 3H), 1.4 (s, 3H), 1.5 (s, 3H), 1.3−1.8 (m, 6H), 2.0−2.2 (m, 3H), 1.9 (br, exch, 1H), 2.2 (br s, 1H), 2.3 (m, 1H), 4.1 (d, J = 5.5 Hz, 1H), 4.4 (m, 1H), 4.7 (t, J = 5.5 Hz, 1H), 5.9 (d, J = 5.5 Hz, 1H), 7.3 (d, J = 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 8.3 (d, J_{C-F} = 3 Hz, CH_3), 19.1 (CH_3), 20.0 (CH_2), 22.9 (CH_2), 23.8 (CH_3), 25.9 (CH_3), 32.6 (d, J_{C-F} = 19 Hz, CH), 33.5 (CH_2), 35.4 (CH_2), 38.2, 39.1 (d, J_{C-F} = 6 Hz, CH), 39.5 (d, J = 3 Hz, CH), 42.2, 52.7 (d, J_{C-F} = 27 Hz), 69.9 (d, J_{C-F} = 37 Hz, CH), 79.6 (CH), 86.4 (CH), 95.5 (d, J_{C-F} = 175 Hz), 109.6, 132.0 (CH), 164.9 (CH), 205.3. The structural attribution was based on correlations

similar to those observed with the above 'lumiketones'. In the HMBC spectrum H-1 (2.2 ppm) correlated with C-6 (22.9 ppm) and C-4 (132.0 ppm), H-19 (1.3 ppm) with C-5 (38.2 ppm); C-5 with H-3 (5.9) and H-4 (7.3).

Quantum Yield Measurements. Quantum yield measurements were carried out in 3 mL samples of solutions (1×10^{-3} M for steroids **4** and **8**, 5×10^{-3} M for **5** and **6**) in spectrophotometric sealed couvettes. The light source was a low-pressure mercury arc for 254 nm, a focalized high-pressure mercury arc fitted with the appropriate interference filter for 313 and 366 nm. The extent of light absorbed was determined by means of a photon-counter. The extent of the reaction was assessed by HPLC. The light flow was measured by ferrioxalate actinometry.

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