79. Photo-oxygenation of Styrenic Estrogens: Product Characterization and Kinetics of the Dye-Sensitized Photo-oxygenation of 9,11-Didehydroestrone Derivatives[1])

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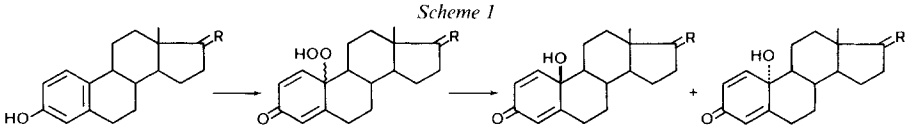
(20.III.89)

The dye-sensitized photo-oxygenation of 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**8**) gives a complex mixture from which only the 1,4-endo-peroxide **10** can be isolated in low yield. In contrast, the 3-methoxy derivative **9** yields the C-seco-aldehyde **11** as a major product, suggesting that 1,2-dioxetane is a primary photo-oxygenation intermediate. As the electron-donating character of the substituent at C(3) decreases in the sequence **12** (R = PhCO), **13** (R = Ac), and **14** (R = Ts), the rate constant in substrate disappearance becomes drastically smaller as compared with **8** and **9**, and no photoproducts are detected. The results are rationalized by means of electronic and conformational factors.

Introduction. – Research in singlet-oxygen chemistry has expanded to include singlet-oxygen oxidations of natural products in biological systems in order to further understand light-induced metabolic diseases and tissue damage. For several years, our group has been engaged in the study of the behavior of estrogenic steroids under dye-sensitized photo-oxygenation conditions. The natural sex hormones, estrone (3-hydroxyestra-1,3,5(10)-trien-17-one; **1**) and estradiol (estra-1,3,5(10)-triene-3,17-diol; **2**), when oxydized by singlet oxygen, give the corresponding hydroperoxides **3** and **4**, respectively, which are easily reduced to the *p*-quinols **5, 6,** and **7** [2] *(Scheme 1)*. The 3-methoxy derivatives of **1** and **2** do not react under these conditions, which is indicative of oxygen addition to **1** and **2**, *via* phenoxy-radical species. This result is in accordance with the known photo-oxygenation of *p*-substituted phenols to yield 4-(hydroperoxy)cyclohexa-2,5-dien-3-ones [3].

Subsequently, the biological significance of singlet-oxygen oxidation of estrogenic steroids *in vivo* has been frequently reported. In particular, *Seede et al.* [4] have studied the interaction of the photosensitized-decomposition products of contraceptives steroids with proteins and DNA. They found that the photoproducts of estrone and 17α-ethynyl-

Scheme 1



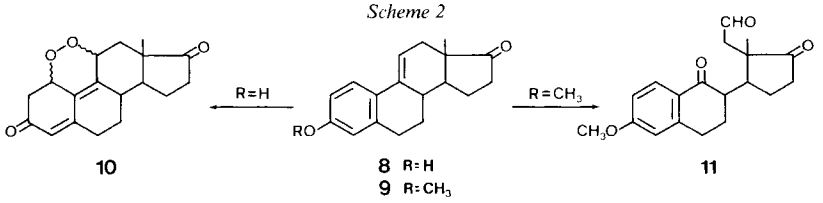
[1]) Photochemical Reactions, Part 23. Part 22: [1].

estradiol, upon irradiation with hematoporphyrin as sensitizer, interact with DNA and bind irreversibly to protein. After identifying the reactive intermediates as the hydroperoxides **3** and **4** (R = β-OH, α-ethynyl), the authors concluded that the photosensitized oxidation of estrogens may be the cause of the photoallergic side-effects of oral contraceptives.

We now report the dye-sensitized photo-oxygenation of 9,11-didehydroestrone derivatives, characterized by the addition of a double bond conjugated with ring A in the estrogenic skeleton. The influence of the substitution at C(3) of the substrate towards oxidation by singlet oxygen is analyzed applying kinetic techniques.

Results. – The photo-oxygenation of **9** [5] in MeOH at 0° using rose bengal as sensitizer afforded a mixture of compounds which was separated by chromatography on

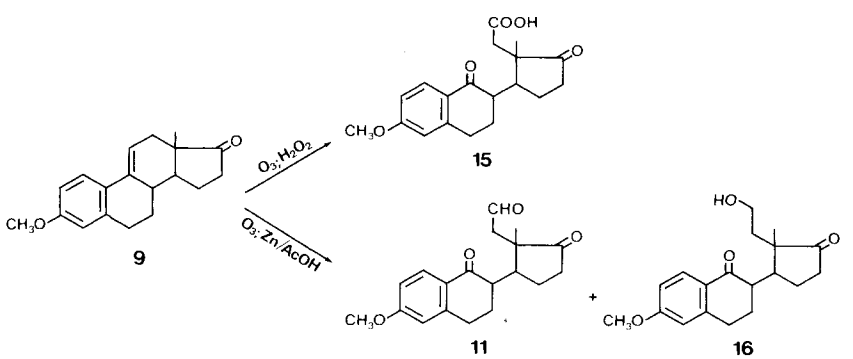
Scheme 2



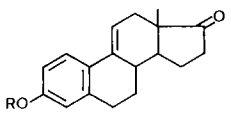
SiO_2 *(Scheme 2)*. Unreacted starting material **9** (3% of the mixture) and 3-methoxy-9,17-dioxo-9,11-secoestra-1,3,5(10)-trien-11-al (**11**), in *ca.* 50% yield, were identified on the basis of their analytical and spectral properties. In spite of the higher yield of **11** in the reaction mixture (60–70% by HPLC), it was isolated in only 50% yield due to slow decomposition during the purification process. The C-seco-aldehyde **11** arises from an oxidative cleavage of the C(9)=C(11) bond of **9** thus suggesting the intermediacy of a 1,2-dioxetane. The same product was obtained by ozonolysis of **9** followed by Zn/AcOH treatment, although at lower yields (30–40%) *(Scheme 3)*.

When 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**8**) was photo-oxygenated under the same conditions, no ring-C-fragmentation product was detected. From the complex mixture obtained, only the endoperoxide **10** could be isolated in 3% yield.

Scheme 3



The different behavior of both compounds shows the determining influence of the substitution at C(3) on the substrate reactivity towards singlet oxygen. Five different C(3)-substituted 9(11)-didehydroestrone derivatives have been synthetized in order to analyze the effect of the substitutions at C(3) on reactivity. From these results, we will be able to find which substitution gives the highest reactivity, and what are the optimal experimental conditions for future synthetic application. In decreasing order of electron-donating character, the groups chosen are: R = H (**8**), R = CH_3 (**9**), R = PhCO (**12**), and R = Ts (**14**).



8 R = H
9 R = Me
12 R = PhCO
13 R = Ac
14 R = Ts

Kinetic Analysis. The kinetic mechanism of the dye-sensitized photo-oxygenation of organic acceptors in liquid phase is well established [6]:

$$\text{sens} \xrightarrow{h\nu} {}^1\text{sens} \xrightarrow[k_{isc}]{} {}^3\text{sens} \xrightarrow[k_T]{{}^1O_2} {}^1O_2 + \text{sens}$$

$${}^1O_2 \xrightarrow{k_d} O_2$$

$${}^1O_2 + A \xrightarrow{k_r} AO_2$$

where A is the organic acceptor and AO_2 the oxygen addition product. Once singlet oxygen is formed by photosensitization, it may decay to its ground triplet state by solvent-induced relaxation with a pseudo-first-order rate constant k_d or react with the substrate A to yield photoproducts with a second-order rate constant k_r. Thus, the instantaneous quantum yield for product formation, $\Phi(AO_2)$, is given by the expresion[2]) [6] [7]:

$$\Phi(AO_2) = \Phi({}^1O_2)\frac{k_r[A]}{k_d + k_r[A]} \tag{1}$$

where $\Phi({}^1O_2)$ is the instantaneous quantum yield of singlet-oxygen formation and $\beta = k_d/k_r$. Essentially, the β value is an index of the reactivity of a particular organic acceptor towards singlet oxygen. Values of β can be determined directly from the preceding equation. A plot $1/AO_2$ *vs.* 1/[A] at initial convertions will give a straight line in which β is the ratio of slope to intercept. The reaction rate is used instead of $\Phi(AO_2)$, since it is proportional to the quantum yield (assuming light flux is constant within a set of experiments).

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[2]) Singlet oxygen may undergo other physical deactivation processes such as quenching by the substrate (rate constant k_q) or collisional decomposition of two $^1O_2$ molecules (rate constant k_c) leading to their triplet ground state. Accordingly, the quantum yield for product formation would be:

$$\Phi(AO_2) = \Phi({}^1O_2)\frac{k_r[A]}{k_d + k_r[A]\,k_q[A] + 2k_c[{}^1O_2]}$$

These two processes of deactivation of singlet oxygen have been neglected by the authors in their kinetic calculations, as they assume the corresponding rates to be much smaller than those of the chemical reaction $k_r[A][^1O_2]$ and of the physical deactivation by the solvent $k_d[^1O_2]$.

From the previous equation, the rate of product formation may be expressed as $V(AO_2) = k_r[A][^1O_2]$. If light flux, molecular-oxygen concentration, and sensitizer concentration are constant during the course of the reaction, a stationary $[^1O_2]$ is assumed, and the kinetics of product formation will be pseudo-first-order:

$$V(AO_2) = k_r[A][^1O_2] = K[A] = -V_A \quad (2)$$

The disappearance of starting material is measured and K (rate constant for pseudo-first-order kinetics) and V_0 (initial rate of disappearance of substrate) are evaluated.

All the photo-oxygenation experiments were carried out in a tubular photoreactor with a halogen lamp in MeOH at 0° with rose bengal as sensitizer.

1. *Kinetics of 3-Methoxy-1,3,5(10),9(11)-estratetraen-17-one* (**9**). To study the kinetics of the oxidative fragmentation process **9**→**11**, two sets of experiments were performed: *a*) evaluation of the effect of sensitizer concentration and *b*) measurement of the β value for **9**.

a) *Effect of Sensitizer Concentration on the Pseudo-First-Order Rate Constant.* Five irradiation experiments were performed at fixed rose bengal concentrations ranging from $1.6 \cdot 10^{-5}$ to $3.3 \cdot 10^{-4}$ M, while the initial steroid concentration was kept constant at $3.5 \cdot 10^{-3}$ M. The results are shown in *Fig. 1*, and kinetic data is summarized in *Table 1*. A plot of initial reaction rate *vs.* photosensitizer concentration *(Fig. 2)* reveals two distinct regions (A and B). At concentrations higher than *ca.* $1.1 \cdot 10^{-4}$ M, the observed rate is

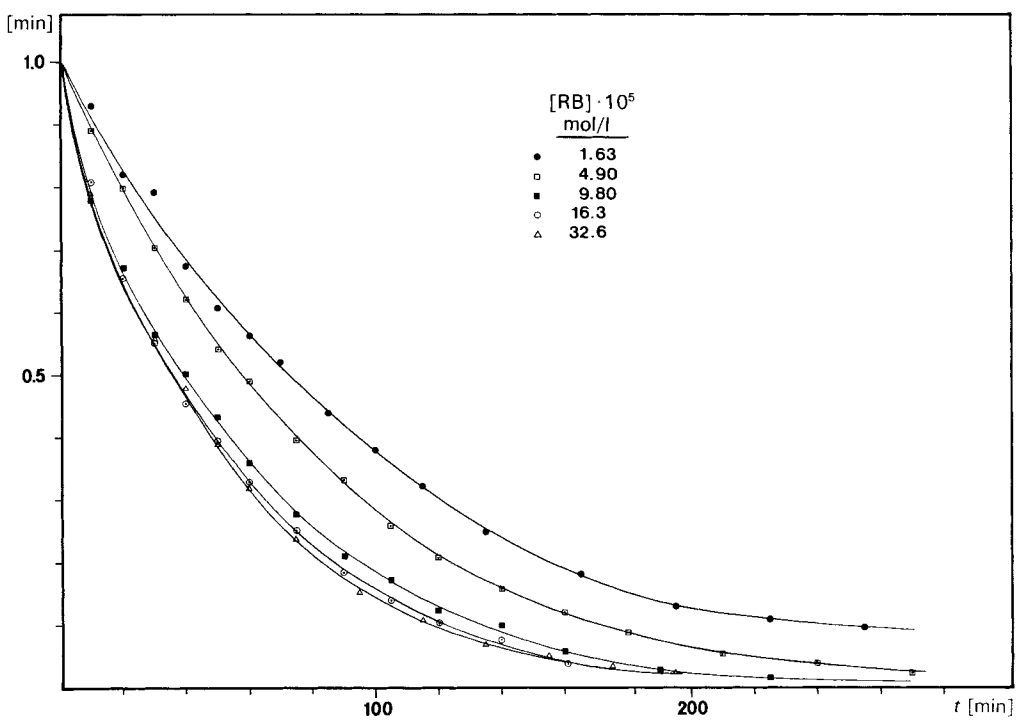

Fig. 1. *Kinetics of* **9** ($C_0 = 3.5 \cdot 10^{-3}$ M) *at different sensitizer concentrations.* C/C_0: Relative concentration of starting material, t [min]: duration of irradiation.

Table 1. *Kinetic Parameters for the Dye-Sensitized Photo-oxygenation of* **9** *at Constant Steroid Concentration* ($C_0 = 3.5 \cdot 10^{-3}$ M) (*cf. Fig. 1*)[a])

[RB] [mol · l^{-1}]	K [min^{-1}]	V_0 [M · min^{-1}]	e_r e [%] (s)	t_{irr} [min]
$1.63 \cdot 10^{-5}$	$9.7 \cdot 10^{-3}$	$3.5 \cdot 10^{-5}$	4.6 (5.5)	255
$4.90 \cdot 10^{-5}$	$1.3 \cdot 10^{-2}$	$4.6 \cdot 10^{-5}$	7.8 (8.3)	360
$9.80 \cdot 10^{-5}$	$1.7 \cdot 10^{-2}$	$6.2 \cdot 10^{-5}$	5.7 (5.5)	225
$1.63 \cdot 10^{-4}$	$1.9 \cdot 10^{-2}$	$6.7 \cdot 10^{-5}$	3.8 (4.5)	162
$3.26 \cdot 10^{-4}$	$1.9 \cdot 10^{-2}$	$6.6 \cdot 10^{-5}$	7.7 (4.4)	195

[a]) K: pseudo-first-order rate constant (*Eqn. 2*); V_0: initial rate in product disappearance; e_r [%]: average relative error of the fitting curve; s: standard deviation; t_{irr}: duration of irradiation.

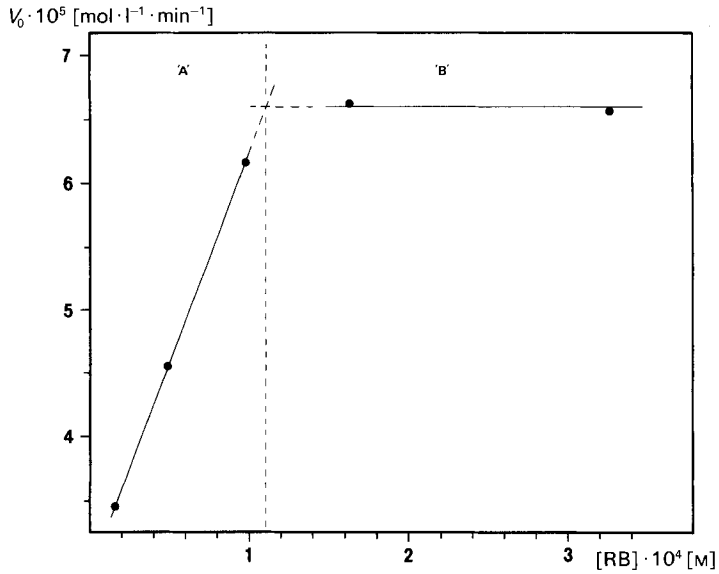

Fig. 2. *Initial rate* (V_0) vs. *sensitizer concentration* (RB) *at* $C_0 = 3.5 \cdot 10^{-3}$ M. Data from *Fig. 1*.

constant, while a linear correlation is observed at lower sensitizer concentrations. This behavior has been described in other works [7] and is interpreted to be a change of the rate-limiting step in the two-phase system. At [RB] $< 1.1 \cdot 10^{-4}$ M, a diffusion-controlled process is dominant, and the rate determining step in the overall process is the chemical reaction between singlet oxygen and the substrate. At [RB] $> 1.1 \cdot 10^{-4}$ M, however, the initial rate becomes independent of sensitizer concentration and the rate-determining step is assumed to be the interphase mass transfer of molecular oxygen from the gas phase to the liquid phase. In this region, the observed initial rate can not be ascribed to the chemical reaction. To determine the kinetic parameters under diffusion controlled conditions, the following experiments were carried out at [RB] $= 9.8 \cdot 10^{-5}$ M.

b) *Evaluation of β Value.* At variable steroid concentration ($1.8 \cdot 10^{-3}$ to $7.1 \cdot 10^{-3}$ M) and fixed rose bengal concentrations ($9.8 \cdot 10^{-5}$ M), a plot of $1/V_0$ *vs.* $1/C_0$ yields a straight line (*Fig. 3* and kinetic data in *Table 2*). If mass transfer of molecular oxygen is rate-limiting at high substrate concentrations, V_0 will approach asyntotically a maximum value.

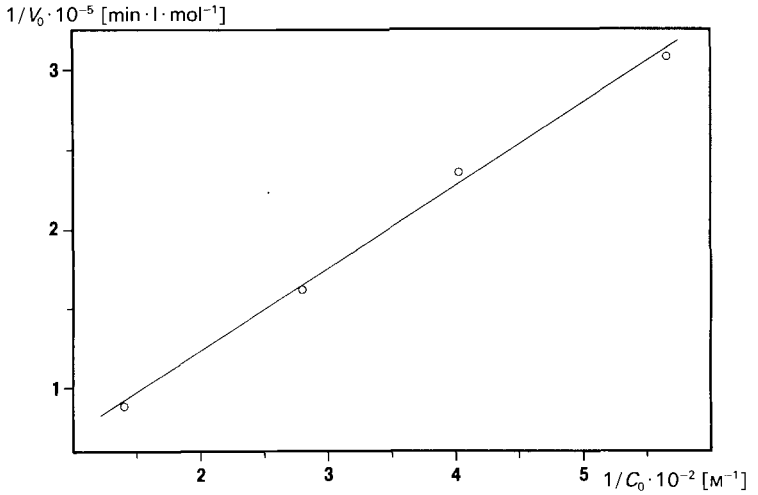

Fig. 3. $1/V_0$ vs. $1/C_0$ *Plot at constant sensitizer concentration.* [RB] = $9.8 \cdot 10^{-5}$ M (data from *Table 2*). Fitting curve: $1/V_0 = 1.6 \cdot 10^{-3} + 52.6\ (1/C_0)$, $r^2 = 0.996$, $\beta = 3.3 \cdot 10^{-2}$ M.

Table 2. *Kinetic Parameters for the Dye-Sensitized Photo-oxygenation of* **9** *at Constant Sensitizer Concentration* ([RB] = $9.8 \cdot 10^{-5}$ M[a])

C_0 [mol · l^{-1}]	K [min^{-1}]	V_0 [M · min^{-1}]	e_r e [%] (s)	t_{irr} [min]
$1.77 \cdot 10^{-3}$	$1.8 \cdot 10^{-2}$	$3.2 \cdot 10^{-5}$	1.7 (0.9)	180
$2.48 \cdot 10^{-3}$	$1.7 \cdot 10^{-2}$	$4.2 \cdot 10^{-5}$	2.1 (1.4)	202
$3.55 \cdot 10^{-3}$	$1.7 \cdot 10^{-2}$	$6.2 \cdot 10^{-5}$	5.7 (5.5)	225
$7.09 \cdot 10^{-3}$	$1.6 \cdot 10^{-2}$	$1.1 \cdot 10^{-4}$	3.6 (2.9)	270

[a]) For abbreviations, see *Footnote* in *Table 1*. C_0: initial steroid concentration.

Since *Eqn. 1* does not apply to the oxygen mass-transfer-controlled process, the plot of $1/V_0$ *vs.* $1/C_0$ will no longer be linear over the entire range of C_0. Therefore, in the range of steroid concentrations studied, a diffusion-controlled system for both sensitizer and substrate is dominant. The value of β for **9** in MeOH (calculated as the ratio of slope to intercept according to *Eqn. 1*) is $\beta = 3.3 \cdot 10^{-2}$ mol l^{-1}. Assuming a lifetime for singlet oxygen in MeOH, $\tau_\Delta = 7$ µs [8], the rate constant k_r *(Eqn. 1)* is evaluated from the relation $k_r = 1/\beta\tau_\Delta$ and is found to be $4.3 \cdot 10^6$ M^{-1} · s^{-1}. Comparing this value with other kinetic parameters described in [9] [10], **9** has a rate constant for singlet oxygen addition comparable to those substrates which undergo an oxidative fragmentation *via* a 1,2-dioxetane.

2. *Kinetics of C(3)-Substituted 9,11-Didehydroestrone Derivatives.* Preliminary assays showed that **12**, **13**, and **14** did not yield detectable photoproducts (TLC, HPLC), but a slight decrease in substrate concentration was observed. Their kinetics were also determined by measuring the disappearance of starting material.

All the irradiations were carried out at identical reagents concentrations: [RB] = $9.8 \cdot 10^{-5}$ M and [steroid] = $3.5 \cdot 10^{-3}$ M. *Fig. 4* and *Table 3* summarize the kinetic results.

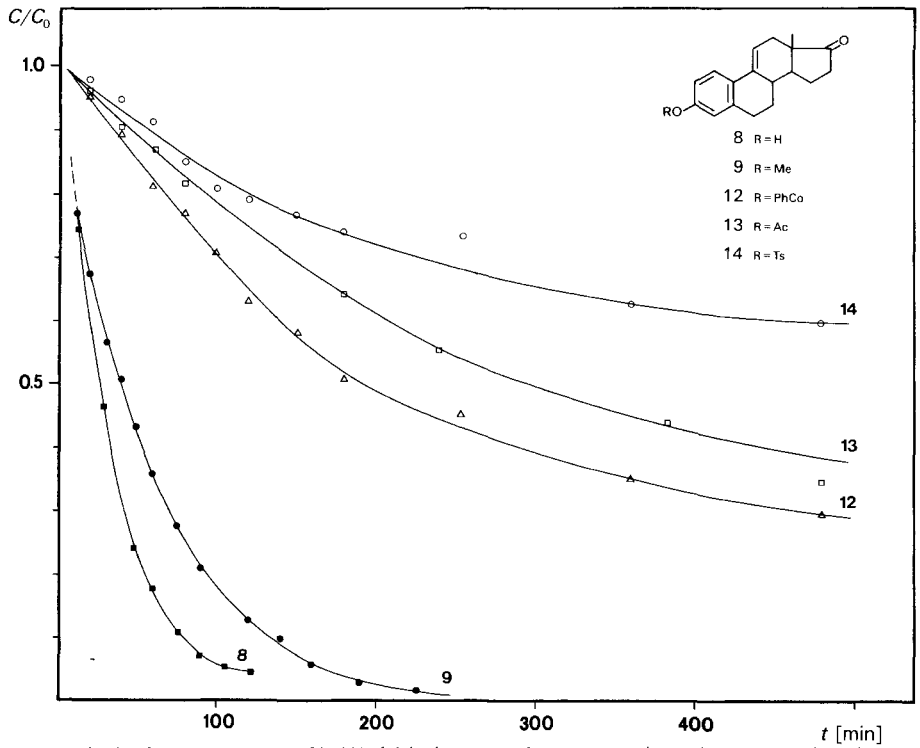

Fig. 4. *Photo-oxygenation of 9(11)-didehydroestrone derivatives at identical experimental conditions* ($C_0 = 3.5 \cdot 10^{-3}$ M, [RB] = $9.8 \cdot 10^{-5}$ M).

Table 3. *Kinetic Parameters for the Dye-Sensitized Photo-oxygenation of* **8**, **9**, **12**, **13**, *and* **14** (*cf. Fig. 4*)[a])

	K [min^{-1}]	V_0 [M · min^{-1}]	e_r e [%] (s)	t_{irr} [min]	Rel. react.
8	$1.8 \cdot 10^{-2}$	$9.8 \cdot 10^{-5}$	9.8 (5.4)	121	1
9	$1.7 \cdot 10^{-2}$	$6.2 \cdot 10^{-5}$	5.7 (5.5)	225	0.63
12	$3.0 \cdot 10^{-3}$	$1.1 \cdot 10^{-5}$	4.1 (3.3)	480	0.11
13	$2.2 \cdot 10^{-3}$	$7.8 \cdot 10^{-6}$	2.3 (1.8)	480	0.04
14	$1.0 \cdot 10^{-3}$	$3.7 \cdot 10^{-6}$	4.2 (1.3)	480	0.04

[a]) For abbreviations, see *Footnote* in *Table 1*. $C_0 = 3.5 \cdot 10^{-3}$ M, [RB] = $9.8 \cdot 10^{-5}$ M; Rel. react.: relative reactivity.

While **8** and **9** readily react to yield photoproducts, **12**, **13**, and **14** show a one order of magnitude lower rate constant in product disappearance. To assess, whether they also react with singlet oxygen or simply undergo a thermal or photosensitized decomposition, some additional experiments were performed. Irradiation of **13** under the same conditions but in absence of oxygen showed almost no decrease in steroid concentration, indicating that the substrate does not undergo any photochemical reaction either *via* triplet sensitization or radical formation by means of the triplet sensitizer. Likewise, the absence of dark reactions was demonstrated by recovery of only starting material from

oxygenated solutions stored for days in the absence of light. Therefore, singlet oxygen addition to **12**, **13**, and **14** takes place, and the photoproducts, formed in low concentration, are unstable in the reaction medium.

Since steric factors are equal in all the substrates, the different observed reactivities can be explained in terms of electronic factors. The sequence of V_0 values *(Table 3)* is in agreement with the electron-donating character of the substituents: HO > MeO ≫ PhCOO > AcO > TsO.

Discussion. – The C-ring fragmentation of **9** may be caused either by thermal fragmentation of a 1,2-dioxetane to yield the dicarbonylic compound **11** or by an ene-type reaction to form an allylic hydroperoxide which suffers a secondary *Hock* cleavage reaction leading to the same product **11** [10]. In this case, the second pathway is not likely to take place. An ene-type reaction is disfavored by conformational factors, because the allylic H-atoms (at C(12) and C(8)) are not orthogonally oriented to the π-system plane. Besides, *Hock* cleavage of a hydroperoxide intermediate, which has not been detected in our study, would require strong acidic conditions [11]. On the other hand, the strong dependence of the reactivity upon electronic factors, shown by the lower rate constant for **12**, **13**, and **14** as compared with **9**, also agrees with the intermediacy of a dioxetane. Thus, both conformational factors and rate constant measurements suggest a single oxygen addition to **9** *via* a 9,11-dioxetane as well as the unhability of an ene-type reaction to take place in a 9(11)-didehydroestrogenic system.

The styrenic system in **8** is also activated by the *p*-OH group, but a complex mixture of products is obtained. This different behavior can be explained by the fact that the free OH group may generate PhO radical species by the action of singlet oxygen or triplet sensitizer as in the case of estrone and estradiol *(cf. Introduction)*. Direct oxygen addition, such as in **9**, and radical reactions may compete leading to a mixture of oxygenated products.

The photo-oxygenation of other styrenic estrogens changing the double bond position as well as conformational calculations are under study in order to analyze geometric factors and assess the proposed interpretation. From the synthetic point of view, the oxidative fragmentation of **9** (→**11**) is a simple method to open the C ring of the steroid skeleton and is used in a new partial synthesis of 11-heteroestrogens [13], sex hormone analogs with potential annovulatory activity and low estrogenic character.

Experimental Part

General. TLC plates were purchased from *Merck* (silica gel *60 F-254*), and silica gel *Merck* 70-230 mesh was used for prep. chromatography columns. HPLC: *Hewlett-Packard-6000 A* coupled to a *Hewlett-Packard-3390 A* integrator using a *Sherisorb ODS 2* column, 15 cm length, 0.39 cm diameter, and 5-µl injection loop. M.p. were determined on a *Gallenkamp* apparatus and are uncorrected. UV: *Hewlett-Packard-8450 A* spectrophotometer (λ_{max} in nm (ε)). IR (in cm^{-1}): *Perkin-Elmer-683* instrument. ^{1}H-NMR: *Bruker AC-80* or *Varian XL-200* spectrometer. The chemical shifts are reported in δ values relative to TMS as internal standard. MS: *Hewlett-Packard-5995 A* instrument; *m/z* for the main peaks (relative intensity).

3-Hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (**8**) *and Derivatives* **9**, **12**, **13**, *and* **14**. Compound **8** and its 3-*O*-methyl derivative **9** were prepared from estrone according to the method described by *Collins* and *Sjovall* [12]. Compounds **12**, **13**, and **14** were obtained from **8** by standard acylation procedures with PhCOCl, Ac_2O, and TsCl in pyridine solution, respectively.

General Irradiation Procedure and Kinetic Measurements. A soln. of the substrate and rose bengal in dry MeOH was placed in a 300 ml tubular photoreactor and irradiated with a halogen lamp (*Sylvania*, 500 W) fitted with a cooling jacket. O_2 was bubbled through the soln. at constant flux (0.5 ml·s^{-1}). Temp. was kept at 0° by an axiliary external cooling system and solvent evaporation avoided by means of a gas trap. Samples were taken at regular time intervals directly from the reaction vessel through a rubber septum. Analysis was performed by HPLC with MeCN/H_2O 7:3 (1.5 ml·min^{-1} at 25°) and UV detector at 270 nm. Absolute concentration of substrates were calculated by calibrating the detector in each run with standardized solns. of substrates. Kinetic parameters were calculated by linear least-square fitting of experimental data to *Eqn. 2* and *1*, and relative errors by standard statistical methods.

Prep. Photo-oxygenation of **8**. Compound **8** (720 mg) and rose bengal (88 mg) in 130 ml of MeOH were irradiated at r.t. in a tubular photoreactor while O_2 was bubbled through the soln. Solvent evaporation gave 982 mg of a complex mixture (TLC). Flash chromatography on silica gel (AcOEt/$CHCl_3$ 3:7) yielded three main fractions; the less polar one was re-chromatographed (SiO_2, $CHCl_3$/AcOEt 14:1) affording 30 mg of **10**. M.p. 162–164° (Et_2O). UV (EtOH): 292 (16400). IR (KBr): 1730, 1670, 1650, 1590, 1250. ^{1}H-NMR ($CDCl_3$): 1.07 (*s*, CH_3); 2.82 (*dd*, *J* = 15, 6, H–C(2)); 4.90 (*m*, H–C(1), H–C(11)); 5.83 (*s*, H–C(4)). MS: 300 (M^+).

Attempts to isolate other components from the remaining fractions were unsuccesful.

Prep. Photo-oxygenation of 3-Methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**9**). Irradiation of **9** (1 g) and rose bengal (50 mg) in 180 ml of MeOH and 20 ml of CH_2Cl_2 for 3 h at 9–10° in the photo-oxygenation equipment described above, afforded one major product. After chromatography on SiO_2, unreacted starting material (30 mg) and *3-methoxy-9,17-dioxo-9,11-secoestra-1,3,5(10)-trien-11-al* (**11**; 550 mg) were obtained. In spite of the higher yield in the mixture, **11** was isolated in 50% yield from **9** due to slow decomposition during purification. However, it proved to be stable at r.t. when stored for a long time. UV (MeOH): 206 (14700), 224 (10800), 274 (14700). IR: 2950, 2820, 1735, 1720, 1670, 1600, 1495, 1260. ^{1}H-NMR ($CDCl_3$): 9.25 (*s*, CHO); 7.75 (*d*, *J* = 8, H–C(1)); 6.70 (*dd*, *J* = 8, 2, H–C(2)); 6.55 (*d*, *J* = 2, H–C(4)); 3.75 (*s*, CH_3O); 2.90 (*m*, 2 H–C(6)); 1.02 (*s*, CH_3). MS: 314 (12, M^+), 287 (8), 229 (22), 177 (18), 176 (100), 175 (15), 161 (12), 148 (16), 120 (19), 91 (14), 77 (12).

The 2,4-dinitrophenylhydrazone derivative of **11** was prepared by dissolving 93 mg (0.30 mmol) of **11** in a soln. of 200 mg (1.01 mmol) of 2,4-dinitrophenylhydrazine in 20 ml MeOH and 10 drops of conc. HCl. The yellow crystals obtained after filtration of the precipitate and crystallization from CH_2Cl_2/$(i\text{-}Pr)_2O$ were identified as the 11,17-bis(2,4-dinitrophenylhydrazone) of **11**. M.p. 249°. IR (KBr): 3320, 3300, 1670, 1625, 1600, 1520, 1510, 1340, 1260. Anal. calc. for $C_{31}H_{30}N_8O_{10}$ (674.63): C 55.20, H 4.48, N 16.61; found: C 55.46, H 4.48, N 16.34.

Ozonolysis of **9**. a) *H_2O_2 Treatment.* O_3 in O_2 was bubbled through a soln. of 1 g of **9** in 12 ml of MeOH and 20 ml of CH_2Cl_2 at –78° while stirring. After purging O_3 and warming the soln. up to 0°, 20 ml of H_2O_2 were added and the temp. kept at 0° for 2 h. The excess oxidant was destroyed by an aq. soln. of Na_2SO_3. CH_2Cl_2 extraction afforded 1.2 g of a yellowish oil. Chromatography on SiO_2 (with cyclohexane/AcOEt 4:1 for the less polar impurities followed by $CHCl_3$/AcOEt 5:1) yielded *3-methoxy-9,17-dioxo-11-nor-9,11-secoestra-1,3,5(10)-triene-12-carboxylic acid* (**15**) (strong decomposition during the purification process). UV (MeOH): 205 (14500), 224 (10700), 275 (14000). IR: 3500–3000, 1735, 1710, 1670, 1600, 1490, 1260. ^{1}H-NMR ($CDCl_3$): 7.90 (*d*, *J* = 7, H–C(1)); 7.45 (br. COOH, disappears after shaking with D_2O): 6.80 (*dd*, *J* = 7, 2.5, H–C(2)); 6.70 (*d*, *J* = 2.5, H–C(4)); 3.80 (*s*, CH_3O); 2.90 (*m*, 2 H–C(6)); 1.0 (*s*, CH_3). MS: 330 (8, M^+), 177 (15), 176 (100), 175 (13), 161 (10), 148 (15), 120 (12).

b) *Zn/AcOH Treatment.* A soln. of 100 mg of **9** in 20 ml of CH_2Cl_2 was ozonized as described above. After purging O_3, 150 mg of Zn powder and 3 ml of AcOH were added and the mixture stirred at r.t. for 12 h under N_2. Usual workup yielded 93 mg of a mixture of two products which were separated by chromatography (silica gel) resulting in 37 mg (33%) of **11** (identical spectral data as the product obtained by photo-oxygenation) and 23 mg (23%) of *3-methoxy-9,17-dioxo-9,11-secoestra-1,3,5(10)-trien-11-ol* (**16**). UV (MeOH): 204 (14100), 224 (9100), 274 (10700). IR: 3450, 1735, 1670, 1600, 1495, 1260. ^{1}H-NMR ($CDCl_3$): 7.75 (*d*, *J* = 8, H–C(1)); 6.60 (*dd*, *J* = 8, 2, H–C(2)); 6.50 (*d*, *J* = 2, H–C(4)); 3.75 (*s*, CH_3O); 3.60 (*m*, 2 H–C(11)); 2.85 (*m*, 2 H–C(6)); 2.10 (br., OH, disappears after shaking with D_2O): 1.05 (*s*, CH_3). MS: 316 (1, M^+), 260 (4), 243 (4), 177 (4), 176 (16), 149 (12), 148 (3), 95 (17), 94 (100).

Upon shorter Zn/AcOH treatment (1 h), the yield in **11** was increased up to 40–45%.

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