93. Photolysis of Steroidal 20-Aryl-Substituted 11-Nitrites

by **Jaroslav Kalvoda**[1][2]* and **Jürgen Grob**

Research Laboratories, Pharma Division, *Novartis AG*, CH-4002 Basel

and **Mira Bjelaković, Ljubinka Lorenc**, and **Mihailo Lj. Mihailović**

Faculty of Chemistry, University of Belgrade, Studentski trg 12–16, P.O. Box 815, YU-11001 Belgrade

Dedicated to Prof. *O. Jeger* on the occasion of his 80th birthday

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The two structurally similar 20-phenyl- and 20-(4-methoxyphenyl)-11-(nitrosooxy)pregnan-20-ol derivatives **4** and **7** behave differently under photolytic conditions, the former nitrous acid ester affording, as a main product, the benzo-fused hexacyclic compound **9**, and the latter the 21-nitro derivative **12**. Mechanistic aspects of these transformations are discussed.

Introduction. – Some time ago, in studying the mechanism of the 'cyanohydrin-cyano ketone rearrangement' in steroids [1][3], a new sequential type of a radical-induced intramolecular rearrangement of a cyano group was conceived [3].

In this transformation, 11β-alkoxy radical **b** (obtained by photolysis of a 20-hydroxy-11β-(nitrosooxy)pregnene-20-carbonitrile of type **a**, according to *Barton*'s procedure) is used to generate a C-radical **c** at C(18) (*Scheme 1*). Intramolecular addition of this species to the multiple bond of the cyano function induces, by intermediacy of the cyclic imino radical **d** and the oxygenated tertiary C-radical **e**, a shift of the CN group from C(20) to the C(18) position. After formal H* elimination, the 18-carbonitrile derivative **f** is obtained.

At a later stage of the project, an analogous radical-induced 1,4-transfer of a formyl group was described [4].

In the context of the present paper, we have tried to answer the question whether an aryl group, situated at the C(20) position in similar substrates, could also migrate to C(18) when subjected to analogous photolytic conditions. Such an assumption seemed to be reasonable, since radical-induced 1,4-aryl rearrangements are well documented [5] [6][4]).

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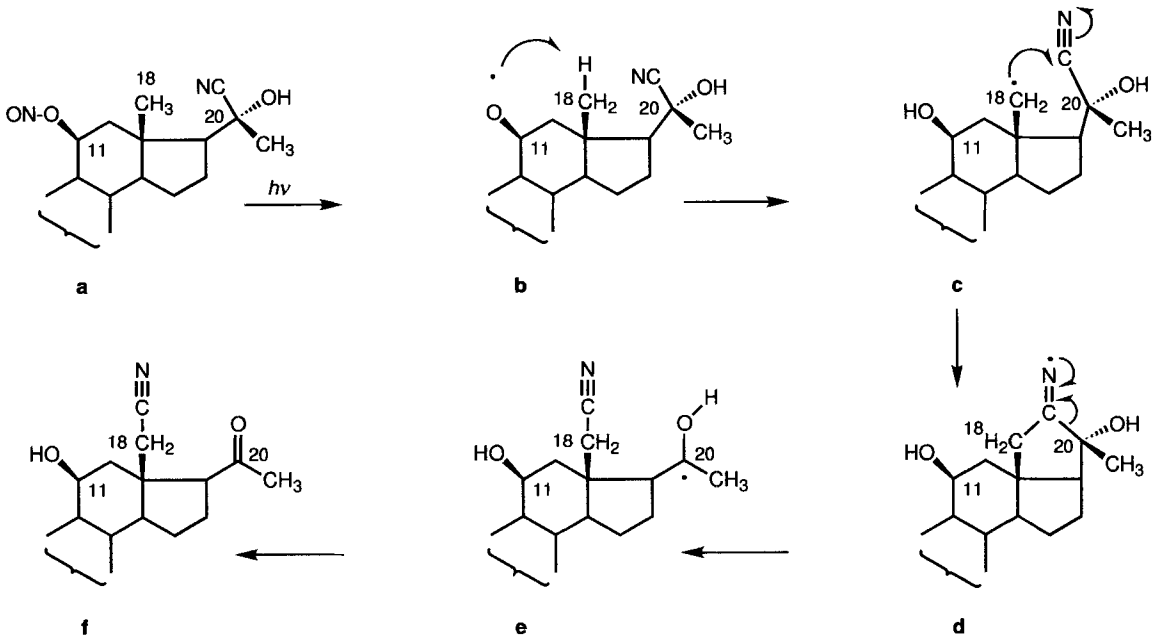
[1]) Presented in part by *J.K.* at the 2nd International Symposium on Organic Free Radicals, Aix-en-Provence, 1977.

[2]) Present address: Leimgrubenweg 21, CH-4102 Binningen.

[3]) *Cf.* a similar type of reaction the photolysis of α-peracetoxynitriles, described by *Watt* and coworkers [2].

[4]) According to the work of *Winstein* and coworkers [5], *Chottard* and *Julia* [6], and others, the non-steroidal 4-arylbutyl radicals can react in two ways. Either they substitute the aromatic ring directly in the 2-position or they form σ-complexes containing a spiro structure (*ipso* substitution) [7] [8]. The latter nonclassical radicals can undergo either a 1,2-rearrangement or fragmentation by splitting one of the two 'spiro bonds', thereby forming the ring-opened radical of the same or the 1,4-rearranged structure, respectively.

Scheme 1



Results. – The starting materials for this study, *i.e.*, (20*R*)-20-phenyl- and (20*R*)-20-(4-methoxyphenyl)-11β-(nitrosooxy)pregnane derivatives **4** and **7** (*Scheme 2*), were derived from (20*R*)-3,3-(ethylenedioxy)-20-phenylpregn-5-ene-11β,20-diol (**1**) and (20*R*)-3,3-(ethylenedioxy)-20-(4-methoxyphenyl)pregn-5-ene-11β,20-diol (**5**)[5] in the following way. Acetal **1** was treated with *p*-toluenesulfonic acid in acetone/H_2O 20:1 at room temperature for 72 h to give the free pregn-4-en-3-one **2** (83% yield). On the other hand, when 4-methoxyphenyl analogue **5** was treated under similar conditions or with anhydrous $MgSO_4$ in wet benzene [11], elimination of the 20-OH group (accompanied by partial deprotection of the 3-oxo function) produced a mixture of the C(20)=C(21) methylidene compounds **8a** and **8b**. Therefore, in the 4-methoxyphenyl series, due to lability of the 20-OH group, further reactions were performed using as substrates the corresponding pregn-5-en-3-one acetal derivatives[6]). Treatment of diols **2** and **5** with an excess of nitrosyl chloride afforded the bis(nitrosooxy) compounds **3** and **6**, respectively, which, by partial hydrolysis (AcOH in toluene) were transformed to the corresponding 11β-mononitrites **4** and **7**.

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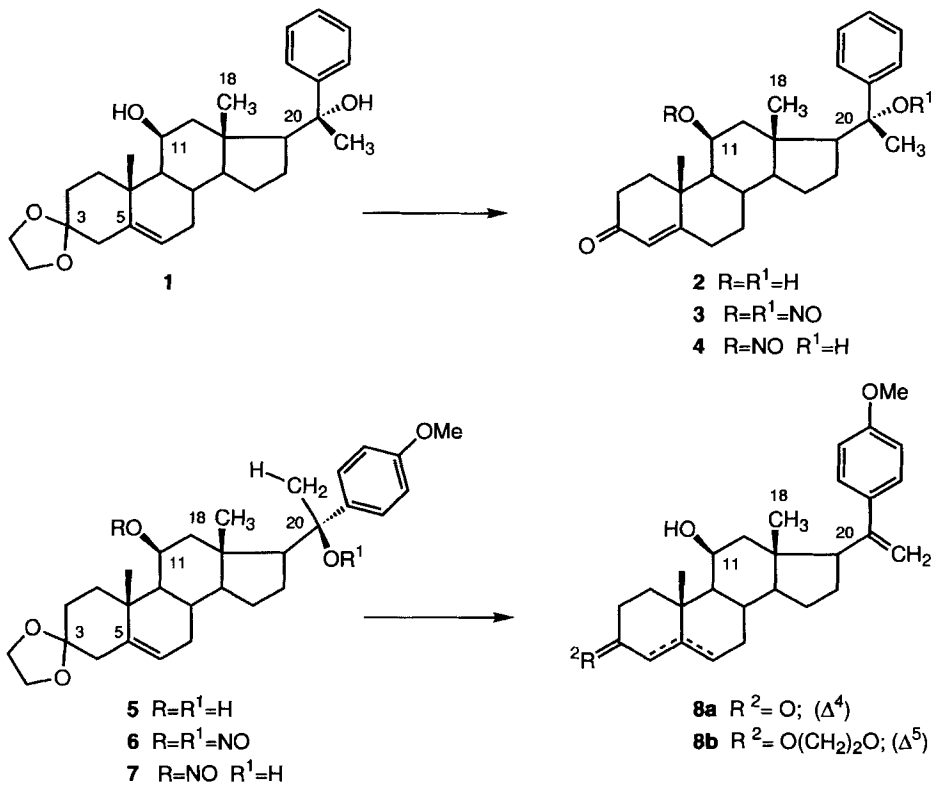
[5]) The synthesis of the pregn-5-en-3-one acetals **1** and **5** has been previously reported [9]. The (20*R*)-configuration of 20-phenylpregn-4-en-3-one **2** was determined by X-ray analysis [10], while that of the 20-(4-methoxyphenyl) products was deduced by comparison of their spectral data (mainly ^{1}H-NMR) with those of the corresponding 20-phenyl analogues.

[6]) Although *Barton* and coworkers [12] have shown that steroidal 3-oxo-4-en-11β-yloxy radicals (in comparison to the corresponding 5-en-3-one-acetal analogues) abstract a H-atom from the Me(18) group more readily than from the almost equidistant Me(19) group, it was expected that the different positions of the olefinic double bond in the molecules of both substrates could not have much influence on the reactivity of the respective C(18) C-radicals when formed.

Scheme 2



Nitrite **4** was irradiated in dry toluene with a high-pressure mercury lamp (*Q81*) for 1 h to afford a complex mixture, from which the cyclic 18,20-benzo-fused compound **9** and 11β,20-dihydroxypregnenon **2** were isolated (*Scheme 3*) in *ca.* 24 and 6% yield, respectively. However, no trace of the expected rearranged compound **A** was detected[7]). Compound **9** was transformed to the corresponding 21-methylidene analogue **10**, the spectral characteristics of which confirmed the proposed structure **9**.

In the ^{1}H-NMR spectrum of **9**, the original 18-methyl group (*s* at 0.94 ppm) was missing. Instead, an *AB q* appeared at 2.66 and 3.53 ppm (J = 17 Hz), assignable to the CH_2(18) group. In accordance with the benzo-fused structure, the spectrum contained signals for only four aromatic protons (2*d* each 1 H) at 7.16 and 7.54 ppm (J = 7 Hz), arising from H–C(3′) and H–C(6′), and a *m* (2 H) at 7.22 ppm, attributable to H–C(4′) and H–C(5′).

On the other hand, when nitrite **7** was irradiated under similar conditions, it gave a mixture which contained (*Scheme 4*) the 21-methylidene compound **11** (7.6%), arising from dehydration of diol **5**, the 21-nitro derivative **12** (*ca.* 17%), and diol **5** (*ca.* 11%).

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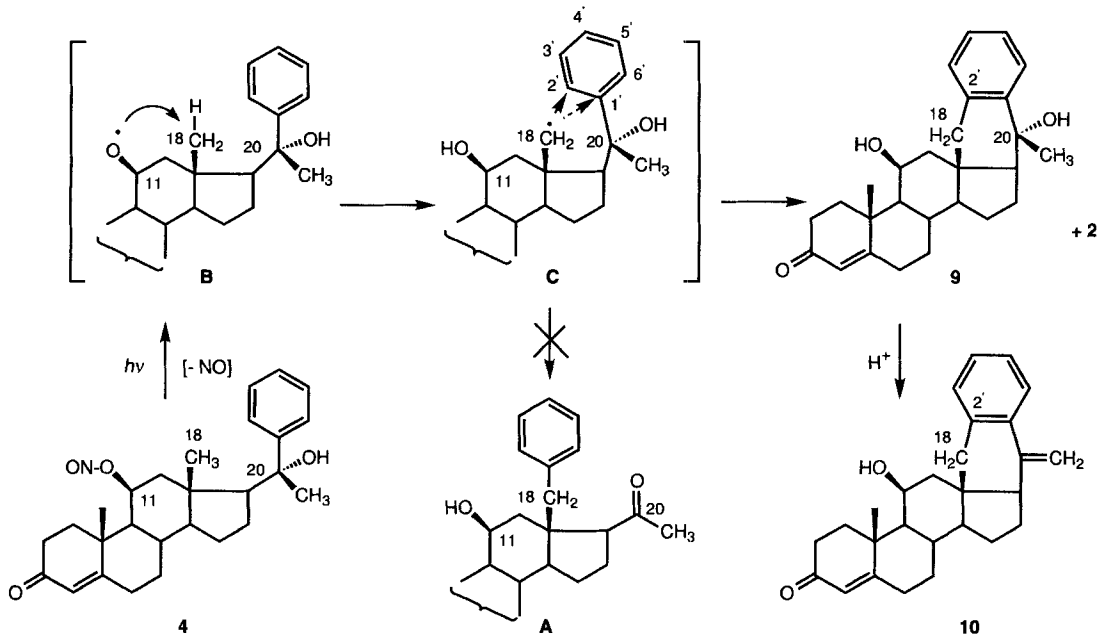
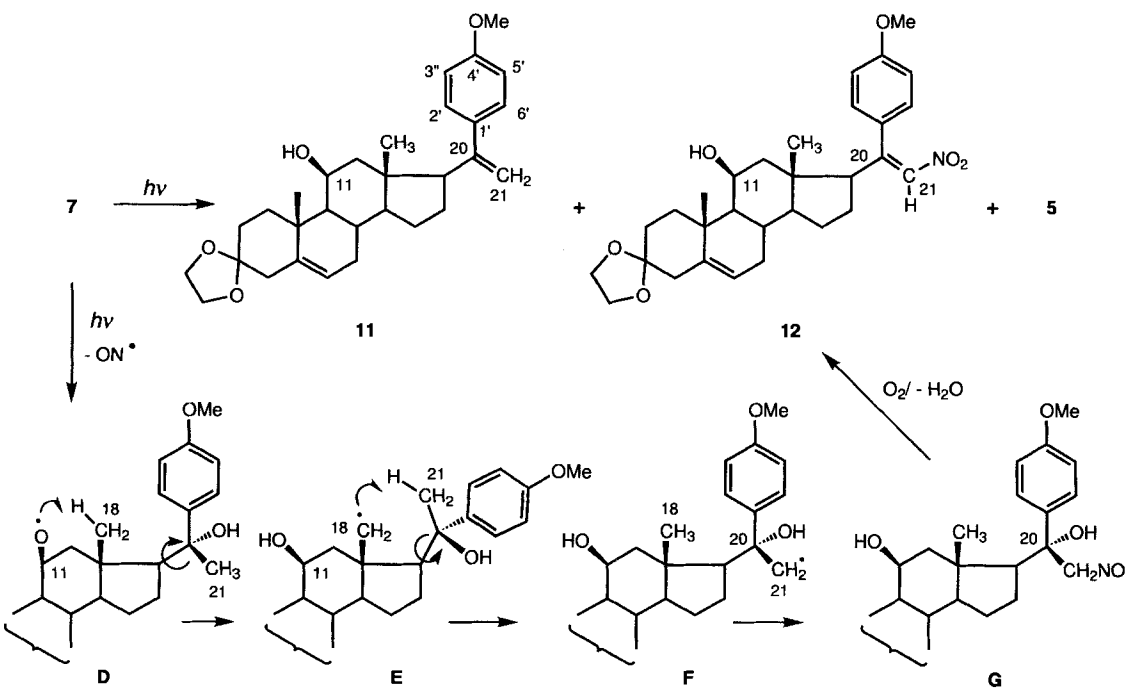
[7]) In one experiment, minute amounts of two additional compounds, the internal 11,20-acetal and the corresponding oxim of the 18-oxo derivative, were isolated.

Scheme 3



Scheme 4



The structure **12** was established as follows. The MS (M^+ at 509, facile loss of NO_2) and IR absorption at 1520 and 1341 cm^{-1} indicated the presence of a NO_2 group. The ^{1}H-NMR spectrum showed the unchanged pattern of a *p*-substituted aromatic ring (2*d* (2 H) at 6.71 and 6.90 ppm, $J \approx 9$ Hz) and a *s* (1 H) at 6.75 ppm, assignable to an olefinic proton geminal to the NO_2 group and *trans* to the aromatic ring. Besides, the number of the primary, secondary, tertiary, and H-free C-atoms detectable in the DEPT ^{13}C-NMR spectrum of **12** (3 Me, 9 CH_2, 11 CH (of which 2 olefinic, 4 aromatic, 1 bearing OH), and 7 H-free C-atoms) can be well accomodated in the structure **12**.

Discussion. – The above results indicate that photolyses of the nitrites **4** and **7** proceed as expected *via* the corresponding C(18) C-radicals **C** and **E**, respectively (*Schemes 3* and *4*), which are formed according to the generally accepted mechanism (homolysis of the O–NO bond and H-abstraction from the Me(18) group by the thus generated 11β-yloxy radicals **B** and **D**, resp.).

The *ipso* attack mentioned above seems to play an important role in intra- and intermolecular [8] free-radical aromatic substitution reactions. Therefore, also in our case, besides the possibility of a direct *ortho* attack, this type of substitution has to be taken into consideration. In this connection, the nucleophilic nature of the attacking C(18) radical as well as the electron distribution in the aromatic ring should be of relative importance.

The preferred conformation of the side chain in the starting compounds **4** and **7** might be indicative of the direction of the reaction. As can be seen in the *Figure*, the X-ray conformation of **4** strongly deviates from the optimal arrangement to be postulated for the transition state for either one of the two reactions observed. One of the conformations, **I**, obtained by 'energy minimization' using the simple CS Chem3D Pro program (MM2 force field), might correspond to one local energy minimum and could be responsible for an *ipso*-type substitution. The higher energy conformation **II** should, however, allow the abstraction of a H-atom from the Me(21) group.

The difference observed for the two substrates **4** and **7** concerning the reaction of the respective C(18) radical could be explained by the following arguments. The C(18) radical **C** (*Scheme 3*) adds to C(1′) of the aromatic ring in the expected *ipso* fashion and the formed σ-complex rearranges to the hexacyclic steroid **9**[8])[9]).

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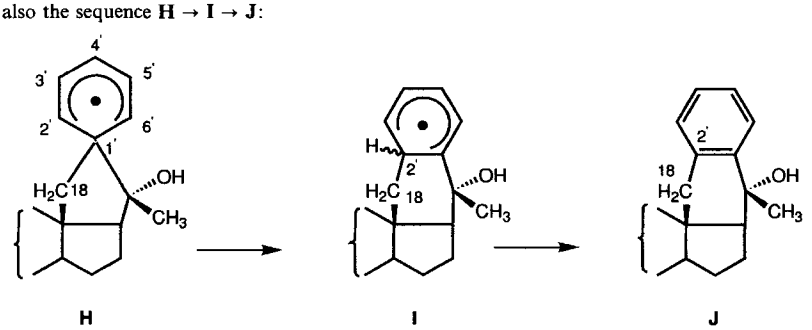
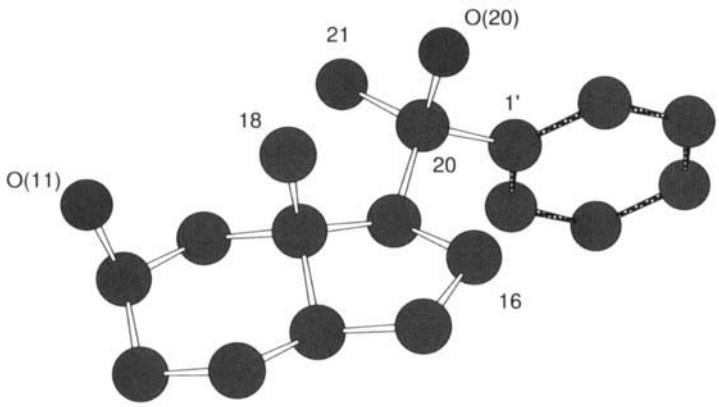
[8]) *Cf.* also the sequence **H** → **I** → **J**:



H **I** **J**

[9]) The less probable direct *ortho*-substitution could, on the other hand, explain the missed formation of the 18-phenyl compound of type **A**.



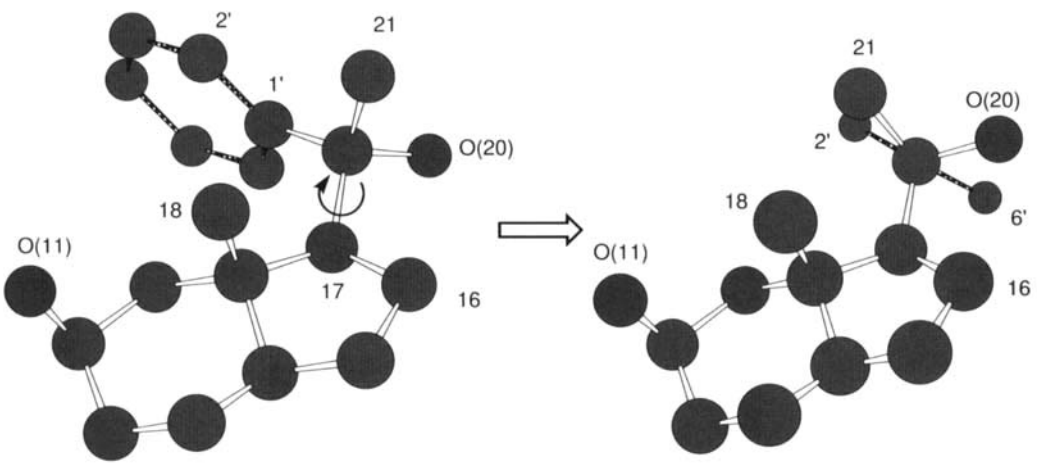
X-Ray conformation [6]

C(18).....C(1') = 4.627 Å

C(18).....C(21) = 3.740 Å

O-C(20)-C(17)-C(16) = - 55.9°

Steric energy: ca. 47.13 kcal/mol



Conformation I

C(**18**).....C(**1'**) = 3.715 Å

C(18).....C(2') = 3.850 Å

C(21)-C(20)-C(17)-C(16) = - 53°

Steric energy: ca. 28.83 kcal/mol

Conformation II

C(**18**).....C(**21**) = 2.910 Å

C(18).....C(2') = 3.850 Å

C(21)-C(20)-C(17)-C(16) = -101.90°

Steric energy: ca. 36.92 kcal/mol

Fig. 1. *Conformations of the side chain of* **4**

The *p*-methoxy group in compound **7**, however, reduces the electrophilicity of C(1'), and thereby also the tendency of the rather nucleophilic [8] C(18) radical (in **E**) to add to this center. In this case, the alternative pathway involving H-abstraction at C(21) becomes more important. The resulting C(21)-centered C-radical **F** is trapped by the NO' fragment present in the reaction mixture to give the nitroso intermediate **G** which, by air oxidation[10]) and subsequent H_2O elimination, can be transformed into the 21-nitro compound **12.** A low occupancy of the conformation **II** could, thereby, explain the rather low yield of **12.**

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Experimental Part

General. Column chromatography: silica gel 0.063–0.200. TLC: control of reactions and separation of products on silica gel *G* (*Stahl*), detection with aq. 50% H_2SO_4 soln. M.p.: uncorrected. IR Spectra: *Perkin-Elmer-337* spectrophotometer: ν in cm^{-1}. NMR Spectra: *Bruker AM-250*, *AM-360*, and *AM-600* (^1H at 250, 360, or 600 MHz, ^{13}C at 62.9 or 90.5 MHz); $CDCl_3$ or C_6D_6 soln. at r.t.; $SiMe_4$ as internal standard; δ in ppm, *J* in Hz. Mass spectra: *Finnigan-MAT 8230*; *m/z* (rel. intensity in %); ionization energy 70 eV.

*(20*R*)-11β,20-Dihydroxy-20-phenylpregn-4-en-3-one* (**2**). A soln. of (20*R*)-3,3-(ethylenedioxy)-20-phenylpregn-5-ene-11β,20-diol **1**; (470 mg, 1.0 mmol) in acetone/H_2O 20:1 (42 ml) and *p*-toluenesulfonic acid monohydrate (80 mg) was shaken at r.t. for 72 h and the acid neutralized with aq. $NaHCO_3$ soln. The mixture was extracted several times with benzene/Et_2O and the combined extract washed with H_2O and evaporated to give a crude product (450 mg) which was recrystallized from benzene: pure **2** (275 mg, 64.8%). M.p. 208–211° (from CH_2Cl_2/Et_2O). $[\alpha]_D^{24} = +50.6$ (*c* = 0.5, $CHCl_3$). IR (KBr): 3451, 3052, 3025, 1631, 1601, 759, 707. ^1H-NMR (360 MHz, $CDCl_3$): 1.05 (*d*, *J* = 4.2, OH–C(11)); 1.16 (*s*, Me–C(13)); 1.36 (*s*, Me–C(10)); 1.65 (*s*, OH–C(20)); 1.67 (*s*, Me–C(20)); 4.32 (*m*, H_α–C(11)); 5.66 (br. *s*, H–C(4)); 7.20 (*t*, *J* = 6.6, H–C(4')); 7.30 (*t*, *J* = 6.6, H–C(3'), H–C(5')); 7.38 (*d*, *J* = 6.6, H–C(2'), H–C(6')). ^{13}C-NMR (90.5 MHz, $CDCl_3$): 199.4 (*s*, C(3)); 172.2 (*s*, C(5)); 149.5 (*s*, C(1')); 127.9 (*d*, C(3'), C(5')); 126.3 (*d*, C(4')); 124.6 (*d*, C(2'), C(6')); 122.3 (*d*, C(4)); 76.3 (*s*, C(20)); 66.6 (*d*, C(11)); 61.2 (*d*, C(17)); 57.6 (*d*, C(14)); 56.5 (*d*, C(9)); 49.5 (*t*, C(12)); 42.3 (*s*, C(13)); 39.2 (*s*, C(10)); 35.0 (*t*, C(1)); 33.8 (*t*, C(2)); 32.5 (*t*, C(6)); 32.1 (*t*, C(7)); 30.9 (*d*, C(8)); 29.7 (*q*, C(21)); 23.3 (*t*, C(15)); 22.4 (*t*, C(16)); 21.0 (*q*, C(19)); 16.4 (*q*, C(18)). MS: 390 (20, $[M-18]^+$), 372 (24, $[M-2\times18]^+$), 121 (100, $C_8H_9O^+$). Anal. calc. for $C_{27}H_{36}O_3$ (408.58): C 79.37, H 8.88; found: C 79.15, H 9.01.

The filtrate was evaporated and the residue (170 mg) chromatographed on silica gel (10 g, toluene/AcOEt 85:15): additional **2** (76.5 mg, 18.0%).

*(20*R*)-20-Hydroxy-3-oxo-20-phenylpregn-4-en-11β-yl Nitrite* (**4**). A soln. of **2** (340 mg) in pyridine (4 ml) was cooled to −15° and treated with an excess of nitrosyl chloride (0.5 ml). The mixture was allowed to warm to r.t., diluted with H_2O, and extracted with benzene. The extracts were washed with 1M aq. NaOH and H_2O and evaporated: 11β,20-dinitrite **3** (380 mg, 97.9%). The dinitrite (340 mg) in toluene (60 ml) and AcOH (1 ml) was stirred at r.t. for 15 min and the mixture worked up as above: **4** (306 mg, 96.0%)[11]). ^1H-NMR (600 MHz, $CDCl_3$): 0.94 (*s*, Me–C(13)); 1.16 (*s*, Me–C(10)); 1.68 (*s*, Me(21)); 5.69 (br. *s*, H–C(4)); 6.04 (*m*, H_α–C(11)); 7.21 (*t*, *J* = 7.4, H–C(4')); 7.30 (*t*, *J* = 7.4, H–C(3'), H–C(5')); 7.38 (*d*, *J* = 7.4, H–C(2'). H–C(6')).

*(20*R*)-3,3-(Ethylenedioxy)-20-hydroxy-20-(4-methoxyphenyl)pregn-5-en-11β-yl Nitrite* (**7**). A soln. of **5** (450 mg) in pyridine (5 ml) was treated with nitrosyl chloride as above to give dinitrite **6** (450 mg, 89.3%). The latter was stirred in toluene (140 ml) and AcOH (0.72 ml) at r.t. for 1 h. Workup as above gave **7** (410 mg, 96.3%)[11]). ^1H-NMR (600 MHz, C_6D_6): 0.90 (*s*, Me–C(13)); 0.99 (*s*, Me–C(10)); 1.34 (*s*, Me–C(20)); 3.38 (*s*, MeO); 3.54 (*m*, $(CH_2O)_2$); 5.20 (br. *s*, H–C(6)); 5.98 (br. *s*, H_α–C(11)); 6.86 (*d*, *J* = 8.6, H–C(3'), H–C(5')); 7.31 (*d*, *J* = 8.6, H–C(2'), H–C(6')).

*(20*R*)-11β,20-Dihydroxy-18,20-(1,2-phenylene)pregn-4-en-3-one* (= *(20*R*)-11β,20-Dihydroxybenzo[18,20]pregn-4-en-3-one*; **9**). A soln. of **4** (200 mg) in dry toluene (110 ml) was irradiated with a high-pressure

[10]) The air oxidation of some nitroso compounds to the corresponding nitro analogues is well established [13].

[11]) Due to the relative instability of the 11β-nitrites **4** and **7**, they were used in the next irradiation step directly without purification.

Hg lamp (*Q81*) placed in a central-water-cooled jacket for 1 h. The usual workup gave a mixture (196 mg) which was chromatographed on silica gel (10 g). Elution with toluene/AcOEt 85:15 afforded **2** (12 mg, 6.0%) which was identified by direct comparison with an authentic sample. Toluene/AcOEt 82:18 eluted **9** (44 mg, 23.7%). M.p. (Et_2O) 170–171°. IR (neat): 3414, 1653, 1616, 1259, 1233, 1060, 760. ^{1}H-NMR (600 MHz, $CDCl_3$): 1.51 (*s*, Me–C(10)); 1.58 (*s*, Me–C(20)); 2.66, 3.53 (*AB*, J = 17, CH_2(18)); 4.38 (br.*s*, H_α–C(11); 5.70 (*s*, H–C(4)); 7.16 (*d*, J = 7, H–C(3′), 7.22 (*m*, H–C(4′), H–C(5′)); 7.54 (br. *d*, J = 7, H–C(6′)).

11β-Hydroxy-18,20-(1,2-phenylene)pregna-4,20-dien-3-one (= *11β-Hydroxybenzo[18,20]pregna-4,20-dien-3-one*; **10**). A soln. of **9** (20 mg) in $CHCl_3$ (5 ml) containing cat. amounts of HCl was stirred at r.t. for 24 h. The usual workup gave **10**. $[\alpha]_D^{25}$ = + 122.9 (c = 0.5, $CHCl_3$). ^{1}H-NMR (360 MHz, $CDCl_3$): 1.50 (*s*, Me–C(10)); 2.68, 3.43 (*AB*, J = 17, CH_2(18)); 4.32 (*m*, H_α–C(11)); 4.95, 5.61 (2*s*, CH_2(21)); 5.68 (*s*, H–C(4)); 7.11–7.55 (*m*, arom. H). ^{13}C-NMR (90.5 MHz, $CDCl_3$): 199.2 (*s*, C(3)); 171.9 (*s*, C(5)); 144.2 (*s*, C(20)); 136.1 (*s*, C(2′)); 133.4 (*s*, C(1′)); 129.2 (*d*, C(5′)); 127.4 (*d*, C(4′)); 125.6 (*d*, C(3′)); 123.5 (*d*, C(6′)); 121.9 (*d*, C(4)); 109.4 (*t*, C(21)); 68.1 (*d*, C(11)); 56.1 (*d*, C(17)); 56.1 (*d*, C(9)); 52.3 (*d*, C(14)); 42.8 (*t*, C(12)); 42.0 (*s*, C(13)); 39.0 (*s*, C(10)); 34.5 (*t*, C(1)); 33.4 (*t*, C(6)); 32.4 (*t*, C(2)); 31.7 (*t*, C(7)); 31.3 (*d*, C(8)); 30.1 (*t*, C(18)); 29.7 (*t*, C(16)); 24.4 (*t*, C(15)); 20.7 (*q*, C(19)). MS: 388 (21, M^+), 370 (59, $[M - 18]^+$), 355 (10, $[M - 18 - 15]^+$).

Photolysis of **7**. A soln. of **7** (410 mg) in dry toluene (110 ml) was irradiated for 1.5 h and worked up as above. The residue (380 mg) was separated by prep. TLC: **11** (28 mg, 7.5%), more polar **12** (69 mg, 17%), and the most polar 11β,20-dihydroxy compound **5** (45 mg, 11%; identified by comparison with an authentic sample).

3,3-(Ethylenedioxy)-20-(4-methoxyphenyl)pregna-5,20-dien-11β-ol (**11**): M.p. 179–181°. IR (neat): 3522, 3094, 3037, 1608, 1509, 1244, 1176, 1141, 833. ^{1}H-NMR (250 MHz, C_6D_6): 0.92 (*s*, Me–C(13)); 1.34 (*s*, Me–C(10)); 3.35 (*s*, MeO); 3.56 (*m*, $(CH_2O)_2$); 3.76 (br. *s*, H_α–C(11)); 5.09, 5.26 (2*s*, CH_2(21)); 5.26 (br. *s*, H–C(6)); 6.82 (2*d*, J = 8.7, H–C(3′), H–C(5′)); 7.21 (2*d*, J = 8.7, H–C(2′), H–C(6′)). ^{13}C-NMR (62.9 MHz, C_6D_6): 159.4 (*s*, C(4′)); 149.5 (*s*, C(20)); 141.8 (*s*, C(5)); 137.9 (*s*, C(1′)); 127.6 (*d*, C(2′), C(6′)); 120.7 (*d*, C(6)); 113.7 (*d*, C(3′), C(5′)); 112.5 (*t*, C(21)); 109.6 (*s*, C(3)); 68.0 (*d*, C(11)); 64.2 (*t*, $(CH_2O)_2$); 22.2 (*q*, C819)); 15.2 (*q*, C(18)). MS: 464 (16, M^+), 446 (5, $[M - 18]^+$).

3,3-(Ethylenedioxy)-20-(4-methoxyphenyl)-21-nitropregna-5,20-dien-11β-ol (**12**): IR (KBr): 3492, 1609, 1520, 1341, 1250, 1092, 1033, 756. ^{1}H-NMR (600 MHz, C_6D_6): 0.80 (*s*, Me–C(13)); 1.29 (*s*, Me–C(10)); 3.26 (*s*, MeO); 3.50–3.59 (*m*, $(CH_2O)_2$, H_α–C(11)); 5.25 (br. *s*, H–C(6)); 6.71 (2*d*, J = 8.6, H–C(3′), H–C(5′)); 6.75 (*s*, H–C(21)); 6.90 (2*d*, J = 8.6, H–C(2′), H–C(6′)). ^{13}C-NMR (62.9 MHz, C_6D_6): 160.3 (*s*, C(4′)); 150.2 (*s*, C(20)); 141.8 (*s*, C(5)); 136.4 (*d*, C(21)); 130.1 (*s*, C(1′)); 129.0 (*d*, C(2′), C(6′)); 120.5 (*d*, C(6)); 114.0 (*d*, C(3′), C(5′)); 109.5 (*s*, C(3)); 67.7 (*d*, C(11)); 64.2, 64.3 (2*t*, $(CH_2O)_2$); 58.5 (*d*, C(17)); 57.4 (*d*, C(14)); 54.7 (*d*, C(9)); 53.3 (*q*, MeO); 47.8 (*t*, C(12)); 43.6 (*s*, C(13)); 41.4 (*t*, C(4)); 37.0 (*s*, C(10)); 35.8 (*t*, C(7)); 32.2 (*t*, C(1)); 31.7 (*t*, C(2)); 28.9 (*d*, C(8)); 24.6 (*t*, C(15)); 23.8 (*t*, C(16)); 22.2 (*q*, C(19)); 15.2 (*q*, C(18)). MS: 509 (1.5, M^+), 463 (0.7, $[M - 46]^+$), 445 (0.9, $[463 - 18]^+$), 408 (1.7, $[M - 101]^+$), 99 (100, $C_5H_7O_2^+$).

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