A NOVEL PATHWAY TO 11-OXA STEROIDS. SYNTHESES OF 11-OXAESTRADIOL AND A NEW SYNTHESIS OF 11-OXA-1-DEHYDRO-11-DEOXYCORTISOL[1,*]

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Abstract — The synthesis of 11-oxaestradiol, a product with antifertility activity but very low uterotropic potency, is reported. It was first prepared in moderate yield by a Dryden aromatization from 17β-acetoxy-11-oxa-androsta-1,4-dien-3-one and, secondly, from estrone or dehydroestrone, by a new and efficient route involving a photolytic chlorinating decarboxylation of a 9-oxo-9,11-seco-11-acid and cyclization of the 9β-hydroxy-9,11-seco-11-nor-12-chloride derived from the degradation product. By the latter procedure, 11-oxa-1-dehydro-11-deoxycortisol and its acetate, anti-inflammatory agents with no mineralocorticoid and, at the dose levels to be considered, insignificant glucocorticoid responses, were also prepared from 17,21-dihydroxylated 5α-pregnan-20-ones.

Among the various hormonal 11-oxasteroids which we synthesized,[2,3,6-10] two products seemed of particular biological interest. The first of them, 11-oxaestradiol (5, Scheme I) showed only extremely low estrogenic (uterotropic) activity, but still significant antifertility potency in a post-coital test in rats, the ratio of antifertility to estrogenic activity being increased by a factor of 10.[11]

In our first synthesis of this hormone analogue (5), already reported in a preliminary fashion,[3] the 11-oxa structure was elaborated by our original method,[7] consisting in the ozonolysis of a 9(11)-unsaturated 12-ketone of the A/B-trans series, reduction of the resulting 11-nor-9,12-seco-9-oxo-12-acid to the corresponding 9β,12-diol, and cyclization with p-toluenesulfonic acid, hecogenin (1) having served as starting material. The synthetic precursor of

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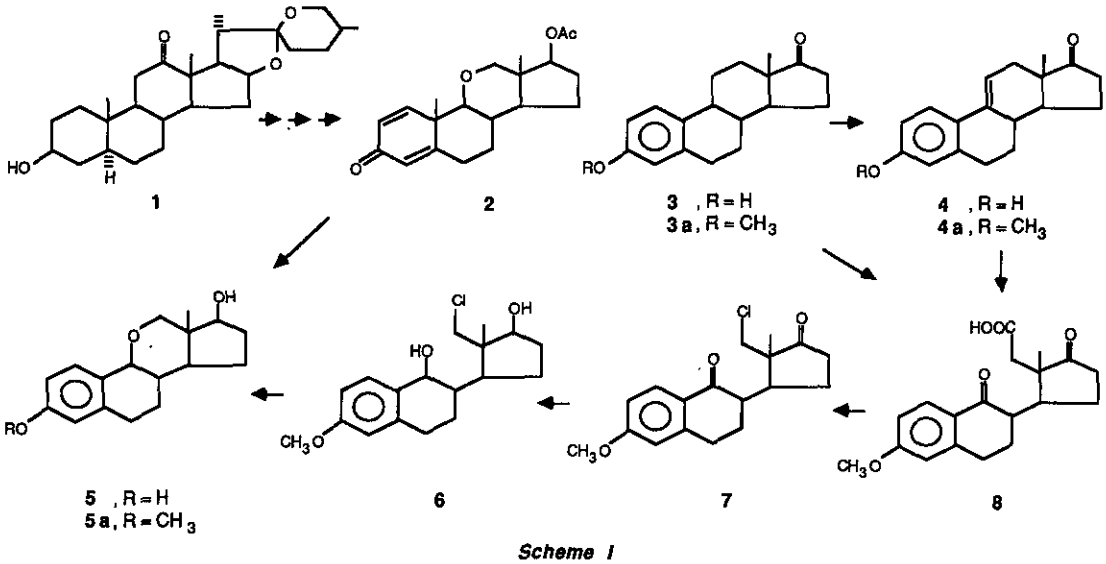
* Dedicated with admiration to Professor Sir Derek Barton on the occasion of his 70th birthday.

11-oxatestosterone,[2] 17β-acetoxy-11-oxaandrosta-1,4-dien-3-one (2), was reductively aromatized, according to Dryden,[12] with the radical anion obtained from diphenyl and lithium. In contradistinction to the situation in the carbocyclic series, the desired 11-oxaestradiol (5) was generally formed only in yields between 25 and 28%. We therefore developed another approach, in which the number of steps required for a synthesis from abundant steroids is considerably reduced and which avoids the disappointing aromatization in the presence of an 11-oxa structure.



Scheme I

For these experiments, the starting material chosen was 3-methoxy-9,17-dioxo-9,11-seco-estra-1,3,5(10)-trien-11-oic acid (8)(Scheme I),[13] which was readily obtained from estrone methyl ether (3a) in 46% yield by an improvement of the procedure of Nasipuri and Gosh,[13b,14] or in 83% yield by ozonolysis of 9(11)-dehydroestrone methyl ether (4a) under conditions previously elaborated.[15] To shorten the carboxylic acid chain of seco acid **8**, to allow formation of the 11-oxa ring, the product was subjected to the Lal and Ray modification[16] of Barton's photolytic decarboxylation procedure,[17] in which trityl chloride serves as source of atomic chlorine.[18] We thus obtained in 72% yield the crude labile 9,17-dioxo-9,12-seco-11-nor-12-chloride **7** which was immediately reduced with sodium borohydride to the corresponding 9β,17β-diol **6**. This product, again labile, was cyclized without prior purification with sodium methoxide to 11-oxaestradiol 3-methyl ether (5a). The yield from the crude 9,17-dioxo-12-chloride **8** amounted to 89%. Ether hydrolysis with boron tribromide in dichloromethane[19] afforded 11-oxaestradiol (5) in 91% yield.

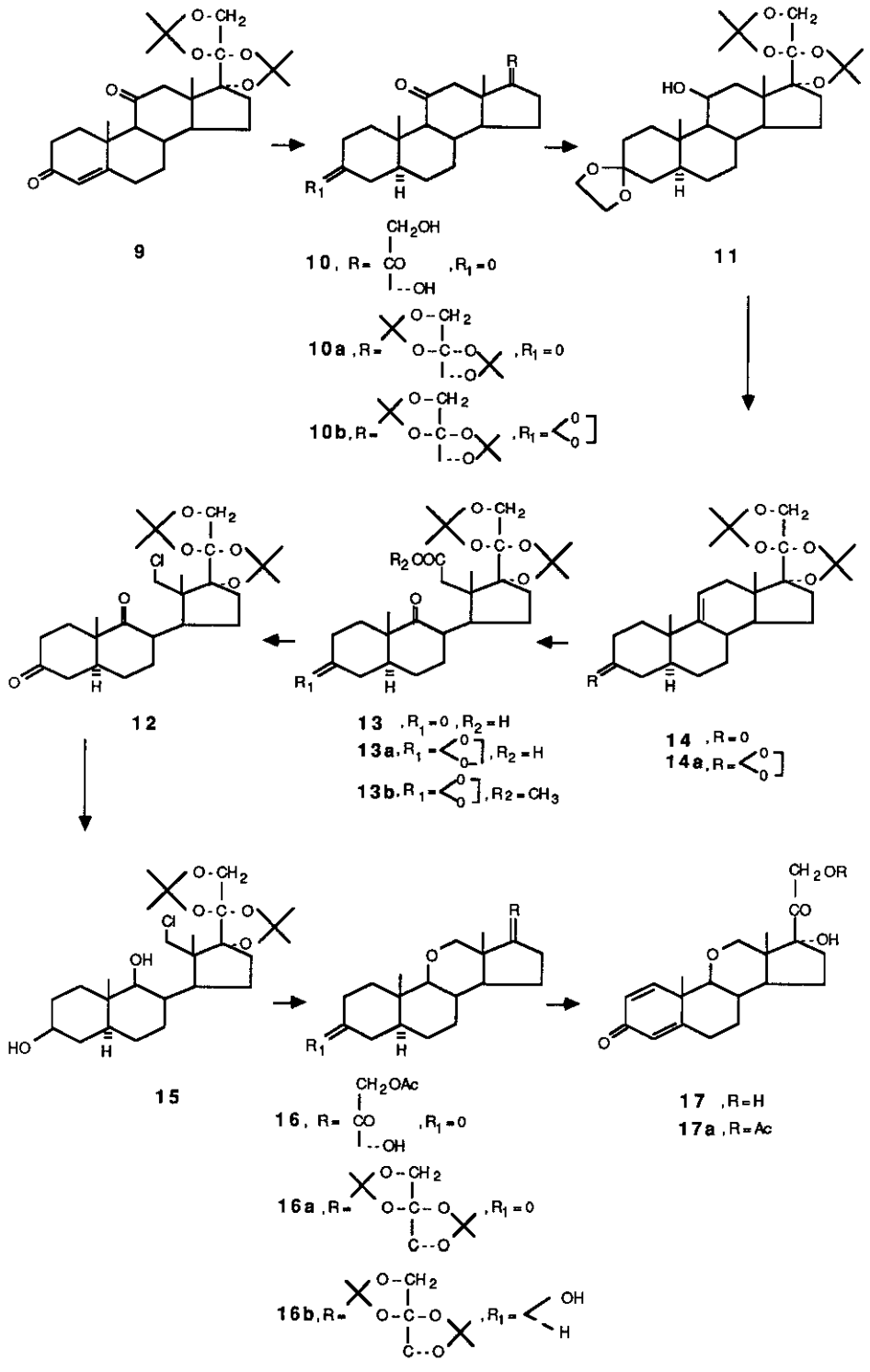
The second 11-oxa analogue of particular biological interest was 17,21-dihydroxy-11-oxapregna-1,4-diene-3,20-dione (17), whose acetate **17a** had been a precursor in our synthesis of the 11-oxa analogue of 11-deoxycortisol.[9] The acetate **17a** showed very significant antiinflammatory

activities but, although having some affinity to a mineralocorticoid receptor, it had even at high doses, no mineralocorticoid activity in the rat.[20] It has some affinity to a glucocorticoid receptor and increases at high doses potassium excretion, but exhibits at dose levels resulting in marked antiinflammatory responses no significant systemic glucocorticoid activity.[20] According to Chrousos and collaborators,[21] the free alcohol **17** shows some glucocorticoid antagonistic effects.

While none of the steps in our original synthesis,[9] essentially followed by Wani and collaborators at the Research Triangle Institute,[21] presented difficulties, the over-all length of the pathway prompted us to apply the above described route to 11-oxasteroids from 9(11)-unsaturated starting materials, to the synthesis of 11-oxa-1-dehydro-11-deoxycortisol (**17**), particularly since 9(11)-unsaturated steroids are readily obtained from abundant 11-oxygenated products.

The tetramethylbismethylenedioxy (TMBMD) derivative **10a** of 17,21-dihydroxy-5α-pregnane-3,11,20-trione (**10**)(Scheme II), readily obtained by Birch reduction of the TMBMD derivative **9** of cortisone[22] and also from the triketone **10**,[23] served as starting material. Its 3-ethylenedioxy derivative **10b** was reduced in 90% yield with lithium aluminum hydride to the 11ß-hydroxy derivative **11** which was dehydrated in 94% yield with thionyl chloride in pyridine to the 9(11)-olefinic product **14a**. Ozonolysis in ethyl acetate, followed by hydrogen peroxide oxidation, under the conditions previously described,[15] gave the seco acid **13a** and a product tentatively assigned the structure of an anhydride[24] [ν_{max} (KBr) 1800 and 1730 cm^{-1}]. On hydrolysis with potassium carbonate in aqueous methanol, this mixture afforded the pure 9-oxo-9,11-seco-11-acid **13a** in 76% yield, calculated from the 9(11)-olefin **14a**. The identity and purity of the seco-acid **13a** were confirmed by conversion with diazomethane in 99% yield to the corresponding methyl ester **13b**. In another experiment in which the product obtained by potassium carbonate hydrolysis had been longer in contact with the sulfuric acid used in the acidification and had been stored for a longer time in solution, the 3-deprotected 3,9-dioxo-9,11-seco-11-acid **13** was formed in 69.5% yield from the 3-ethylenedioxy-9(11)-olefin **14a**. The same product (**13**) was obtained in 65% yield directly, by ozonolysis followed by hydrogen peroxide oxidation and hydrolysis with potassium carbonate, from the 3-oxo-9(11)-olefin **14**, readily prepared from the 3-ketal derivative **14a** by treatment with silica gel, impregnated with hydrochloric acid, according to Conia and collaborators.[25]

The 3,9-dioxo-9,11-seco-11-acid **13** was degraded by photolysis with lead tetraacetate and trityl chloride to the 3,9-dioxo-9,12-seco-11-nor-12-chloride **12** which was reduced, without purification, with sodium borohydride to the corresponding 3ß,9ß-diol **15** which, again without purification, was treated with sodium methoxide. This gave in 61% yield, calculated from the


9
10, R= CH2OH CO --OH , R1=O
10a, R= O-CH2 O-C-O --O , R1=O
10b, R= O-CH2 O-C-O --O , R1= O O
11
12
13 , R1=O , R2=H
13a, R1= O O , R2=H
13b, R1= O O , R2=CH3
14 , R=O
14a, R= O O
15
16, R= CH2OAc CO --OH , R1=O
16a, R= O-CH2 O-C-O C--O , R1=O
16b, R= O-CH2 O-C-O C--O , R1= OH H
17 , R=H
17a, R=Ac

Scheme II

3,9-dioxo-9,11-seco-11-acid **13**, the 3β-hydroxy-11-oxasteroid **16b**. In another series of experiments, the crude 3-ketal **13a** of the seco acid **13** was subjected to the same reactions as the 3-unprotected acid **13**. Since the 3-ketal protection of acid **13a** seems not to resist the conditions employed in the degradation reaction and in its work-up, the sodium borohydride reduction of the 9-oxo-12-chloro intermediate also led in this case to diol **15**. The over-all yield of the transformation of acid **13a** into the 3β-hydroxy-11-oxasteroid **16b** amounted to 63%. Jones' oxidation[26] of the 3β-hydroxy adduct **16b** to the corresponding 3-ketone **16a** proceeded in 82-85% yield. Removal of the side-chain protection with 50% acetic acid and acetylation afforded in 71% yield 21-acetoxy-17-hydroxy-11-oxa-5α-pregnane-3,20-dione (**16**), identical with the product described previously.[9] This steroid was transformed as before[9] into 11-oxa-1-dehydro-11-deoxycortisol 21-acetate (**17a**). Previously[9] we did not publish its hydrolysis to the free 17,21-diol **17**; we describe it in the Experimental.

The application of the new route to 11-oxasteroids, developed in the estrogen series, thus represents indeed an efficient pathway to 11-oxa analogues of corticoids, even though we have not yet optimized the yields of all the synthetic steps.[27] Detailed biological investigations of the here described hormone analogues will be published elsewhere.

EXPERIMENTAL

Melting points were taken in evacuated capillaries and the temperatures were corrected. For column chromatography, neutral aluminum oxide Woelm and Davison's silica gel 923 were employed. For thin-layer chromatography, Merck Darmstadt silica gel G was used. The infrared spectra were recorded on a Beckman IR-12 instrument, the nmr spectra at 60 MHz on a Varian A-60 spectrometer, at 90 MHz on a Bruker XFX-90 instrument, at 200 MHz on a Varian XL-200 spectrometer, in deuteriochloroform with tetramethylsilane as internal standard, if not otherwise stated. The microanalyses were performed by Dr. C. Daesslé, Montréal, by Ayerst Laboratories, Montreal, Canada, under the direction of Dr. G. Schilling, and by the Pascher Micro-analytical Laboratories in Bonn and Remagen, Germany. To the heads of these laboratories and to their collaborators we express our sincere appreciation.

3-Methoxy-9,17-dioxo-9,11-seco-estra-1,3,5(10)-trien-11-oic Acid (**8**). (a) From Estrone Methyl Ether (**3a**). — The methyl ether of estrone (**3a**) was transformed with chromic acid in acetic acid and water into the seco-acid **8**, following the procedure of Nasipuri and Ghosh,[13b] with the exception that after the treatment in the cold the reaction mixture was left for 1 h at room temperature and that the acid **8**, formed by acidification of the bicarbonate extract of the

chloroform solution of the reaction product, was not isolated by filtration but by ether extraction. Thus the yield of acid **8**, mp 153-154°C, was raised from 27[13b] to 46%. Analysis sample: mp 155-156°C (lit.[13a] 158-160°C); $[\alpha]_D^{25}$ -88.2° (c, 0.85 in $CHCl_3$); uv, ir, and nmr spectra in agreement with lit.[13] Anal. calcd for $C_{19}H_{22}O_2$: C, 69.07; H, 6.71. Found: C, 69.11; H, 6.94.

(b) From 9(11)-Dehydroestrone Methyl Ether (**4a**). — According to the procedure of Engel and Rakhit,[15] 950 mg of 3-methoxy-estra-1,3,5(10),9(11)-tetraen-17-one (**4a**), mp 141-143°C, was ozonized at -10°C in 25 ml of ethyl acetate with oxygen containing 1.75% of ozone, for 2 h, at a flow rate of 220 l/h. As described earlier,[15] the product was oxidized with 1 ml of a 30% hydrogen peroxide solution for 20 h and extracted with chloroform. The organic solution was washed with water and was extracted with 2 N sodium hydroxide. From the chloroform solution 7 mg of an oily product was obtained; it was not further investigated. Acidification with sulfuric acid of the alkaline extract and extraction with chloroform furnished after the usual work-up 935 mg (84%) of the crude seco acid **8**, crystallization of which from ether afforded 928 mg (83%) of product, mp 153-155°C, identical with the one described under (a).

12-Chloro-3-methoxy-9,12-seco-11-nor-estra-1,3,5(10)-triene-9,17-dione (**7**). — Following the procedure of Lal and Ray,[16] a solution of 1 g of 3-methoxy-9,17-dioxo-9,11-seco-estra-1,3,5(10)-trien-11-oic acid (**8**), mp 153-155°C, and of 2.4 g of lead tetraacetate in 20 ml of anhydrous carbon tetrachloride was refluxed under illumination with a 300 W tungsten lamp in a nitrogen atmosphere. In the course of 2 h, a solution of 2.1 g of trityl chloride in 20 ml of anhydrous carbon tetrachloride was added dropwise and the mixture was refluxed for an additional 4 h. Ethylene glycol (0.5 ml) was added and the product was filtered through celite. The filtrate was washed with water, a cold 0.1 N sodium hydroxide solution and with water, and dried over sodium sulfate. Removal of the solvent gave 1.084 g of an oil, which was subjected to flash chromatography on 65 g of silica gel, benzene-hexane (1:1) serving as eluent. This afforded 699 mg (72%) of an unstable oily product, giving a positive chlorine test, which could not be crystallized; $[\alpha]_D^{25}$ -44° (c, 0.75 in chloroform), ν_{max} (NaCl film) 1740 (17-ketone), 1670 (9-ketone), 1600, 1500 (aromatic), 735 cm^{-1} (chlorine); δ (90 MHz): 1.00 (s, 3 H, 18-CH_3), 3.60 (s, 2 H, 12-H_2), 3.75 (s, 3 H, OCH_3), 6.70 (d, J = 2 Hz, 1 H, 4-H), 6.90 (dd, J = 8.5 and 2 Hz, 1 H, 2-H), 8.00 (d, J = 8.5 Hz, 1 H, 1-H); mass calcd for $C_{18}H_{21}{}^{37}ClO_3$: 322. Found: 322; calcd for $C_{18}H_{21}{}^{35}ClO_3$: 320. Found: 320. The product was used without purification in the next reaction.

3-Methoxy-11-oxaestra-1,3,5(10)-trien-17β-ol (5a). — To a solution of 850 mg of the crude, amorphous 9,17-dioxo-12-chloride **7** in 20 ml of methanol, 700 mg of sodium borohydride was added at room temperature, portionwise and with stirring. The reaction mixture was kept for another 2 h at room temperature and then poured into 250 ml of water. Its chloroform extract was washed with water and was dried over sodium sulfate. Removal of the solvent afforded 763 mg of amorphous **12-chloro-3-methoxy-9,12-seco-11-nor-estra-1,3,5(10)-triene-9β,17β-diol** (**6**), ν_{max} (NaCl film) 3420-3320 (hydroxyl), 1600, 1570, 1500 (aromatic), 735 cm^{-1} (chlorine); δ (90 MHz): 0.94 (s, 3 H, 18-CH_3), 2.68 (t, J = 10 Hz, 1 H, 9α-H), 3.39 (d, J = 4.5 Hz, 2 H, 12-H_2), 3.75 (s, 3 H, CH_3O), 3.92 (m, 1 H, 17α-H), 6.75 (d, J = 2 Hz, 1 H, 4-H), 6.85 (dd, J = 8.5 and 2 Hz, 1 H, 2 H), 8.00 (d, J = 8.5 Hz, 1 H, 1-H); mass calcd for $C_{18}H_{25}{}^{37}ClO_3$: 326. Found: 326; mass calcd for $C_{18}H_{25}{}^{35}ClO_3$: 324. Found: 324. The product gives a positive Beilstein test.

A quantity of 760 mg of the above crude chloro-diol **6** was dissolved in 25 ml of methanol and 500 mg of sodium methoxide was added. The mixture was refluxed for 1 h. After cooling, the product was poured into ice water and the mixture was extracted with chloroform. The organic solution was washed with water, with 1% sulfuric acid, and again with water, and dried over sodium sulfate. Removal of the solvent gave 751 mg of a white foam which was subjected to flash chromatography on 65 g of silica gel. Elutions with benzene-ethyl acetate (9:1) afforded 692 mg (90%) of crude crystalline **3-methoxy-11-oxa-estra-1,3,5(10)-trien-17β-ol** (**5a**), mp 144-145°C. A sample was recrystallized twice from hexane for analysis; colorless prisms, mp 144.5-145°C; $[\alpha]_D^{25}$ +48° (c, 0.75 in $CHCl_3$); λ_{max} (EtOH) 278 nm (log ε = 3.2); ν_{max} (KBr) 3420 (OH), 1610, 1570, 1500 (aromatic), 1055, 1040, 1025 cm^{-1} (ether linkages); δ (200 MHz): 0.97 (s, 3 H, 18-CH_3), 2.83 (d, J = 5 Hz, 1 H, 12α-H), 3.43 (d, J = 5 Hz, 1 H, 12β-H), 3.78 (s, 3 H, CH_3O), 3.85 (m, 1 H, 17α-H), 4.09 (d, J = 10 Hz, 9α-H), 6.70 (d, J = 2 Hz, 1 H, 4-H), 6.85 (dd, J = 8.5 and 2 Hz, 1 H, 2-H), 7.50 (d, J = 8.5 Hz, 1 H, 1-H); mass spectrum: m/e: 288 (M^+), 270, 258. Anal. calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.60.

11-Oxaestradiol (5). (a) By Reductive Aromatization of 17β-Acetoxyandrosta-1,4-dien-3-one (2). — Following Dryden's method,[12] 60 mg of lithium was cut into small pieces and added to 1.325 g of diphenyl in 15 ml of absolute tetrahydrofuran in a nitrogen atmosphere at room temperature. The mixture was stirred for 2 h and to the solution which had turned blue, 284 mg of 17β-acetoxy-11-oxaandrosta-1,4-dien-3-one (**2**)[2] and 434 mg of diphenylmethane, dissolved in 5 ml of absolute tetrahedrofuran, were added. The product was heated in an oil bath at 50°C for 90 min. After cooling, ammonium chloride was added, the mixture was diluted with water and extracted with chloroform. The organic solution was washed with water, dried over sodium sulfate

and the solvent was removed. This gave 1.92 g of an oil, containing diphenylmethane which was removed by filtration through silica gel, deactivated with 10% of water, the diphenylmethane being eluted with benzene, whereas ethyl acetate eluted the portion (314 mg) containing 11-oxa-estradiol (5). This material - a yellowish foam - was subjected to thick-layer (1 mm) chromatography. Thus 64 mg (27% yield) of pure crystalline (ether) 11-oxaestradiol (5), mp 249-250°C, was obtained. A sample was recrystallized from acetone for analysis; mp 249-250°C, $[\alpha]_D^{25}$ +64.9° (c, 0.740 in dioxane); λ_{max} (EtOH) 280 nm (log ε = 3.28); ν_{max} (KBr) 3355 (broad, hydroxyls), 1622, 1586, 1499 (aromatic), 1068, 1045, 1005 cm^{-1} (C-O linkages). Anal. calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found : C, 74.29; H, 7.87.

In another experiment, an analogous reaction was carried out with 120 mg of lithium, 2.6 g of diphenyl in 30 ml of tetrahydrofuran, 800 mg of diphenylmethane, and with 500 mg of the 17-acetoxy-11-oxadienone **2**, and there was obtained 105 mg (25.5%) of crystalline, purified 11-oxa-estradiol (5), the purification having been achieved by two consecutive chromatograms on silica gel, deactivated by addition of 10% of water; similar results were obtained in a series of other experiments, but in some instances the yield of pure 11-oxaestradiol (5) did not exceed 15%, the difficulty residing mostly in the purification.

(b) From 11-Oxaestradiol 3-Methyl Ether (5a), obtained from Estrone (3). — To a solution, cooled to -78°C, of 900 mg of 3-methoxy-11-oxaestra-1,3,5(10)-trien-17β-ol (5a), mp 144-145°C, in 5 ml of dichloromethane, a solution of 4 ml of boron tribromide in 3 ml of dichloromethane was added slowly. The intensely purple colored solution was kept at -75°C for 15 min, and was then removed from the refrigerating bath. After 30 min, the product was taken to dryness in vacuo. Ice water was added and the mixture was extracted with chloroform, the organic solution was washed with water, a saturated sodium bicarbonate solution and again with water, and was dried over sodium sulfate. Removal of the solvent gave 843 mg of an oily product which was subjected to flash chromatography on 65 g of silica gel. Elutions with chloroform-ethyl acetate (98:2) afforded 783 mg (91.5%) of an oily product which gave by crystallization from acetone 778 mg (91%) of 11-oxaestradiol (5), mp 247-248°C. A sample was recrystallized twice from acetone for analysis; colorless prisms, mp 247.5-248°C, $[\alpha]_D^{25}$ +64° (c, 0.75 in $CHCl_3$). The product was identified with the one described under (a) by the determination of a mixture melting point and the comparison of the infrared and ultraviolet spectra; δ (CD_3COCD_3, 90 MHz) 0.90 (s, 3 H, 18-CH_3), 3.30 (d, J = 4.5 Hz, 2 H, 12-H_2), 3.80 (m, 1 H, 17α-H), 4.00 (d, J = 10 Hz, 1 H, 9α-H), 6.50 (d, J = 2 Hz, 1 H, 4-H), 6.70 (dd, J = 8.5 and 2 Hz, 1 H, 2-H), 7.30 (d, J = 8.5 Hz, 1 H, 1-H), 8.45 (s, 1 H, 3-OH); mass spectrum: m/e: 274 (M^+), 256, 244. Anal. calcd for $C_{17}H_{22}O_3$:

C, 74.42; H, 8.08. Found: C, 74.34; H, 8.18.

17,20,20,21-Tetramethylbismethylenedioxy-5α-pregnane-3,11-dione (**10a**). — Under stirring, a solution of 10.005 g of 17,20,20,21-tetramethylbismethylenedioxypregn-4-ene-3,11-dione ("cortisone-TMBMD") (**11**)[22] in 200 ml of tetrahydrofuran was added to a solution prepared from 2 g of lithium wire, flattened and cut into small pieces, and 1 l of anhydrous liquid ammonia, in the course of 20 min. The mixture was stirred for another 20 min and the blue color was discharged by addition of 50 g of solid ammonium chloride. Subsequently, the ammonia was allowed to evaporate in a nitrogen atmosphere, ethyl acetate and water were added carefully and the product was extracted with ethyl acetate. The organic solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave 9.992 g of an oily product which was reoxidized directly in 100 ml of acetone with 15 ml of Jones' reagent,[26] added dropwise and with stirring in the course of 10 min, and left with the mixture for another 3h. After the usual work-up (addition of 3 ml of isopropyl alcohol and, subsequently, of a sodium bisulfite solution), the product was extracted with dichloromethane, the organic solution was washed with water, and was dried over sodium sulfate. Evaporation of the solvent and recrystallization from hexane-acetone gave 8.007 g (80%) of "4,5α-dihydrocortisone-TMBMD" (**10a**), mp 229-230°C. A sample was recrystallized from acetone-hexane for analysis; fine, colorless needles, mp 229-230°C; $[\alpha]_D^{31}$ -30.2° (c, 0.322 in $CHCl_3$); ν_{max} (KBr) 1720 (3-ketone), 1700 (11-ketone), 1380 (gem. dimethyl), 1220 (C-O-C asymmetric), 1070 (C-O-C symmetric); δ (200 MHz) 0.72 (s, 3 H, 18-CH_3), 1.12 (s, 3 H, 19-CH_3), 1.35 and 1.38 (2 signals, 12 H, tetramethyl), 3.95 (q, J = 8 Hz, 2 H, 21-CH_2); mass spectrum: m/e: 460 (M$^+$), 401, 344, 258. Anal. calcd for: $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.70; H, 8.46.

3-Ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregnan-11-one (**10b**). — From a solution of 5.004 g of "4,5α-dihydrocortisone-TMBMD" (**10a**) and of 2 ml of ethylene glycol in 200 ml of dry benzene, 60 ml of solvent was distilled off through a Dean-Stark separator and 50 mg of p-toluenesulfonic acid was added. The solution was refluxed for 3 h with exclusion of moisture and under removal, through the water separator, of moist benzene, and was extracted, after cooling, with dichloromethane. The organic solution was washed with a saturated sodium bicarbonate solution and with water, a few drops of pyridine was added and the solution was dried over sodium sulfate. Removal of the solvents and crystallization from ether-hexane gave 4.946 g (90%) of "4,5α-dihydrocortisone-TMBMD 3-ethylene ketal" (**10b**), mp 172-173°C. A sample was recrystallized from ether-hexane for analysis; colorless needles, mp 172-173°C; $[\alpha]_D^{29}$ -33.8°

(c, 0.527 in $CHCl_3$); ν_{max} (KBr) 1690 (11-ketone), 1380 (gem. dimethyl), 1220 (C-O-C asymmetric), 1090 (C-O-C-symmetric), 1060 cm^{-1} (ketal); δ (200 MHz) 0.71 (s, 3 H, 18-CH_3), 0.95 (s, 3 H, 19-CH_3), 1.35, 1.37, 1.39, 1.40 (4 s, 12 H, tetramethyl), 3.84 (s, 4 H, ethylene ketal), 3.93 (q, J = 8 Hz, 2 H, 21-CH_2). Mass spectrum: m/e: 504 (M^+), 431, 388, 318. Anal. calcd for: $C_{29}H_{44}O_7$: C, 69.05; H, 8.73. Found: C, 69.27; H, 8.67.

3-Ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregnan-11β-ol (11). — A solution of 1.78 g of 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregnan-11-one (**10b**) in 80 ml of tetrahydrofuran was added dropwise, with stirring and at 5°C, to a suspension of 350 mg of lithium aluminum hydride in 80 ml of tetrahydrofuran. The mixture was refluxed for 2 h with exclusion of moisture and, after cooling, the excess reagent was destroyed by addition of aqueous methanol. The product was extracted with dichloromethane and the organic solution was washed with water and dried over sodium sulfate. Removal of the solvent gave an oily product which was crystallized from ether-hexane to give 1.62 g (90%) of the TMBMD derivative **13** of 3-ethylenedioxy-4,5α-dihydro-cortisol, mp 189-190°C. A sample was recrystallized from ether-hexane; colorless, fine needles, mp 189-190°C; $[\alpha]_D^{31}$ -55.9° (c, 0.939 in $CHCl_3$); ν_{max} (KBr) 3500 (OH), 1380 (gem. dimethyl), 1220 (C-O-C asymmetric), 1100 (C-O-C symmetric), 1070 cm^{-1} (ethylenedioxy); δ (200 MHz), 1,00 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.36, 1.37, 1.39, 1.41 (4 s, 12 H, tetramethyl), 3.82 (s, 4 H, ethylenedioxy), 3.93 (q, J = 8 Hz, 2 H, 21-CH_2); mass spectrum: m/e: 506 (M^+), 448, 390, 372. Anal. calcd for $C_{29}H_{46}O_7$: C, 68.74; H, 9.15. Found: C, 68.71; H, 9.00.

3-Ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregn-9(11)-ene (**14a**). — A solution of 3.004 g of 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregnan-11β-ol (**11**) in 15 ml of pyridine was left at 0°C for 3 h with 10 drops of freshly distilled thionyl chloride. Crushed ice and water were added, the precipitate was filtered and washed with water and was subsequently dissolved in dichloromethane. The organic solution was dried over sodium sulfate and the solvent was evaporated. The product was chromatographed on 240 g of silica gel. Petroleum ether-acetone (90:10) eluted 2.438 g (84%) of olefin **14a**, mp 108-109°C. A sample was recrystallized from ether-hexane for analysis; colorless prisms, mp 108-109°C; $[\alpha]_D^{31}$ -69.3° (c, 0.256 in $CHCl_3$); ν_{max} (KBr) 1380 (gem. dimethyl), 1220 and 1070 cm^{-1} (ether linkages); δ (200 MHz) 0.70 (s, 3 H, 18-CH_3), 0.89 (s, 3 H, 19-CH_3), 1.36, 1.39, 1.40, 1.43 (4 s, 12 H, tetramethyl), 3.85 (s, 4 H, ethylenedioxy), 3.95 (q, J = 8 Hz, 2 H, 21-CH_2), 5.27 (d, J = 6 Hz, 1 H, 11-H); mass spectrum: m/e: 488 (M^+), 430, 372, 286, 273. Anal. calcd for $C_{29}H_{44}O_6$: C, 71.28;

H, 9.08. Found: C, 71.11; H, 9.21.

17,20,20,21-Tetramethylbismethylenedioxy-5α-pregn-9(11)-en-3-one (**14**). — Using a slightly modified procedure of the deketalization method of Conia and collaborators,[25] 0.9 ml of 2 N hydrochloric acid was added with stirring to a suspension of 9.002 g of silica gel (Merck 60, for column chromatography, 32-63 mesh) in 40 ml of dichloromethane. After 3-5 min, when the aqueous phase had disappeared, a solution of 900 mg of 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregn-9(11)-ene (**14a**) in 10 ml of dichloromethane was added. The mixture was further stirred at room temperature for 3 h and the product was neutralized with solid sodium carbonate. The mixture was filtered, the residue was washed with dichloromethane and the filtrate and the washings were taken to dryness to give 780 mg (96.5%) of the 3-oxo-olefin **14**, mp 178-180°C. Recrystallization from ether-hexane raised the melting point to 180-181°C; ν_{max} (KBr) 1705 (3-ketone), 1380 (gem. dimethyl), 1220 (C-O-C asymmetric), 1070 cm^{-1} (C-O-C symmetric); δ (200 MHz) 0.71 (s, 3 H, 18-CH_3), 0.90 (s, 3 H, 19-CH_3), 1.37, 1.39, 1.40, 1.42 (4 s, 12 H, tetramethyl), 3.95 (q, J = 8 Hz, 2 H, 21-CH_2), 5.26 (d, J = 6 Hz, 1 H, 11-H); mass spectrum: m/e: 444 (M^+), 429, 272. Anal. calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.78; H, 8.94.

3-Ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-9-oxo-9,11-seco-5α-pregnan-11-oic Acid (**13a**) and Methyl 3-Ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-9-oxo-9,11-seco-5α-pregnan-11-oate (**13b**). — Through a solution of 500 mg of 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregn-9(11)-ene (**14a**) in 40 ml of ethyl acetate was passed, at -20°C, for 3 h, a stream of oxygen containing 1.75% of ozone, at a flow rate of 220 l/h. Subsequently the product was treated at -10°C for 18 h with 1 mL of a 15% aqueous hydrogen peroxide solution. After addition of 150 ml of water the product was extracted with dichloromethane. The organic solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 451 mg of an oily product, representing a mixture of the 9-oxo-9,11-seco-11-acid **13a** and of a derivative to which we tentatively ascribe an anhydride structure [ν_{max} (KBr) 3400-3100, 1800, 1730, 1710, 1370, 1240, 1070 cm^{-1}]. A portion of 200 mg of this mixture was dissolved in 50 ml of methanol and 7 ml of a 5% potassium carbonate solution was added. The mixture was refluxed for 1 h, 80 ml of water was added, and the product was extracted with dichloromethane. The usual work-up of this extract gave 15 mg of a neutral product which was not further investigated. The original aqueous alkaline solution was acidified with 2% sulfuric acid to the Congo-blue reaction and the product was extracted with dichloromethane. The organic solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave

179 mg (76% yield from the 9(11)-olefin **14a**) of amorphous **3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-9-oxo-9,11-seco-5α-pregnan-11-oic acid (13a)**; ν_{max} (KBr) 3800-3000 (acid), 1700 (acid and 9-ketone), 1380 (gem. dimethyl), 1220 and 1070 cm^{-1} (ether linkages); δ (200 MHz) 0.91 (s, 3 H, 18-CH_3), 1.03 (s, 3 H, 19-CH_3), 1.41 and 1.45 (2 signals, 12 H, tetramethyl), 2.40 (m, 1 H, 8β-H), 2.70 (m, 2 H, 12-H_2), 3.88 (s, 4 H, ethyleneketal), 4.00 (q, J = 8 Hz, 2 H, 21-CH_2); mass spectrum: m/e: 536 (M^+), 492, 477, 417.

This product was dissolved, without further purification, in dry ether and methylated at room temperature with a 0.6% ethereal diazomethane solution (10 ml). The mixture was left at that temperature for 5 h, the excess diazomethane was destroyed by addition of a few drops of acetic acid and the solvents were removed. The resulting white foam was chromatographed on 5 g of silica gel. Petroleum ether-acetone (95:5) eluted 188 mg (99% from **13a**) of **methyl 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-9-oxo-9,11-seco-5α-pregnan-11-oate (13b)**, mp 69-71°C. A sample was recrystallized twice from ether-hexane for analysis, colorless needles, mp 72-73°C; $[\alpha]_D^{27}$ -72.9° (c, 1.087 in $CHCl_3$); ν_{max} (NaCl, film) 1730 (ester), 1710 (9-ketone), 1380 (gem. dimethyl), 1220 and 1070 cm^{-1} (ether linkages); δ (200 MHz) 1.07 (s, 3 H, 18-CH_3), 1.39 (s, 3 H, 19-CH_3), 1.40, 1.44, 1.50 (3 signals, 12 H, tetramethyl), 2.39 (m, 1 H, 8β-H), 2.75 (d, J = 6 Hz, 1 H) and 3.01 (d, J = 6 Hz, 1 H) (12-H_2), 3.56 (s, 3 H, methyl ester), 3.89 (s, 4 H, ethylene ketal), 3.97 (q, J = 8 Hz, 2 H, 21-CH_2); mass spectrum: m/e: 491 (M^+ -$COOCH_3$), 430, 304, 791. Anal. calcd for $C_{30}H_{46}O_9$: C, 65.45; H, 8.36. Found: C, 65.53; H, 8.26.

3,9-Dioxo-17,20,20,21-tetramethylbismethylenedioxy-9,11-seco-5α-pregnan-11-oic Acid (13). — In another ozonolysis experiment, 1.201 g of 3-ethylenedioxy-17,20,20,21-tetramethylbismethylenedioxy-5α-pregn-9(11)-ene (**14a**) was ozonized in 45 ml of ethyl acetate as described above and the product was treated for 18 h at -10°C with 2.4 ml of 15% hydrogen peroxide. The work-up was performed as described above and the crude product [ν_{max} (KBr) 3400-3100, 1800, 1730, 1700, 1370, 1240, 1070 cm^{-1}] was treated for 1.5 h in 100 ml of methanol with 15 ml of a 5% potassium carbonate solution at reflux temperature. Dichloromethane extraction afforded 45 mg of a neutral product which was not further investigated. The aqueous alkaline layer was acidified with 2% sulfuric acid and was extracted after 20 min with dichloromethane. The organic extract was washed with water several times, and dried over sodium sulfate. The solution was stored for approximately 2 h, and taken to dryness. This gave 839 mg (70%) of the amorphous 3,9-dioxo-seco-acid **13**; ν_{max} (NaCl, film), 3600-3000 (acid), 1700 (3,9-ketones and acid), 1380 (gem. dimethyl), 1220 and 1070 cm^{-1} (ether linkages); δ (200 MHz) 0.90 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 1.42 and 1.45 (2 signals, 12 H, tetramethyl), 3.98 (q, J = 8 Hz, 2 H, 21-CH_2); mass

spectrum: m/e: 492 (M^+), 448, 433, 276.

A quantity of 212 mg (63.5% yield) of the same 3,9-dioxo-9,11-seco-11-acid **13** was obtained by an analogous procedure from 300 mg of 17,20,20,21-tetramethylbismethylenedioxy-5α-pregn-9(11)-en-3-one (**14**), prepared as described above. The 3-oxo-seco-acid **13** was used without further purification in the next experiment.

17,20,20,21-Tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3β-ol (**16b**). — A solution of 1.002 g of the amorphous seco acid **13** and of 2.1 g of lead tetraacetate in 20 ml of carbon tetrachloride was refluxed for 2 h under illumination with a 300 W tungsten lamp, in a nitrogen atmosphere. A solution of 1.9 g of trityl chloride in 20 ml of carbon tetrachloride was now added dropwise in the course of 2 h, always under illumination and reflux, and subsequently the mixture was refluxed under illumination for another 4 h. Ethylene glycol (0.5 ml) was added to decompose the excess lead tetraacetate and the lead salts were removed by filtration through celite. The filtrate was washed with water, with a cold 0.1 N sodium hydroxide solution, and with water, and dried over sodium sulfate. Removal of the solvent gave 1.875 g of crude **12-chloro-17,20,20,21-tetramethylbismethylenedioxy-9,12-seco-11-nor-5α-pregnane-3,9-dione** (**12**), giving a positive Beilstein test; ν_{max} (NaCl, film) 1720 (3-ketone), 1710 (9-ketone), 1370 (gem. dimethyl), 1225 (C-O-C asymmetric) 1070 (C-O-C symmetric), 760 (chlorine). To a solution of this unstable product in 40 ml of methanol, 700 mg of sodium borohydride was added portionwise at room temperature and with stirring. The mixture was kept for an additional 2 h and was then poured into 250 ml of water. The precipitate was extracted with dichloromethane, the organic solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 1.764 g of crude **12-chloro-17,20,20,21-tetramethylbismethylenedioxy-9,12-seco-11-nor-5α-pregnane-3β,9β-diol** (**15**), giving a positive Beilstein test; ν_{max} (NaCl, film) 3490 (hydroxyls), 1370 (gem. dimethyl), 1220 (C-O-C-asymmetric), 1070 (C-O-C symmetric), 740 cm^{-1} (chlorine). To a solution of the major portion of this unstable product (1.622 g) in 30 ml of methanol, 500 mg of sodium methoxide was added and the mixture was refluxed for 1 h with the exclusion of moisture. After cooling, the product was poured into ice water and the precipitate was extracted with dichloromethane. The organic solution was washed with water, with 1% sulfuric acid, and with water. After drying with sodium sulfate, the solvent was removed and the resulting amorphous product was chromatographed on 80 g of silica gel. Elutions with petroleum ether-acetone (95:5) afforded 552 mg (60% from the seco acid **13**) of **17,20,20,21-tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3β-ol** (**16b**), mp 152-154°C. A sample was recrystallized from ether; fine colorless needles, mp 153-154°C, $[\alpha]_D^{23}$ +13° (c, 0.820 in $CHCl_3$); ν_{max} (NaCl, film) 3440 (OH), 1680 (gem. dimethyl),

1220 (C-O-C asymmetric), 1070 (C-O-C symmetric), 1020 cm^{-1} (ether); δ (200 MHz), 0.84 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), 1.34, 1.36, 1.45, 1.47 (4 s, 12 H, tetramethyl), 2.30 (m, 1 H, 8β-H), 2.76 (d, J = 11 Hz, 1 H, 12α-H), 2.89 (broad, 1 H, OH), 3.57 (d, J = 11 Hz, 12β-H), 3.95 (m, 1 H, 3α-H), 4.00 (q, J = 8 Hz, 2 H, 21-CH_2), 4.28 (d, J = 11 Hz, 1 H, 9α-H); mass spectrum: m/e: 432 ($M-H_2O$), 417, 392, 275. Anal. calcd for $C_{26}H_{42}O_6$: C, 69.33; H, 9.33. *Found*: C, 69.15; H, 9.29. — In another experiment, 1.025 g of the 3-ethylenedioxy-9-oxo-9,11-seco-11-acid **13a** was subjected, in 50 ml of carbon tetrachloride, under analogous conditions to those described above for acid **13**, to the photolytic degradation with 2 g of lead tetraacetate and 1.8 g of trityl chloride and the resulting crude **3,9-dioxo-9,12-seco-12-chloride 14** was reduced with 720 mg of sodium borohydride in 50 ml of methanol to the **12-chloride 15**, cyclized with 450 mg of sodium methoxide in 50 ml of methanol to crude **17,20,20,21-tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3β-ol (16b)**, which was purified as above to give 542 mg of pure product, mp 153-154°C (over-all yield from acid **13a**: 63%).

17,20,20,21-Tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3-one (16a). — To a solution of 500 mg of the 3β-hydroxy-11-oxa-pregnane **16b**, mp 152-154°C, in 25 ml of acetone, 2 ml of Jones' reagent was added at 0°C, dropwise and with stirring. The mixture was left at room temperature for 2 h, 2 ml of isopropyl alcohol was added and, subsequently, a sodium bisulfite solution. The product was extracted with dichloromethane and the organic solution was washed with water, a cold 2 N sodium carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated and the residue was chromatographed on 200 g of silica gel. Elutions with petroleum ether-acetone (95:5) gave 433 mg (82%) of 17,20,20,21-tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3-one (**16a**), mp 131-132°C. A sample was recrystallized from ether-hexane for analysis; colorless needles, mp 131-132°C; $[\alpha]_D^{23}$ +19.3° (c, 0.613 in $CHCl_3$); ν_{max} (NaCl, film), 1705 (3-ketone), 1380 (gem. dimethyl), 1220 (C-O-C asymmetric), 1070 (C-O-C symmetric), 1010 cm^{-1} (ether); δ (200 MHz) 1.05 (s, 3 H, 18-CH_3), 1.37 (s, 3 H, 19-CH_3), 1.43, 1.45, 1.48 (3 signals, 12 H, tetramethyl), 2.39 (m, 1 H, 8β-H), 3.19 (m, 1 H, 12α-H), 3.92 (m, 1 H, 12β-H), 3.98 (q, J = 8 Hz, 2 H, 21-CH_2), 4.35 (d, J = 11 Hz, 1 H, 9α-H); mass spectrum: m/e: 448 (M^+), 433, 389, 331. Anal. calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.53; H, 8.95.
In another experiment, performed with 350 mg of the 3β-hydroxy-11-oxa-steroid **16b**, a yield of 85% was realized.

21-Acetoxy-17-hydroxy-11-oxa-5α-pregnane-3,20-dione (16). — A quantity of 400 mg of 17,20,20,21-tetramethylbismethylenedioxy-11-oxa-5α-pregnan-3-one (**16a**), mp 131-132°C, was heated

with 20 ml of 50% acetic acid at 95°C for 3 h. The solvent was removed under reduced pressure and the product was completely dried by repeated evaporation of its toluene solutions. Subsequently it was taken up in 2 ml of pyridine and acetylated in the usual fashion with 0.7 ml of acetic anhydride. The crude reaction product was purified by chromatography on 75 g of silica gel. Elutions with petroleum ether-acetone (9:1) gave 250 mg (71%) of 21-acetoxy-17-hydroxy-11-oxa-5α-pregnane-3,20-dione (**16**). After one recrystallization from ether-dichloromethane the product melted at 239-241°C (lit.[9]: 242-244°C); $[\alpha]_D^{23}$ +72° (c, 0.90 in $CHCl_3$) (lit.[9]: $[\alpha]_D^{23}$ +72°). The identity of the products was confirmed by the comparison of their infrared and nmr spectra.

21-Acetoxy-17-hydroxy-11-oxa-pregna-1,4-diene-3,20-dione (**17a**). — According to the method published previously,[9] 250 mg of the 11-oxa-11-deoxy-4,5α-dihydrocortisol acetate (**16**) was transformed via the corresponding 2α,4α-dibromide into 110 mg (44.5%) of 21-acetoxy-11-oxa-pregna-1,4-diene-3,20-dione (**17a**) which was recrystallized from dichloromethane-methanol; mp 239-241°C; (lit.[9] mp 244-246°C). The identity of the products was connfirmed by the comparison of their ir, nmr, and uv spectra.

17,21-Dihydroxy-11-oxa-pregna-1,4-diene-3,20-dione (11-Oxa-1-dehydro-11-deoxycortisol, **17**). — To a solution of 70 mg of the 21-acetate **17a** of 11-oxa-1-dehydro-11-deoxycortisol (**17**), mp 239-241°C, in 30 ml of methanol, 1.5 ml of a sodium methoxide solution, prepared from 1 g of sodium and 100 ml of methanol, was added. The mixture was left at room temperature for 0.5 h and 1 g of Dowex H^+ resin was added. After 15 min, the solution was filtered and the filtrate was taken to dryness in vacuo. The solid product gave upon crystallization from ether 58 mg (92%) of 17,21-dihydroxy-11-oxa-pregna-1,4-diene-3,20-dione (**17**), mp 220-221°C. A sample was recrystallized from ether for analysis; colorless fine needles, mp 220-221°C; $[\alpha]_D^{23}$ +163° (c, 0.95 in methanol); λ_{max} (EtOH) 242 nm (log ε 4.08); ν_{max} (KBr) 3600-3300 (hydroxyls), 1720 (20-ketone), 1675 and 1620 ($\Delta^{1,4}$-3-ketone doublet), 1070, 1050 cm^{-1} (ether); δ (200 MHz, DMSO) 0.80 (s, 3 H, 18-CH_3), 1.30 (s, 3 H, 19-CH_3), 3.59 (m, 2 H, 12-H_2), 4.02 (d, J = 17 Hz, 2 H, 21-CH_2), 5.85 (s, 1 H, 4-H), 6.00 (d, J = 10 Hz, 1 H, 2-H), 7.35 (d, J = 10 Hz, 1 H, 1-H); mass spectrum: m/e: 348 (M^+), 330 ($M-H_2O$), 288, 272. Anal. calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.03; H, 8.22.

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27. After completion of the elaboration of this route to 11-oxasteroids and its description in a doctoral thesis,[4] Planas and Bonet reported in an oral communication[28] another synthesis of 11-oxaestradiol (5) from 9(11)-dehydroestrone methyl ether (**4a**) by a dye-sensitized photooxygenation,[29] leading, inter alia, to a 9-oxo-9,11-seco-11-aldehyde, which was degraded by ozonolysis of an 11-monoenamine to the 9,12-seco-12-aldehyde; this was reduced to the 9,12-diol which was cyclized. Even more recently, concurrently with our communication to the 70th Canadian Chemical Conference and Exhibition,[1] summarizing the here described investigations, Suginome et al. reported in Chemistry Letters[30] the synthesis of 3α-methoxy-11-oxa-5β-pregnane by Baeyer-Villiger oxidation of an 11-ketone, reduction of the resulting 11-oxa-C-homo-12-oxo-steroid to the corresponding lactol, followed by conversion to a hypoiodite which was photolyzed[31] to a 12-iodo-9-formate, which in turn was cyclized to the 11-oxasteroid.

28. T. Planas and J. J. Bonet, 11th IUPAC Symposium on Photochemistry, Lisbon, July-August, **1986**, Abstract, p. 269, paper 3P-38.

29. Cf. P. Lupon, F. Gran, and J. J. Bonet, Helv. Chim. Acta, **1984** 67, 332.

30. H.Suginome, J. B. Wang, and S. Yamada, Chem. Lett., **1987**, 783.

31. Cf. H. Suginome and S. Yamada, J. Org. Chem., **1985**, 50, 2489.

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