15-Oxa-*D*-homosteroids

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Novel 15-oxa-*D*-homosteroids related to pregnane and estrane derivatives have been prepared.

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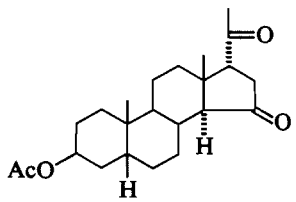
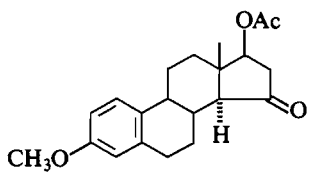
On a préparé des stéroides 15-oxa-*D*-homo dont les structures sont reliées à celles des pregnanes et des estranes.

In a previous paper (1) we described the preparation of novel 15-oxa-*D*-homocardenolides which retain some of the essential stereochemical features of natural cardiotonic agents. It appeared interesting to prepare similar types of products related to pregnane and estrane derivatives.

The key intermediates to achieve the preparation of such products were the 15-oxa-14α-steroids of type **A** and **B**.



A

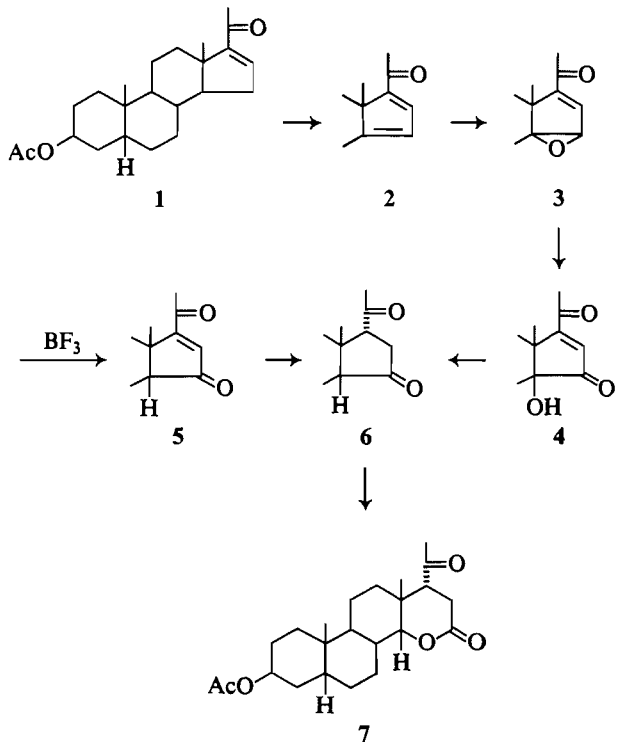


B

An attractive route to the preparation of such compounds has been described by Tschesche and Müller-Albrecht (2) in their partial synthesis of dehydrodiginigenon. However, the treatment with BF_3 of the epoxide **3** obtained from the known derivatives **1** and **2** (3) yielded the 14β-unsaturated ketone **5** which, on hydrogenation or treatment with zinc in acetic acid, gave the diketone **6**. This latter product was again obtained when the oxido derivative (**3**) was oxidized (CrO_3/AcOH) to the hydroxyketone **4** which was transformed to diketone **6** on treatment with zinc in acetic acid. In the 5α-series (4, 5), the more stable 14β,17α-pregnane-15,20-dione was obtained when the epoxide was treated under similar conditions. This discrepancy between Tschesche's results and ours is most certainly due to the lack of the proper substitution in ring C of our derivatives.

The 14β-configuration of the 15-ketones **4**, **5**, and **6** was further confirmed in the transformation of the last derivative **6** to the lactone **7** through a Baeyer–Villiger oxidation. This reaction is known to proceed with retention of configuration. The nmr spectrum of lactone **7** shows a band at 3.9 ppm with a $W/2$ equal to 3.5 Hz, a value in agreement with a dihedral angle of 0° to 10° and indicative (7) of a 14β-stereochemistry. The results are presented in Scheme 1 and Table 1.

In order to overcome this difficulty, the oxido derivative (**3**) was reduced with sodium borohydride. The 17α-derivative **8** obtained was then transformed into the esters **8***a* or **8***b*. On treatment with BF_3, the epoxide **8***a* rearranged to the 14α,15-oxo derivative **9***a* as evidenced by positive ord and cd curves (2, 6, 8). The epimeric ketone **10** (ord and cd curves are negative (2, 6, 8)) was obtained when **9***a* was treated under basic conditions followed by reacetylation. The nmr signal of the $18CH_3$ of **10** is strongly deshielded in comparison with the $18\text{-}CH_3$ of **9***a* (Table 1), thus further confirming the proposed



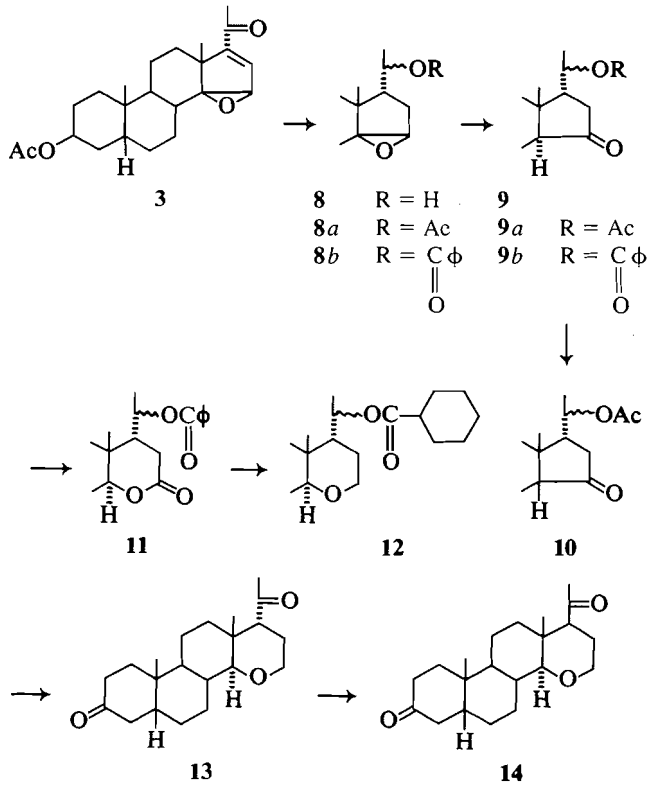
SCHEME 1

TABLE 1. Nuclear magnetic resonance data of some ketones, lactones, and ethers

Products	$18CH_3$ (δ)	14-H (δ)
6	1.32	
9*a*	0.98 (0.97 for **9***b*)	
10	1.25	
15	0.91	
7	1.17	3.90 ($W/2$ = 3.5 Hz)
11	1.09	3.77 (d, J = 8.5 Hz)
16	1.03	3.78 (d, J = 10 Hz)
13	1.12	3.40 (m)
14	1.01	
18	1.03	
21	0.96	
22	0.94	

stereochemistry.

When treated with BF_3, the epoxide **8***b* rearranged to the 14α,15-oxo derivative **9***b* which yielded the lactone **11** through a Baeyer–Villiger oxidation. This latter reaction proceeds with retention of configuration in the 14-position as evidenced by the coupling constant of the doublet for the 14-proton coupled



SCHEME 2

with the 8β-hydrogen which is equal to 8.5 Hz. This value is consistent with an angle of 180° (7), characteristic of a C/D ring junction.

Hydrogenolysis (9) of lactone **11** yielded the ether **12** which was then transformed by hydrolysis and oxidation (Jones' reagent) into diketone **13**. The latter yielded a novel diketone **14** when treated with KOH in MeOH. As demonstrated in Table 1, the position of the 18-CH_3 in **14** as compared with the one of **13** is indicative of the epimerization of the 17α-side chain. This is only possible with the proposed 14α-stereochemistry and constitutes an unequivocal proof. These results are shown in Scheme 2.

In a similar fashion, but starting this time from 15-oxo-estradiol (**15**) (8), the *D*-homo-oxaestradiol **19** and the 19-nor-*D*-homo-oxatestosterone derivatives **20**, **21**, and **22** were prepared. It is worthwhile to note that the ether **19** could not be obtained easily through the usual hydrogenolysis procedure. The aromatic ring of estrone was partially reduced in the presence of platinum. However, this difficulty was circumvented when the lactone **16** was reduced to lactol **17***a* using diisobutyl aluminum hydride. It was then acetylated (**17***b*) and hydrogenolysed to ether **18** using Pd/C. The methyl ether derivative **19** was then prepared (K_2CO_3; $(CH_3)_2SO_4$; KOH) and transformed into the derivatives **20**, **21**, and **22** using the classical Birch reduction method. These reactions are described in Scheme 3.

It is worthwhile to note in Table 1 that the 14β-H of the *cis*-lactone **7** is found at a lower field than the 14α-proton of lactones **11** and **16**. This deshielding effect is due to the anisotropy of the carbon–carbon bond and agrees (7*b*) with values described for ring A *cis* or *trans* lactones.

Experimental

Melting points are uncorrected. The ir spectra were taken on a Perkin–Elmer 225 ir spectrophotometer and nmr were recorded on a Varian A-60A spectrometer operating at 60 MHz; TMS was used as internal standard. Merck silica gel 60 (60–230 mesh) was used. The $[\alpha]_D$ were taken at 20–23°C in 1% chloroform solutions. Otherwise, the solvent is mentioned.

3β-Acetoxy-14,15β-epoxy-5β-pregn-16-en-20-one (3)

This product was prepared from 3β-acetoxy-5β-pregna-14,16-diene-20-one (**2**) (3) (520 g) using 85% *m*-chloroperbenzoic acid (200 g) according to the methods described by Nambara *et al.* (4) or by Tschesche and Müller-Albrecht (2).

The crude product obtained (520 g) was chromatographed on silica gel (ether–hexane, 1:1) to give the title product (220 g). The analytical sample was obtained after two crystallizations from methanol, mp 105–108°C $[\alpha]_D$ +60.2°; ir ($CHCl_3$): 3630, 3480, 1720, 1663, 1590, and 1250 cm^{-1}; nmr ($CDCl_3$): 1.00 (C19—CH_3), 1.32 (C18—CH_3), 2.05 (OAc), 2.26 (C21—CH_3), 3.84 (C15—H), 5.20 (C3—H), and 6.94 (C16—H) ppm. *Anal.* calcd. for $C_{23}H_{32}O_4$: C 74.16, H, 8.66; found: C 74.00, H 8.68

3β-Acetoxy-5β,14β,17α-pregnane-15,20-dione (6). Tschesche's method (2)

Method A

A freshly distilled solution of BF_3–ether complex (2.5 mL) in anhydrous ether (25 mL) was added, dropwise, to a stirred solution of the epoxide **3** (5.0 g) in dry benzene (1.25 L). The mixture was then stirred at room temperature for 64 h. It was washed with water, dried, and evaporated.The crude product obtained was chromatographed on silica gel (hexane–ether, 1:1) to give **5** (3.5 g).

A solution of the crude 16-ene derivative **5** (3.0 g) in absolute ethanol (75 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd on barium sulfate (1.5 g) until no more hydrogen was absorbed (0.5 hour). The catalyst was removed by filtration and the filtrate evaporated. The crude product obtained was chromatographed on silica gel (ether–hexane, 1:1). The fractions containing the pure title product were mixed together and evaporated (1.3 g). The analytical sample was crystallized from CH_2Cl_2–ether, mp 188–190°C, $[\alpha]_D$ −40.1°; ir ($CHCl_3$): 1725, 1718, 1698, 1252, and 1018 cm^{-1}; nmr ($CDCl_3$): 0.92 (C19—CH_3), 1.43 (C18—CH_3), 2.04 (OAc), and 2.25 (C21—CH_3) ppm. *Anal.* calcd. for $C_{23}H_{34}O_4$: C 73.76, H 9.15; found: C 73.84, H 9.21.

Method B

On a treatment of the 16-ene derivative **5** (3.0 g) with zinc powder (12 g) in glacial acetic acid, the pure title product was again obtained after one crystallization from CH_2Cl_2–ether, yield 50%, mp 188–190°C.

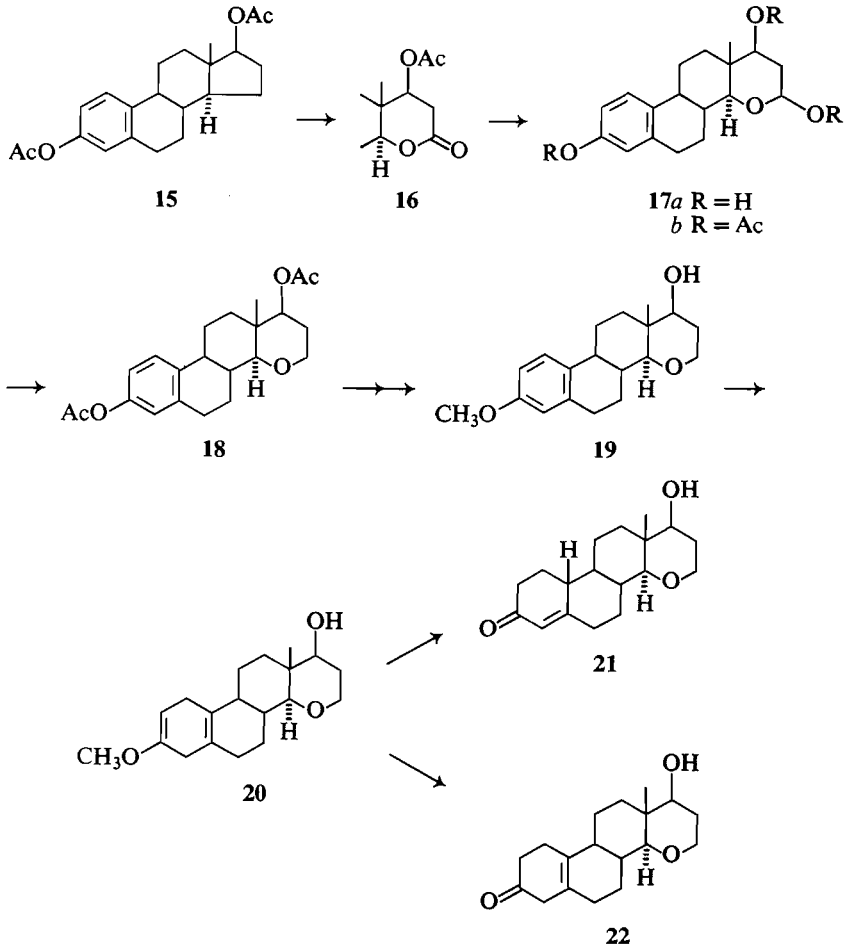
Method C

3β-Acetoxy-14β-hydroxy-5β-pregn-16-ene-15,20-dione (4) (Method described by Mitsuhashi and Fukuoka (5))

A mixture of the epoxide (**3**) (44 g) in AcOH (1320 mL) was treated with CrO_3 (15.4 g) in AcOH (660 mL) and stirred at room temperature for 24 h. The acetic acid was removed under reduced pressure and the solid obtained taken into CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, water dried, and evaporated. The residue was chromatographed on silica gel (benzene–EtOAc, 4:1) and the title product obtained crystallized from CH_2Cl_2–hexane to give the analytical sample, 19 g, mp 163–165°C, $[\alpha]_D$ +19.1°; nmr ($CDCl_3$): 0.93 (C19—CH_3), 1.26 (C18—CH_3), 2.46 (C21—CH_3), and 6.64 (=CH) ppm. *Anal.* calcd. for $C_{23}H_{32}O_5$: C 71.10, H 8.30; found: C 71.01, H 8.44.

3β-Acetoxy-5β,17α-pregnane-3,20-dione (6)

Zinc granules (70 g) were added to a solution of the dione (**4**) (7.0 g) and the mixture was heated under reflux for 1.5 hours. The solvent was removed under reduced pressure and the residue obtained was chromatographed on silica gel (benzene–EtOAc, 4:1). The title product obtained (5.6 g) was crystallized twice from CH_2Cl_2–ether (3.0 g), mp 186–189°C $[\alpha]_D$ −37.1°; nmr ($CDCl_3$): 0.92 (C19—CH_3), 1.43 (C18—CH_3), and 2.25 (C21—CH_3) ppm. *Anal.* calcd. for $C_{23}H_{34}O_4$: C 73.76, H 9.15; found: C 73.78, H 9.16.



SCHEME 3

3β-Acetoxy-hydroxy-15-oxa-pregnan-16,20-dione (7)

A mixture of the dione (**6**) (1.0 g), $NaHCO_3$ (1.5 g), and *m*-chloroperbenzoic acid (2.0 g) was stirred in CH_2Cl_2 for 20 h. It was then heated under reflux for 3 hours. The mixture was diluted with more chloroform and washed in succession with $NaHCO_3$, water, 5% $Na_2S_2O_3$, water, dried, and evaporated. The crude product obtained was chromatographed on silica gel (benzene–EtOAc, 7:3) to give the title product (0.56 g). It was crystallized twice from ethane–hexane, mp 138–140°C, $[\alpha]_D$ +30.5°; ir ($CHCl_3$): broad C=O at 1715 cm^{-1}; nmr ($CDCl_3$): 0.96 (C19—CH_3), 1.17 (C18—CH_3), and 3.90 (C14—H, $W/2$ = 3.5 Hz) ppm. *Anal.* calcd. for $C_{23}H_{34}O_5$: C 70.74, H 8.78; found: C 70.91, H 8.81.

3β-Acetoxy-20-benzoyloxy-14,15β-epoxy-5β,17α-pregnane (8b)

A solution of $NaBH_4$ (50 g) in water (300 mL) was added to a solution at 0°C of the unsaturated ketone **3** (50 g) in methanol (3 L). The mixture was stirred at room for 2 hours and poured into water. The solid obtained was filtered, washed with water, dried, and crystallized from CH_2Cl_2–hexane to give the 20-alcohols (**8**) (25 g).

To a solution at 0°C of these alcohols (10 g) in pyridine (60 mL) was added benzoyl chloride (6 mL). The solution was let at room temperature overnight. It was then poured into water and the solid obtained filtered and dried. It was crystallized twice from EtOAc–hexane to give the pure title product (8.5 g), mp 204–206°C $[\alpha]_D$ +89.4°; ir ($CHCl_3$): 0.95 (C18—CH_3), 1.19 (C19—CH_3), 1.28 (C21—CH_3, d, J = 7 Hz), and 7.5 and 8.0 (5 aromatic H) ppm. *Anal.* calcd. for $C_{30}H_{40}O_5$: C 74.97, H 8.39; found: C 75.15, H 8.45.

3β,20-Diacetoxy-14,15β-epoxy-5β,17α-pregnane (8a)

The 20-alcohols **8** (1.0 g) were acetylated in the usual fashion and the product isolated used as such.

3β,20-Diacetoxy-5β,14α-17α-pregnan-15-one (9a)

A freshly distilled solution of ethereal BF_3 (0.55 mL) in dry ether (15 mL) was added dropwise over a period of 10 min to a solution of the diacetate **8***a* (1.0 g) in dry benzene (100 mL). The mixture was stirred overnight, washed with water, dried, and evaporated.

The crude product obtained (1.0 g) was chromatographed on silica gel (EtOAc/C_6H_6, 5:1) and the product obtained crystallized twice from ether–hexane to give the pure title product (315 mg), mp 136–138°C; ir: ($CHCl_3$): 1718, 1245, and 1014 cm^{-1}; ord (*C* 10.4 mg/mL; CH_3OH) 20°C: $[\phi]_{350}$ + 960°; $[\phi]_{316}$ + 3460°; $[\phi]_{298}$ O°; $[\phi]_{274}$ −5600; $[\phi]_{249}$ −3900; $[\phi]_{227}$ −5100; cd Mμ (ΔE); 320 (+0.4), 296 (+1.6), 267 (+0.4); nmr ($CDCl_3$): 0.88 (C19—CH_3), 0.98 (C18—CH_3), 1.25 (C21—CH_3, d, J = 6 Hz), and 2.04 (OAc) ppm. *Anal.* calcd. for $C_{25}H_{38}O_5$: C 71.74, H 9.15; found: C 71.71, H 9.13.

3β-Acetoxy-20-benzoyloxy-5β,17α-pregnan-15-one (9b)

This compound was prepared as for **9***a*, starting from **8***b* (8.6 g). The crude product isolated was chromatographed on silica gel to give the title product (6.2 g) which was used as such for the following reaction. The nmr spectrum ($CDCl_3$): 0.92 (C19—CH_3), 0.97 (C18—CH_3), 1.78 (C21—CH_3, d, J = 7 Hz), and 2.04 (OAc) and 7.56 and 8.0 (5 ar H) ppm.

3β,20-Diacetoxy-5β,14α,17α-pregnan-15-one (10)

A solution of the diacetate **9***a* (200 mg) in methanol (40 mL) containing KOH (2.0 g) was stirred at 60°C for 2 hours. Most of the methanol was evaporated under reduced pressure, water was added, and the solid obtained filtered. It was taken into CH_2Cl_2, the organic solution was washed with water, dried, and evaporated.

The crude product obtained (0.165 g) was acetylated (pyridine–Ac_2O) and the product isolated chromatographed on silica gel

(EtOAc–hexane, 1:5). The material obtained was crystallized twice from ether–hexane to give the pure title product (127 mg), yield 63%, mp 170–172°C; ir ($CHCl_3$): 1720, 1240, and 1017 cm^{-1}; ord (c 10.8 mg/mL; CH_3OH), 20°C: $[\phi]_{350}$ −670°; $[\phi]_{326}$ −2350°, $[\phi]_{308}$ 0°; $[\phi]_{285}$ +3400; $[\phi]_{233}$ +1800°; cd Mμ (ΔE) = 320 (−0.8), 305 (−1.48), 287 (−0.8); nmr ($CDCl_3$): 0.91 (C19—CH_3), 1.18 (C21—CH_3, d, J = 6 Hz), 1.25 (C18—CH_3), and 2.04 (OAc) ppm. *Anal.* calcd. for $C_{25}H_{38}O_5$: C 71.74, H 9.15; found: C 71.60, H 9.15.

*3β-Acetoxy-20-benzoyloxy-*D*-homo-15-oxa-17a-pregnan-16-one (**11**)*

An ice-cold solution made of trifluoroacetic anhydride (18.6 mL) and 90% hydrogen peroxide (3.7 mL) in CH_2Cl_2 (125 mL) was added dropwise to a stirred suspension of the 15-ketone **9***b* (6.2 g) and disodium hydrogen phosphate (12.4 g) in CH_2Cl_2 (150 mL). The mixture was then stirred at room temperature for 48 h, diluted with more CH_2Cl_2, washed with saturated solutions of $NaHCO_3$, NaI, $Na_2S_2O_3$, water, dried, and evaporated.

The product was chromatographed on silica gel (EtOAc–benzene, 1:1) to give the title product (3.8 g) as an oil. It was used as such for the following reaction. The nmr ($CDCl_3$): 0.96 (C19—CH_3), 1.09 (C18—CH_3), 1.38 (C21—CH_3, d, J = 5 Hz), 3.77 (C14—H, d, J = 8.5 Hz), and 7.54 and 8.03 (5 aromatic H) ppm.

*3β-Acetoxy-20-cyclohexylcarbonyloxy-*D*-homo-15-oxa-5β,17α-pregnane (**12**)*

A solution of lactone (**11**) (3.8 g) in acetic acid (50 mL) was added to a mixture of prehydrogenated 83% PtO_2 (1.8 g) in acetic acid (20 mL) containing perchloric acid (0.18 mL). The whole was stirred at room temperature and atmospheric pressure until no more hydrogen was absorbed.

The catalyst was removed by filtration and the filtrate diluted with CH_2Cl_2. The organic solution was washed with water, dried, and evaporated. The crude product obtained (3.5 g) was chromatographed on silica gel (ether/hexane, 1:1) to give the title product (1.2 g).

The analytical sample was crystallized three times from cold petroleum ether (30–60°C), mp 133–134°C, $[\alpha]_D$ −3.4°; nmr ($CDCl_3$): 0.96 (C19—CH_3), 1.10 (C18—CH_3), 1.25 (C21—CH_3, d, J = 7 Hz), and 5.25 (C20—H, quartet, J = 6.5 Hz) ppm. *Anal.* calcd. for $C_{30}H_{48}O_5$: C 73.73, H 9.90; found: C 73.67, H 10.00.

*D-Homo-15-oxa-5β,17aα-pregnan-3,20-dione (**13**)*

A solution of the diester (**12**) (1.0 g) in ethanol (50 mL) and water (10 mL) was heated under reflux in presence of KOH (1.0 g). Most of the ethanol was evaporated under reduced pressure, water was added, and the solid obtained filtered and dried.

A solution of the crude diol isolated (0.8 g) in acetone (30 mL) was oxidized with Jones' reagent in the usual fashion. The product obtained was chromatographed on silica gel (EtOAc/benzene, 1:3) to give the title product (0.5 g). The analytical sample was crystallized twice from acetone–hexane, mp 159–161°C, $[\alpha]_D$ −61.9°; ir ($CHCl_3$): 1698 and 1080 cm^{-1}; nmr ($CDCl_3$): 1.01 (C19—CH_3), 1.12 (C18—CH_3), 2.20 (C21—CH_3), and 3.40 (C14—H) ppm. *Anal.* calcd. for $C_{21}H_{32}O_3$: C 75.85, H 9.70 found: C 75.50, H 9.69.

*D-Homo-15-oxa,5β,17aβ-pregnane-3,2-dione (**14**)*

A solution of the dione (**13**) (6.0 g) in 5% KOH in methanol (1.2 L) was heated at 60°C for 2 hours. Most of the methanol was evaporated and the remaining diluted with water and extracted with EtOAc. The organic solution was washed until neutral, dried, and evaporated. The crude product isolated was chromatographed on silica gel (ether–hexane, 2:1) to give the title product (4.2 g). The analytical sample was crystallized twice from acetone–hexane (3.2 g), mp 133–135°C, $[\alpha]_D$ +42.1°; ir ($CHCl_3$): 1698 and 1100 cm^{-1}; nmr ($CDCl_3$): 1.01 (C19—CH_3 and C18—CH_3) and 2.16 (C21—CH_3) ppm. *Anal.* calcd. for $C_{21}H_{32}O_3$: C 75.86, H 9.70; found: 76.00, H 9.85.

*3β,17β-Diacetoxy-estra-1,3,5 (10)-trien-15-one (**15**)*

This compound was prepared from estrone as described by Pettit and Brown (8); mp 174–176°C, $[\alpha]_D$ 71.3°; (lit. mp 173–174°C, $[\alpha]_{589}$ + 90°, $[\alpha]_{350}$ +54°); nmr ($CDCl_3$): 0.91 (C18—CH_3) and 5.03 (C17—H, t, J = 8.5 Hz) ppm. *Anal.* calcd. for $C_{22}H_{26}O_5$: C 71.33, H 7.07; found: C 71.14, H 6.91.

*3,17aβ-Dihydroxy-*D*-homo-15-oxaestra-1,3,5(10)-trien-16-one (**16**)*

m-Chloroperbenzoic acid (13 g) was added to a cooled suspension of the 15-ketone (20 g) and sodium bicarbonate (10 g) in CH_2Cl_2 (400 mL). The mixture was stirred at room temperature for 24 h. More peracid (13 g) and bicarbonate (10 g) were added and stirring continued for two more hours. The material in suspension was removed by filtration and the filtrate washed with a 5% solution of sodium bisulfite, water, dried, and evaporated. The crude product obtained was chromatographed on silica gel (C_6H_6/EtOAc, 9:1). Some starting ketone (4.7 g) was recuperated, followed by the title product (16 g).

The latter was crystallized from CH_2Cl_2/ether, mp 156–158°C, $[\alpha]_D$ +12.9°; ir ($CHCl_3$): 1740, 1610, 1580, and 1495 cm^{-1}; uv (EtOH): λ_{max} 267, 274; ϵ, 695 and 665; nmr ($CDCl_3$): 1.03 (C18—CH_3), 3.78 (C14—H, d, J = 10.7 Hz), and 6.65 and 7.50 (3 ar H) ppm. *Anal.* calcd. for $C_{22}H_{20}O_6$: C 68.38, H 6.78; found: C 68.64, H 6.78.

*3,16,17aα-Triacetoxy-*D*-homo-15-oxaestra-1,3,5,(10)-triene (**17**b)*

A solution of 3.2 equiv. of diisobutyl aluminum hydride in hexane was added dropwise to a solution at −20°C of lactone **16** (2.0 g) in dry THF (60 mL). The mixture was stirred at −20°C for 30 min and the reaction quenched with a saturated solution of sodium potassium tartrate. The organic layer was separated and diluted with EtOAc. It was washed with water, dried, and evaporated. The crude product obtained was filtered on silca gel (acetone/benzene, 1:2) to give the triol **17***a* (1.3 g) which was acetylated in the usual fashion. The crude triacetate isolated was crystallized twice from i-propyl ether to give the pure title product, mp 184–185°C, $[\alpha]_D$ +43.9°; ir ($CHCl_3$): 1747, 1725 inflexion, and 1060 cm^{-1}; nmr ($CDCl_3$): 1.05 (C18—CH_3), and 6.67 and 7.50 (3 ar H) ppm. *Anal.* calcd. for $C_{24}H_{30}O_7$: C 66.96, H 7.06; found: C 66.77, H 7.05.

*3,17aα-Diacetate-*D*-homo-15-oxaestra-1,3,5(10)-triene (**18**)*

A solution of the triacetate **17***b* (6.0 g) in acetic acid (250 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (3.0 g) until no more hydrogen was absorbed (~48 h). The catalyst was removed by filtration and the filtrate evaporated. The crude product obtained was chromatographed on silica gel (hexane/EtOAc, 5:1) to give the title product (3.6 g). It was crystallized from hexane, mp 148–150°C, $[\alpha]_D$ +10.6°; ir ($CHCl_3$): 1748, 1723, 1608, 1580, and 1493 cm^{-1}; nmr ($CDCl_3$): 1.03 (C18—CH_3), and 6.67 and 7.50 (3 ar H) ppm. *Anal.* calcd. for $C_{22}H_{28}O_5$: C 70.94, H 7.58; found: C 70.94, H 7.39.

*The 15-oxa-*D*-homoestren-3-one derivatives **21** and **22***

A mixture of the diacetate **18** (3.2 g) and sodium carbonate (2.4 g) in methanol (380 mL) containing water (120 mL) was heated under reflux for 4 hours. Most of the methanol was evaporated and the remaining mixture extracted with CH_2Cl_2. The organic solution was dried and evaporated. The crude oil obtained (2.3 g) was treated with dimethylsulfate (18.5 mL) and 50% KOH (18.5 mL) in the usual manner to give the *3,17aβ-dihydroxy-*D*-homo-15-oxaestra-1,3,5(10)-triene-3-methylether (2.2 g) (**19**)*; uv (MeOH): λ_{max} 286, 275; ϵ = 2056, 2142. This product was used as such for the following reaction.

Lithium wire (2.25 g) was added in portions over a period of 10 min to a stirred solution at reflux of the 3-methyl ether **19** (2.1 g) in dry ether (120 mL) and distilled ammonia (~200 mL). Absolute ethanol (45 mL) was then added dropwise over a period of 1 hour. Ammonia was evaporated and the mixture diluted with water. The ether layer was recuperated and the water layer extracted once more with ether. The ethereal solution was washed with a solution made of KOH (35 g) in water (25 mL) and MeOH (100 mL) then with water, dried, and evaporated. The crude crystalline *17aβ-hydroxy-3-methoxy-15-oxa-*D*-homo-ester,2,5(10)-diene (**20**) isolated* (2.1 g) was used for the following reactions without further purification. Infrared ($CHCl_3$): 1695 and 1665 cm^{-1}.

A suspension of the methoxy-diene (**20**) (1.05 g) in methanol (20 mL) containing concentrated HCl (2.1 mL) was stirred at room temperature for 1 hour. It was then diluted with water and most of

the methanol evaporated under reduced pressure. The mixture was extracted with CH_2Cl_2. The organic solution was washed with water, dried, and evaporated. The crude product obtained was chromatographed on silica gel (EtOA/C_6H_6, 1:5) and the *17aβ-hydroxy-15-oxa-D-homoestr-4-en-3-one* obtained was crystallized from CH_2Cl_2/hexane to give the analytical sample, mp 162–164°C, $[\alpha]_D$ +13.7°; ir ($CHCl_3$): 3600, 3460, 1658, 1610, and 1095 cm^{-1}; nmr ($CDCl_3$): 0.96 (C18—CH_3), 2.03 (OH), 3.45 (C15—H, m), 4.04 (C17—H, m), and 5.86 (C4—H, s) ppm. *Anal.* calcd. for $C_{18}H_{26}O_3$: C 74.45, H 9.02; found: C 74.28, H 9.06.

A suspension of the methoxydiene (**20**) (1.05 g), methanol (21 mL), and acetic acid (2.1 mL) was heated under reflux for 15 min. It was cooled and poured into ice-cold water. The solid obtained was filtered, washed, and dried.

The crude product obtained was crystallized from CH_2Cl_2–hexane to give the *17αβ-hydroxy-15-oxa-D-homoestr-5(10-ene-3-one (22)* (0.5 g), yield 50%, mp 178–180°C; ir ($CHCl_3$): 3600, 3470, 1704, and 1090 cm^{-1}; nmr ($CDCl_3$): 0.94 (C18—CH_3), 1.85 (OH), 2.44 (C18—2H, m), 2.75 (C4–2H, m), 3.45 (C15—H, m) and 4.05 (C17—H, m) ppm. *Anal.* calcd. for $C_{18}H_{20}O_3$: C 74.45, H 9.02; found: 74.01, H 9.17.

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