Antiandrogen. IV.[1] C-17 Spiro 2-Oxasteroids

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The preparation of 6- and/or 7-substituted 3-oxo-2-oxasteroids having a spirotetrahydrofuran ring at the 17-position is described. These compounds showed high antiandrogenic potency in the castrated male rat.

Key words antiandrogen; prostate; 2-oxasteroid; steroidal spirocompound

Spironolactone (7α-acetylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone), spiroxasone [2′,3′α-tetrahydrofuran-2′-spiro-17-(7α-acetylthioandrost-4-en-3-one)], and 2′,3′α-tetrahydrofuran-2′-spiro-17-(6α,7α-difluoromethylene-1α,2α-methyleneandrost-4-en-3-one) (KNP 215) are antiandrogens synthesized by Merck Sharp & Dohme Research Laboratories.[2-4] We have previously reported that the replacement of the methylene group at the 2-position in chlormadinone acetate with an oxygen atom increased the antiandrogenic activity.[5] These observations led us to prepare 2-oxasteroid analogs having the spirotetrahydrofuran ring at the 17-position. Herein, we describe the preparation and the antiandrogenic activity of 2-oxasteroidal 17-spiroethers (**6** and **9**) and 17-spirolactone analogs (**15**, **16** and **19**).

Chart 1 shows the synthetic route for these compounds, which is analogous to the reaction previously reported.[5] The triene compounds (**1**[4] and **10**[6]) were chosen as starting materials, and were converted with *m*-chloroperbenzoic acid (*m*-CPBA) into the 6α,7α-epoxides[7] (**2** and **11**) in satisfactory yield. Ozonolysis of **2** and **11** in pyridine at −78 °C gave the lactols (**3** and **12**), the NMR spectra of which showed the configuration of the 1-hydroxyl group to be α on the basis of the peak pattern.[5] The lactols (**3** and **12**) were reduced by sodium borohydride to the lactones (**4** and **13**), which, on treatment[8] with phosphorus tetraiodide in dichloromethane, afforded the 4,6-dienones (**5** and **14**). Addition of difluorocarbene[9] to **5** and **14** afforded the difluoromethylene derivatives (**6** and **15**) in moderate yield.

For the preparation of the 6-chloro compounds (**9** and **19**), **4** and **13** were allowed to react with hydrochloric acid in THF to furnish the chlorohydrins (**7** and **17**) in high yield. After acetylation of **7** and **17** in the usual manner, the acetylated compounds (**8** and **18**) were treated with potassium acetate in dimethylformamide (DMF) to yield the desired compounds, **9** and **19**.

Heating of **14** with thioacetic acid gave a complex mixture, which was submitted to preparative TLC to give **16** in low yield. The chemical structures of **6**, **9**, **15**, **16** and **19** were supported by spectral analyses (see Experimental).

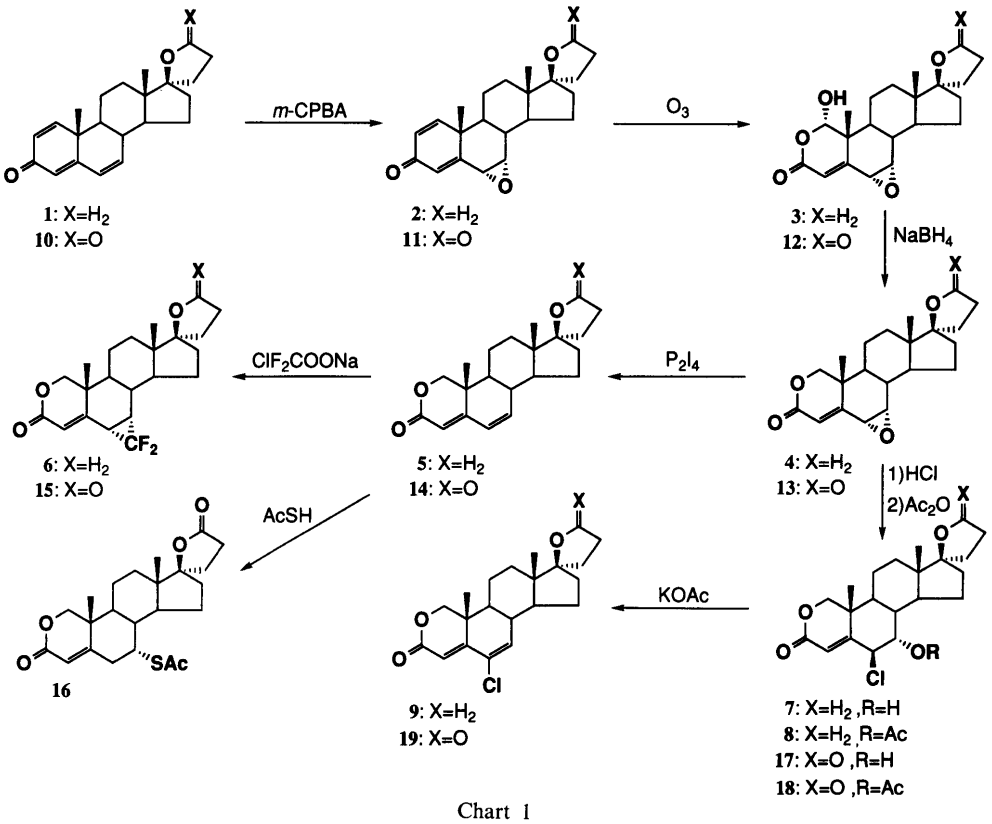

Chart 1

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Table 1. The Effect of 2-Oxasteroidal 17-Spiro Compounds on Accessory Sex Organ Weights in Castrated Rats Given Testosterone Propionate (50 μg/Rat, s.c.[a])

Compound	Dose (mg/kg/*p.o.*[a])	Organ weight[b] (mg/100 g body weight)	
		Ventral prostate	Seminal vesicle
6	3.3	22.1±1.8	25.4±0.7[c]
6	10	14.3±1.4[d]	21.3±2.2[c]
9	3.3	19.8±0.7[e]	35.0±2.6
9	10	18.6±2.2	27.6±1.8[d]
15	5	17.4±1.3[e]	25.9±1.4[d]
16	3	28.4±2.4	45.7±4.1
KNP215	1.1	22.5±0.7	35.1±1.1
KNP215	3.3	20.7±0.6	29.4±2.2[e]
KNP215	10	15.0±1.3[e]	24.9±2.6[d]
Castrated control		4.7±0.3[c]	5.3±0.2[c]
T.P.[f] control		25.6±2.2	37.2±2.2

a) *p.o.*: *per os*. s.c.: subcutaneous. *b*) Each value represents the mean±S.E. ($n=5$). *c*) Significantly different from the T.P. control ($p<0.001$). *d*) Significantly different from the T.P. control ($p<0.01$). *e*) Significantly different from the T.P. control ($p<0.05$). *f*) T.P.: testosterone propionate.

Biological Activities The organ weights of seminal vesicle and ventral prostate in immature male castrated rats were determined after administration of testosterone propionate with or without a test compound (Table 1). The antiandrogenic ability of the compounds was evaluated in terms of the suppressive effect on the androgen-stimulated weight gain.[10]

As compounds **6** and **15** suppressed the weight gain to a similar extent to KNP-215, the antiandrogenic activities of these 2-oxa-6α,7α-difluoromethylenes (**6** and **15**) were essentially the same as that of the parent compound, KNP 215, used as a positive control drug. The replacement of difluoromethylene with a 6-chloro-6-dehydro moiety decreased the activity, because the suppressive effect of **9** was inferior to that of **6**. 2-Oxaspironolactone (**16**) was found to be inactive at the dose tested.

Experimental

^{1}H-NMR spectra were recorded with a Hitachi R-90H spectrometer using tetramethylsilane as an internal reference. Electron impact-mass spectra (EI-MS) were obtained with a Shimadzu QP1000 spectrometer at 70 eV. High-resolution mass spectra were obtained on a VG Auto SpecQ mass spectrometer. Column chromatography was done on silica gel (Wako-gel, C-200). Preparative thin layer chromatography (TLC) was carried out on silica gel (Merck, Kieselgel 60 GF_{254}). Ozone was generated with a Nippon Ozone O-10-2 instrument.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6α,7α-epoxyandrosta-1,4-dien-3-one) (2) A mixture of **1** (4 g) and *m*-CPBA (4 g) in $CHCl_3$ (20 ml) was stirred at room temperature for 8 h, then poured into water and extracted with AcOEt. The extract was washed with 5% NaOH and brine, and dried over anhydrous Na_2SO_4. Evaporation left a crude product (4 g), which was applied to a column of silica gel (100 g). Elution with benzene–AcOEt (10:1) afforded **2** (2.9 g). mp 192.9—193.9 °C. *Anal.* Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.42; H, 8.40. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, s, 18-H_3), 1.21 (3H, s, 19-H_3), 3.36 (1H, dd, $J=3.5$, 1.5 Hz, 7β-H), 3.64 (1H, d, $J=3.5$ Hz, 6β-H), 3.75 (2H, m, 5′-H_2), 6.22 (1H, dd, $J=10$, 2 Hz, 2-H), 6.47 (1H, d, $J=2$ Hz, 4-H), 7.01 (1H, d, $J=10$ Hz, 1-H). MS *m/z*: 340 (M^+) 325. IR (KBr) cm^{-1}: 1664. UV λ_{max}^{EtOH} nm (ε): 245 (15000).

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6α,7α-epoxy-1α-hydroxy-2-oxaandrost-4-en-3-one) (3) Ozone was bubbled into a solution of **2** (2.9 g) in pyridine (40 ml) at −25 °C for 90 min. The reaction mixture was stirred at room temperature for 10 min, diluted with 20% $NaHSO_3$ (6 ml) and then extracted with AcOEt. The extract was washed with 5% H_2SO_4 and saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by preparative TLC (benzene–AcOEt (5:1)) to give 1.9 g of **3**. mp 169.2—170.8 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s, 18-H_3), 1.16 (3H, s, 19-H_3), 3.37 (1H, d, $J=3.5$ Hz, 7β-H), 3.50 (1H, d, $J=3.5$ Hz, 6β-H), 3.75 (2H, m, 5′-H_2), 5.44 (1H, s, 1β-H), 6.16 (1H, s, 4-H). MS *m/z*: 360 (M^+), 342, 314. HR-MS *m/z*: 360.1949 (M^+). Calcd for $C_{21}H_{28}O_5$: 360.1937. IR (KBr) cm^{-1}: 1726. UV λ_{max}^{EtOH} nm (ε): 226 (11000).

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6α,7α-epoxy-2-oxaandrost-4-en-3-one) (4) A stirred solution of **3** (20 g) in THF (20 ml) and 2-propanol (20 ml) was treated with 2.6% NaOH (19.5 ml) and $NaBH_4$ (380 mg), and the reaction mixture was stirred at room temperature for 20 min. Aqueous 5% H_2SO_4 was added, and the product was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated under vacuum. Purification of the crude product by preparative TLC (benzene–AcOEt (5:1)) afforded 1.3 g of **4**. mp 92.3—93.9 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s, 18-H_3), 1.16 (3H, s, 19-H_3), 3.37 (1H, br d, $J=3.5$ Hz, 7β-H), 3.49 (1H, d, $J=3.5$ Hz, 6β-H), 3.75 (2H, m, 5′-H), 4.01, 4.18 (2H, ABq, $J=11$ Hz, 1-H_2), 6.10 (1H, s, 4-H). MS *m/z*: 344 (M^+), 329, 328. HR-MS *m/z*: 344.1960 (M^+). Calcd for $C_{21}H_{28}O_4$: 344.1988.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(2-oxaandrosta-4,6-dien-3-one) (5) A solution of **4** (890 mg) in CH_2Cl_2 (70 ml) was stirred with P_2I_4 (3 g) for 15 min at room temperature, followed by addition of saturated $NaHCO_3$, and the product was extracted with $CHCl_3$. The organic extract was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent under vacuum gave a crude product, which was purified by preparative TLC (benzene–AcOEt (5:1)) to yield **5** (616 mg), an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-H_3), 1.18 (3H, s, 19-H_3), 3.75 (2H, m, 5′-H_2), 4.02, 4.25 (2H, ABq, $J=11$ Hz, 1-H_2), 5.60 (1H, s, 4-H), 6.15 (2H, s, 6-, 7-H). MS *m/z*: 328 (M^+), 313, 310, 269, 244. HR-MS *m/z*: 328.2035 (M^+). Calcd for $C_{21}H_{28}O_3$: 328.2038.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6α,7α-difluoromethylene-2-oxaandrost-4-en-3-one) (6) A solution of **5** (365 mg) in triglyme (2 ml) was refluxed, and a solution of anhydrous sodium chlorodifluoroacetate (5 g) in triglyme (25 ml) was added dropwise to it over 60 min. The reaction mixture was poured on ice and then extracted with diethyl ether. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The residue was subjected to preparative TLC (benzene–AcOEt (10:1)) to give **6** (268 mg). mp 202.0—203.4 °C. *Anal.* Calcd for $C_{22}H_{28}F_2O_3$: C, 69.82; H, 7.46. Found: C, 69.85; H, 7.55. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, 18-H_3), 1.19 (3H, s, 19-H_3), 3.75 (2H, m, 5′-H_2), 3.98, 4.20 (2H, ABq, $J=11$ Hz, 1-H_2), 5.92 (1H, d, $J=1$ Hz, 4-H). MS *m/z*: 378 (M^+), 363, 358. IR (KBr) cm^{-1}: 1730. UV λ_{max}^{EtOH} nm (ε): 232 (11000).

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6β-chloro-7α-hydroxy-2-oxaandrost-4-en-3-one) (7) Concentrated hydrochloric acid (1 ml) was added to a solution of **4** (115 mg) in THF (3 ml) at 0—5 °C. The mixture was stirred at room temperature for 10 min, then extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by preparative TLC (benzene–AcOEt (10:1)) to yield **7** (117 mg). mp 212.2—214.0 °C. *Anal.* Calcd for $C_{21}H_{29}ClO_4$: C, 66.22; H, 7.67. Found: C, 65.99; H, 7.81. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-H_3), 1.47 (3H, s, 19-H_3), 3.75 (2H, m, 5′-H_2), 3.97 (1H, br s, 7β-H), 4.06, 4.23 (2H, ABq, $J=11$ Hz, 1-H_2), 4.44 (1H, d, $J=2.5$ Hz, 6α-H), 5.97 (1H, s, 4-H). MS *m/z*: 380 (M^+), 365, 344, 328, 313, 258.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(7α-acetoxy-6β-chloro-2-oxaandrost-4-en-3-one) (8) A solution of **7** (107 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with 2 N hydrochloric acid and then with saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated. Purification of the crude product by preparative TLC (benzene–AcOEt (5:1)) gave 102 mg of **8**, an amorphous powder. *Anal.* Calcd for $C_{23}H_{31}ClO_5$: C, 65.32; H, 7.39. Found: C, 65.10; H, 7.59. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-H_3), 1.49 (3H, s, 19-H_3), 2.07 (3H, s, Ac), 3.75 (2H, m, 5′-H_2), 4.02, 4.25 (2H, ABq, $J=11$ Hz, 1-H_2), 4.48 (1H, d, $J=2.5$ Hz, 6α-H), 5.04 (1H, t, $J=2.5$ Hz, 7β-H), 5.93 (1H, s, 4-H). MS *m/z*: 422 (M^+), 363, 344, 326, 258.

2′,3′α-Tetrahydrofuran-2′-spiro-17-(6-chloro-2-oxaandrosta-4,6-dien-3-one) (9) A stirred mixture of **8** (96 mg) and anhydrous potassium acetate (100 mg) in DMF (1 ml) was heated at 70 °C for 4 h. The reaction

mixture was poured into water and extracted with AcOEt. The organic extract was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by preparative TLC (benzene–AcOEt (10:1)) to afford **9** (67 mg), an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-H_3), 1.21 (3H, s, 19-H_3), 3.75 (2H, m, 5'-H_2), 4.04, 4.26 (2H, ABq, J=11 Hz, 1-H_2), 6.18 (1H, s, 4-H), 6.33 (1H, d, J=2 Hz, 7-H). MS m/z: 362 (M^+), 347, 327, 278. HR-MS m/z: 362.1653 (M^+). Calcd for $C_{21}H_{27}ClO_3$: 362.1649.

6α,7α-Epoxy-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (11) A mixture of **10** (1.9 g) and *m*-CPBA (3 g) in $CHCl_3$ (15 ml) was stirred at room temperature for 4 h. The mixture was diluted with AcOEt, washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by preparative TLC (benzene–AcOEt (3:1)), to give **11** (1.1 g). mp 203.1—204.4 °C. *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.36; H, 7.60. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, s, 18-H_3), 1.22 (3H, s, 19-H_3), 3.37 (1H, dd, J=3.5, 1.5 Hz, 7β-H), 3.66 (1H, d, J=3.5 Hz, 6β-H), 6.22 (1H, dd, J=10, 2 Hz, 2-H), 6.47 (1H, d, J=2 Hz, 4-H), 6.99 (1H, d, J=10 Hz, 1-H). MS m/z: 354 (M^+), 339. IR (KBr) cm^{-1}: 1776, 1664. UV λ_{max}^{EtOH} nm (ε): 245 (15500).

6α,7α-Epoxy-1α-hydroxy-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (12) The reaction of **11** (900 mg) with O_3 was carried out and the mixture was worked up by a procedure similar to that described for **3** to give **12** (651 mg). mp 177—179 °C. *Anal.* Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.11; H, 7.13. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, s, 18-H_3), 1.18 (3H, s, 19-H_3), 3.37 (1H, d, J=3.5 Hz, 7β-H), 3.53 (1H, d, J=3.5 Hz, 6β-H), 5.44 (1H, s, 1-H), 6.17 (1H, s, 4-H). MS m/z: 374 (M^+), 356, 328. IR (KBr) cm^{-1}: 1766, 1730. UV λ_{max}^{EtOH} nm (ε): 228 (11000).

6α,7α-Epoxy-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (13) The reaction of **12** (645 mg) with $NaBH_4$ (60 mg) was carried out in a manner similar to that described for **4** to give **13** (546 mg). mp 276.0—277.5 °C. *Anal.* Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.35; H, 7.36. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, s, 18-H_3), 1.18 (3H, s, 19-H_3), 3.37 (1H, br d, J=3.5 Hz, 7β-H), 3.51 (1H, d, J=3.5 Hz, 6β-H), 4.01, 4.18 (2H, ABq, J=11 Hz, 1-H_2), 6.12 (1H, s, 4-H). MS m/z: 358 (M^+). IR (KBr) cm^{-1}: 1768, 1728. UV λ_{max}^{EtOH} nm (ε): 216 (14000).

3-Oxo-2-oxa-17α-pregna-4,6-diene-21,17-carbolactone (14) The reaction of **13** (537 mg) with P_2I_4 (1.3 g) was carried out in a way similar to that described for **5** to yield **14** (373 mg), an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s, 18-H_3), 1.20 (3H, s, 19-H_3), 4.03, 4.26 (2H, ABq, J=11 Hz, 1-H_2), 5.63 (1H, s, 4-H), 6.15 (2H, s, 6-, 7-H). MS m/z: 342 (M^+), 327, 312, 269. HR-MS m/z: 342.1783 (M^+). Calcd for $C_{21}H_{26}O_4$: 342.1831. IR (KBr) cm^{-1}: 1768, 1724. UV λ_{max}^{EtOH} nm (ε): 269 (21000).

6α,7α-Difluoromethylene-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (15) The reaction of **14** (120 mg) with sodium chlorodifluoroacetate (500 mg) was carried out in a manner similar to that described for **6** to give **15** (41 mg). mp 230.1—231.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s, 18-H_3), 1.20 (3H, s, 19-H_3), 3.98, 4.20 (2H, ABq, J=11 Hz, 1-H_2), 5.95 (1H, d, J=1 Hz, 4-H). MS m/z: 392 (M^+), 341, 311, 268. HR-MS m/z: 392.1786 (M^+). Calcd for $C_{22}H_{26}F_2O_4$: 392.1799. IR (KBr) cm^{-1}: 1768, 1730. UV λ_{max}^{EtOH} nm (ε): 231 (11000).

7α-Acetylthio-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (16) A solution of **14** (278 mg) in thioacetic acid (7.5 ml) was refluxed for 6 d, then extracted with AcOEt. The extract was washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. Purification of the crude product by preparative TLC (benzene–AcOEt (4:1)) afforded **16** (20 mg), an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, s, 18-H_3), 1.26 (3H, s, 19-H_3), 2.36 (3H, s, Ac), 3.9—4.3 (3H, m, 1-H_2, 7-H), 5.70 (1H, d, J=2 Hz, 4-H). MS m/z: 418 (M^+), 376, 343, 269. HR-MS m/z: 418.1809 (M^+). Calcd for $C_{23}H_{30}O_5S$: 418.1814.

6β-Chloro-7α-hydroxy-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (17) Compound **13** (91 mg) was treated with hydrochloric acid in a manner similar to that described for **7** to give **17** (87 mg). mp 245—247 °C. *Anal.* Calcd for $C_{21}H_{27}ClO_5$: C, 63.87; H, 6.89. Found: C, 63.66; H, 7.01. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s, 18-H_3), 1.43 (3H, s, 19-H_3), 4.05, 4.23 (2H, ABq, J=11 Hz, 1-H_2), 4.44 (1H, d, J=2.5 Hz, 6α-H), 5.99 (1H, s, 4-H). MS m/z: 394 (M^+), 376, 358, 258.

7α-Acetoxy-6β-chloro-3-oxo-2-oxa-17α-pregn-4-ene-21,17-carbolactone (18) This compound (19 mg), an amorphous powder, was obtained from **17** (24 mg) by using the procedure described for **8**. *Anal.* Calcd for $C_{23}H_{29}ClO_6$: C, 63.23; H, 6.69. Found: C, 63.20; H, 6.76. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s, 18-H_3), 1.50 (3H, s, 19-H_3), 2.08 (3H, s, Ac), 4.02, 4.25 (2H, ABq, J=11 Hz, 1-H_2), 4.48 (1H, d, J=2.5 Hz, 6α-H), 5.05 (1H, t, J=2.5 Hz, 7β-H), 5.94 (1H, s, 4-H). MS m/z: 436 (M^+), 400, 376, 342.

6-Chloro-3-oxo-2-oxa-17α-pregna-4,6-diene-21,17-carbolactone (19) The reaction of **18** (16 mg) with anhydrous KOAc (25 mg) was carried out and work-up similar to that described for **9** gave **19** (10 mg), an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s, 18-H_3), 1.22 (3H, s, 19-H_3), 4.04, 4.26 (2H, ABq, J=11 Hz, 1-H_2), 6.20 (1H, s, 4-H), 6.31 (1H, d, J=2.5 Hz, 7-H). MS m/z: 376 (M^+), 361, 341, 303. HR-MS m/z: 376.1445 (M^+). Calcd for $C_{21}H_{25}ClO_4$: 376.1441. IR (KBr) cm^{-1}: 1768, 1714. UV λ_{max}^{EtOH} nm (ε): 273 (17000).

Antiandrogenic Activity Assay Wistar strain male rats weighing 160—180 g were castrated at about 4 weeks of age. After two weeks, testosterone propionate (50 μg/rat) was administered daily by the subcutaneous route in 0.1 ml of sesame oil to all animals except the controls. The test compounds were given *per os* daily for 5 d. On day 6, the animals were killed, and the seminal vesicles and ventral prostates were secured and weighed.

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