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> Dedicated to the 100th Anniversary of Corresponding Member of the Russian Academy of Sciences A.A. Petrov

## Synthesis and Biological Activity of Some 8α-Analogs of Steroidal Estrogens

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**Abstract**— $8\alpha$ -Analogs of steroidal estrogens containing a methyl group on C<sup>1</sup> or an oxo group on C<sup>6</sup> were synthesized with a view to obtain compounds exhibiting selective biological activity, and their steric structure was studied. As shown with 1,3-*O*-dimethyl- $8\alpha$ -estrone as an example, such compounds in solution can exist as two conformers, whereas the oxo group on C<sup>6</sup> almost does not affect conformation of the modified derivative as compared to the parent structure. Some newly synthesized compounds exhibited hypocholesterolemic activity in combination with reduced uterotropic effect, which is important for the design of drugs for the treatment of atherosclerosis. 6-Oxo- $8\alpha$ -analogs showed osteoprotective activity, so that introduction of an oxo group into the 6-position is promising from the viewpoint of hormone replacement therapy.

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Modified steroidal estrogens are widely used in medical practice as drugs for hormone replacement therapy [1-3] despite serious side effects. Among the latter, the most harmful are increased risks of cancer [4, 5], thrombosis [6, 7], stroke [8], cardiovascular diseases [9], and other complications. It is significant that increased risk of thrombosis was observed not only for estrogen therapy but also for estrogen-receptor modulators [10]. The most serious side effect is increased risk of tumors. It is believed that the main factor responsible for the carcinogenicity of estrogens is activation of proliferative processes in target organs [11, 12] and formation of DNA-damaging metabolites [13, 14]. In the latter case, irreversible depurination of DNA occurs with participation of  $C^1$  in the steroidal estrogen molecule. The above stated stimulates search for new compounds with improved biological properties on the basis of steroidal estrogens.

Obviously, introduction of an inert substituent into position *I* of steroidal estrogen molecule should prevent DNA damage. We previously synthesized  $17\beta$ -acetoxy-1-methyl-3-methoxy-8 $\alpha$ -estra-1,3,5(10)triene (I) [15] and determined its structure in the crystalline state [16] and in solution [15]. The calculated (*ab initio*, PM3, MM+) geometric parameters of molecule I were consistent with those found by X-ray analysis [15]. Docking of other 1-methyl-8 $\alpha$ -analogs of steroidal estrogens into the ligand-binding pocket of nuclear estrogen  $\alpha$ -receptor [17] showed that such analogs should exhibit reduced proliferative activity. As model structures for studying biological activity we selected compounds II–IV.

There are published data indicating that metabolic hydroxylation at the C<sup>6</sup>-position of the estrogen molecule causes damage to DNA [18]. It was interesting to synthesize 6-oxo-8 $\alpha$ -analogs of steroidal estrogens and



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examine their biological properties. It was presumed that the hydroxy group arising from their metabolic hydroxylation at the C<sup>4</sup>-position should be involved in strong intramolecular hydrogen bond with the C<sup>6</sup>=O carbonyl group, which should reduce its reactivity and hence carcinogenic effect. Therefore, compounds V and VI were selected as the next group of model structures. Scheme 1 illustrates the synthesis of model steroidal estrogen analogs.

Compound II was synthesized by condensation of isothiuronium salt VII [19] with 2-methylcyclopentane-1,3-dione, followed by cyclodehydration of 8,14-*seco* derivative VIII, catalytic hydrogenation of estrapentaene IX over Raney nickel in benzene, and oxidation with the Sarett reagent. Unlike the procedure proposed previously [19], our version of synthesis of estrapentaene IX did not include purification of intermediate product VIII; as a result, the yield of IX was



improved from 56 [19] to 69%. Steroid **II** was thus obtained in ~36% yield. Its structure was proved by complete assignment of all signals in the <sup>1</sup>H and <sup>13</sup>C NMR spectra with the aid of a combination of shift correlation techniques DQF-COSY [20], *J*-COSY [21], HSQC [22, 23], and NOESY [24].

Optimization of the geometric parameters of molecule II by the PM3 method [25] revealed two possible conformers A and B (Fig. 1) differing by the conformation of the B ring; conformer A is thermodynamically more stable.

The coupling constant  ${}^{3}J_{6\beta,7\alpha} = 2.7$  Hz in molecule II (20°C) is higher by 0.4 Hz than that in steroid XI having no substituent on C<sup>1</sup> (Fig. 2). The coupling constants  ${}^{3}J_{6\beta,7\beta}$  for conformers **A** and **B** of steroids II and XI are equal within the experimental error (±0.1 Hz): 5.1 (**A**) and 5.0 Hz (**B**). Small differences in the scalar  ${}^{3}J_{6\beta,7\alpha}$  values led us to suppose that steroid II in solu-



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**Fig. 1.** Conformational equilibrium of steroid **II**. Calculated (PM3) coupling constants  ${}^{3}J_{66.7\alpha}$  (Hz) are given.



Fig. 2. Multiplet structure of the  $\beta$ -H signal in the <sup>1</sup>H NMR spectra of compounds XI and II at 20°C and evolution of that signal in the spectrum of II with rise in temperature to 60°C.

tion exists in fast (on the NMR time scale) conformational equilibrium  $A \rightleftharpoons B$  involving inversion of the B ring (*pseudochair*  $\rightleftharpoons$  *pseudoboat*, Fig. 3).

This assumption was confirmed by studying temperature dependence of  ${}^{3}J_{6\beta,7\alpha}$ . Rise in temperature from 20 to 60°C was accompanied by increase of  ${}^{3}J_{6\beta,7\alpha}$  to 3.7 Hz and simultaneous small decrease of  ${}^{3}J_{6\beta,7\beta}$  to 4.8 Hz (Fig. 2). The geminal coupling constant  ${}^{2}J_{6\beta,6\alpha}$  remained unchanged (16.6 Hz), and the sum of all scalar coupling constants (the distance between lines *I* and *8* in Fig. 2) increased by ~0.9 Hz. The observed temperature dependence clearly indicated increase in the population of minor conformer **B** of **II**, where the 6 $\beta$ -H proton occupies axial position. Thus the conformational equilibrium **A**  $\Rightarrow$  **B** of steroid **II** may be regarded as proved.

According to the PM3 calculations, the distance between the  $6\beta$ -H and  $11\beta$ -H protons in the major

conformer is 4.1 Å, and in the minor conformer, 1.9 Å, whereas the distances between 9 $\alpha$ -H and 12 $\alpha$ -H in both conformers are almost similar [2.62 (**A**) and 2.68 Å (**B**)]. The ratio of the intensities of the 9 $\alpha$ /12 $\alpha$  and 6 $\beta$ /11 $\beta$  cross-peaks for conformer **A** should be 14.5:1, and for conformer **B**, 1:10. The experimental intensity of the 6 $\beta$ /11 $\beta$  cross-peak is approximately thrice as high as that calculated for the major conformer, which provides an additional support to the existence of conformational equilibrium. These results can be used to perform docking of analogous compounds to ligand-binding pockets of various proteins.

By oxidation of steroid **XII** [25] with chromium(VI) oxide we obtained compound **V** whose hydrolysis and subsequent oxidation of the alcohol thus formed afforded diketo steroid **VI** (Scheme 2). The structure of compounds **V** and **VI** was proved by <sup>1</sup>H and <sup>13</sup>C NMR. The <sup>1</sup>H and <sup>13</sup>C chemical shifts of the





compounds with an oxo group on  $C^6$  and without it were almost similar, indicating that the  $C^6=O$  group does not affect their conformation.

Biological testing of 1-methyl-substituted steroidal derivatives revealed their hypocholesterolemic activity in combination with weak proliferative effect; therefore, these compounds attract interest from the viewpoint of design of drugs for the treatment of cardiovascular diseases. 6-Oxo analogs showed osteoprotective effect, which is important for hormone replacement therapy.

## **EXPERIMENTAL**

The progress of reactions was monitored by TLC on Silufol plates using hexane–ethyl acetate (4:1 or 3:1) as eluent. Silica gel Merck 60 (0.040–0.063 mm)

was used for column chromatography. The mass spectra were recorded on an MKh-1321 instrument (ion source temperature 200–210°C). The NMR spectra were measured at 295 K on a Bruker DPX-300 spectrometer at 300.130 (<sup>1</sup>H) and 75.468 MHz (<sup>13</sup>C) from solutions of 5–7 (<sup>1</sup>H) or 30–50 mg (<sup>13</sup>C) of compounds in 0.6 ml of CDCl<sub>3</sub>; the chemical shifts were determined relative to tetramethylsilane by assigning standard values ( $\delta$  7.26,  $\delta_{\rm C}$  76.90 ppm) to the solvent signals (CDCl<sub>3</sub>–CHCl<sub>3</sub>, 99.9:0.1) with an accuracy of no less than ±0.01 ppm. The <sup>1</sup>H–<sup>1</sup>H coupling constants were measured with an accuracy of ±0.02 Hz after additional processing of the spectral lines by the Lorentz–Gauss transformation. The principal parameters for NMR data acquisition and processing are given below.

<sup>1</sup>H NMR. Time domain TD = 32 K, spectral width SW = 2.4 kHz, number of scans NS = 128, relaxation



Fig. 3. Conformational equilibrium of steroid II and a fragment of its NOESY spectrum (mixing time 0.5 s); the  $6\beta/11\beta$  cross peak is enclosed in a circle. The distances between the  $6\beta$ -H and  $11\beta$ -H protons in conformers **A** and **B** are shown with double-ended arrows.

delay DI = 3 s; Lorentz–Gauss parameters: LB = -2 Hz, GM = 0.2; zero-filling: SI = 64 or 128 K.

<sup>13</sup>C NMR. TD = 32 K, SI = 64 K, SW = 16.5 kHz, NS = 512, DI = 5 s, exponential weighting function equivalent to a line broadening *LB* of 3 Hz.

2D COSY-90. TD2 = 512, SW1 = SW2 = 2.4 kHz, NS = 4 for each of 256  $t_1$  increments, DI = 3 s,  $512 \times 512$  spectral matrix, apodization function for the coordinates  $t_1$  and  $t_2$ :  $sin(pt/t_{max})$ ; absolute value spectrum.

2D COSY-DQF. TD2 = 2 K, SW1 = SW2 = 2.4 kHz, NS = 16 for each of 512  $t_1$  increments, D1 = 3 s, phasesensitive detection with time-proportional phase increment (TPPI); apodization function  $sin(pt/t_{max})$ ; 2048×1024 spectral matrix.

<sup>13</sup>C<sup>-1</sup>H HETCORR. TD = 1 K, SWI = 1.2 kHz, SW2 = 3.5 kHz, NS = 56 for each of 256  $t_1$  increments, DI = 2 s, direct heteronuclear coupling evolution delays D2 = 3.7, D3 = 2.5 ms; exponential apodization function for  $t_2$  (LB = 3 Hz) and  $sin(pt/t_{max} + p/2)$  for  $t_1$ ; 1024×512 spectral matrix of absolute values.

COLOC. TD2 = 1 K, SWI = 2.4, SW2 = 3.5 kHz; NS = 256 for each of 128  $t_1$  increments; DI = 1 s; heteronuclear coupling evolution delays ( ${}^nJ_{CH}$ , n = 2, 3): D6 = 62.5, D8 = 41.7 ms; apodization function  $\sin(pt/t_{max})$  for  $t_2$  and  $\sin(pt/t_{max} + p/2)$  for  $t_1$ ;  $1024 \times 512$  spectral matrix of absolute values.

NOESY. TD2 = 1 K, SWI = SW2 = 2.4 kHz, NS = 16 for each of 256  $t_1$  increments, DI = 2 s, mixing time D8 = 0.5, 1.0 s; phase-sensitive detection with TPPI, apodization function  $\sin(pt/t_{max} + p/2)$ ,  $1024 \times 512$  spectral matrix.

All isolated compounds were racemic.

1-Methyl-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (IX). Finely powdered 2-methylpentane-1,3-dione, 5.0 g (0.004 mol), was added to a 3.0 g (8.9 mmol) of isothiuronium salt VII [19] in 50 ml of aqueous ethanol (1:1), the mixture was stirred for 24 h at 25°C, and the solvent was removed under reduced pressure. The residue was dissolved in 50 ml of methanol, 3 ml of 37% aqueous HCl was added, and the mixture was heated for 30 min under reflux in an argon atmosphere, left to stand for 24 h at 10°C, poured into 300 ml of water, and extracted with 300 ml of chloroform. The extract was washed thrice with equal portions of 3% aqueous sodium acetate, dried over sodium sulfate, and passed through a layer of aluminum oxide (50 g, Brockmann activity grade III). The solvent was removed under reduced pressure, and the residue was crystallized from chloroform-methanol

(1:8). Yield 1.8 g (69%), mp 99–100°C; published data [19]: mp 97.5–98.5°C. The product showed no depression of the melting point on mixing with an authentic sample; the <sup>1</sup>H NMR spectra of both samples were identical to each other. Found, %: C 81.70; H 7.90.  $C_{21}H_{24}O_2$ . Calculated, %: C 81.78; H 7.84.

3-Methoxy-1-methyl-8a-estra-1,3,5(10)-trien-17one (II). Raney nickel, 8.0 g, was added to a solution of 10.14 g (0.034 mol) of compound IX in 270 ml of benzene, hydrogen was supplied to an initial pressure of 150 atm, and the mixture was hydrogenated at 40-90°C until the amount of absorbed hydrogen exceeded by a factor of 300 that necessary for the hydrogenation of two double bonds and keto group in the initial compound. The catalyst was filtered off, the solvent was distilled off on a rotary evaporator, and the residue was dissolved in 100 ml of pyridine. The solution was cooled to 10°C, and the Sarett reagent prepared from 8.3 g of chromium(VI) oxide and 200 ml of pyridine was added. The mixture was left to stand for 24 h at room temperature, the inorganic precipitate was filtered off and repeatedly washed with diethyl ether, the pyridine filtrate and the ether washings were combined, washed with three portions of water, 10% aqueous HCl, a solution of sodium acetate, and several portions of water until neutral washings, dried over sodium sulfate, and evaporated on a rotary evaporator, and the residue was crystallized from ethanol. Yield 3.68 g (36%), mp 137–139°C. <sup>1</sup>H NMR spectrum, δ, ppm: 1.05 s (3H,  $C^{18}H_3$ ), 1.45 (12 $\alpha$ -H), 1.52 (11 $\beta$ -H), 1.81 (12β-Η), 1.84 (15β-Η), 1.84 (7β-Η), 1.84 (7α-Η), 1.85 (11α-H), 1.94 (14α-H), 2.04 (16β-H), 2.10 (15α-H), 2.15 (8α-H), 2.30 (1-CH<sub>3</sub>), 2.50 (16α-H), 2.70 (9α-Η), 2.70 (6β-Η), 2.87 (6α-Η), 6.49 (4-Η), 6.59 (2-H). <sup>13</sup>C NMR spectrum,  $\delta_{\rm C}$ , ppm: 137.49 (C<sup>1</sup>), 114.25 (C<sup>2</sup>), 157.01 ( $\overline{C}^3$ ), 111.14 ( $\overline{C}^4$ ), 137.35 ( $\overline{C}^5$ ), 31.43 (C<sup>6</sup>), 21.25 (C<sup>7</sup>), 38.94 (C<sup>8</sup>), 39.66 (C<sup>9</sup>), 131.35  $(C^{10})$ , 24.81  $(C^{11})$ , 32.11  $(C^{12})$ , 47.16  $(C^{13})$ , 48.93  $(C^{14})$ , 21.32  $(C^{15})$ , 35.62  $(C^{16})$ , 220.43  $(C^{17})$ , 16.46  $(C^{18})$ , 18.94 (1-CH<sub>3</sub>), 55.97 (CH<sub>3</sub>O). Mass spectrum, m/z (*I*<sub>rel</sub>, %): 298 (100), 283 (2.0), 213 (55.0), 200 (19.5), 187 (7.5), 174 (51.5), 159 (16.5). Found, %: C 80.65; H 8.90. C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>. Calculated, %: C 80.50; H 8.78.

3-Methoxy-1-methyl-8 $\alpha$ -estra-1,3,5(10)-trien-17 $\beta$ -yl acetate (I). Sodium tetrahydridoborate, 0.2 g, was added at room temperature to a solution of 0.7 g (2.34 mmol) of compound II in 25 ml of dioxanewater (10:1), and the mixture was stirred for 1.5 h. After appropriate treatment, the reduction product was dissolved in 5 ml of pyridine, 15 ml of acetic anhydride was added, and the mixture was left to stand for 24 h at room temperature. After appropriate treatment, the product was crystallized from ethanol. Yield 0.56 g (71%), mp 126.5–128.5°C. <sup>13</sup>C NMR spectrum,  $\delta_{\rm C}$ , ppm: 137.8 (C<sup>1</sup>), 114.2 (C<sup>2</sup>), 157.0 (C<sup>3</sup>), 111.1 (C<sup>4</sup>), 137.6 (C<sup>5</sup>), 31.6 (C<sup>6</sup>), 20.6 (C<sup>7</sup>), 38.0 (C<sup>8</sup>), 39.9 (C<sup>9</sup>), 131.9 (C<sup>10</sup>), 25.1 (C<sup>11</sup>), 37.5 (C<sup>12</sup>), 41.9 (C<sup>13</sup>), 47.8 (C<sup>14</sup>), 22.3 (C<sup>15</sup>), 26.8 (C<sup>16</sup>), 82.5 (C<sup>17</sup>), 13.7 (C<sup>18</sup>), 19.0 (1-CH<sub>3</sub>), 54.9 (CH<sub>3</sub>O), 21.1 (CH<sub>3</sub>CO), 171.0 (C=O). Mass spectrum, *m/z* (*I*<sub>rel</sub>, %): 342 (100) [*M*]<sup>+</sup>, 282 (21.2), 267 (5.2), 253 (16.6), 213 (5.7), 200 (47.0), 187 (17.2), 174 (3.1), 159 (15.0). Found, %: C 76.89; H 8.85. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub>. Calculated, %: C 77.16; H 8.83. *M* 342.48.

3-Methoxy-1-methyl-D-homoestra-1.3.5(10),8,14pentaen-17a-one (X). Finely powdered 2-methylcyclohexane-1,3-dione, 10.0 g (0.08 mol), was added to 10.0 g (0.03 mol) of isothiuronium salt VII [19] in 200 ml of aqueous ethanol (1:1), and the mixture was stirred for 48 h at 30°C. The solvent was removed under reduced pressure, the residue was dissolved in 250 ml of ethanol, 10 ml of 37% aqueous HCl was added, and the mixture was heated for 30 min under reflux and left to stand for 24 h at 10°C. The precipitate was filtered off and dissolved in 100 ml of chloroform, the solution was washed with water until neutral washings, dried over sodium sulfate, and passed through a layer of alumina (50 g, Brockmann activity grade III), the solvent was removed under reduced pressure, and the residue was crystallized from chloroform-methanol (1:8). Yield 5.2 g (52%), mp 99-100°C; published data [19]: mp 97.5-98.5°C. The product showed no depression of the melting point on mixing with an authentic sample [19]; the <sup>1</sup>H NMR spectra of both samples were identical to each other. Found, %: C 81.70; H 7.90. C<sub>21</sub>H<sub>24</sub>O<sub>2</sub>. Calculated, %: C 81.78; H 7.84.

**3-Methoxy-1-methyl-D-homo-8a-estra-1,3,5(10)trien-17a-one (III)** was synthesized by catalytic hydrogenation of 4.32 g (0.014 mol) of compound **X**, followed by oxidation of the reduction product with the Sarett reagent as described above for compound **II**. Yield 1.40 g (32%), mp 121–123°C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 1.19 (C<sup>18</sup>H<sub>3</sub>), 1.47 (15 $\alpha$ -H), 1.48 (11 $\beta$ -H), 1.70 (16 $\alpha$ -H), 1.75 (12 $\beta$ -H), 1.76 (14 $\alpha$ -H), 1.77 (11 $\alpha$ -H), 1.84 (7 $\beta$ -H), 1.86 (12 $\alpha$ -H), 1.87 (7 $\alpha$ -H), 1.92 (8 $\alpha$ -H), 2.04 (15 $\beta$ -H), 2.08 (16 $\beta$ -H), 2.25 (17 $\alpha$ -H), 2.29 (1-CH<sub>3</sub>), 2.63 (17 $\beta$ -H), 2.65 (9 $\alpha$ -H), 2.66 (6 $\alpha$ -H), 2.86 (6 $\beta$ -H), 3.75 (CH<sub>3</sub>O), 6.47 (4-H), 6.59 (2-H). <sup>13</sup>C NMR spectrum,  $\delta_{C}$ , ppm: 137.27 (C<sup>1</sup>), 114.16 (C<sup>2</sup>), 156.92 (C<sup>3</sup>), 110.96 (C<sup>4</sup>), 136.99 (C<sup>5</sup>), 31.58 (C<sup>6</sup>), 21.12 (C<sup>7</sup>), 41.22 (C<sup>8</sup>), 39.22 (C<sup>9</sup>), 131.56 (C<sup>10</sup>), 24.48 (C<sup>11</sup>), 32.88 (C<sup>12</sup>), 48.01 (C<sup>13</sup>), 48.22 (C<sup>14</sup>), 25.51 (C<sup>15</sup>), 26.25 (C<sup>16</sup>), 37.59 (C<sup>17</sup>), 215.25 (C<sup>17a</sup>), 19.05 (C<sup>18</sup>), 18.66 (1-CH<sub>3</sub>), 54.78 (CH<sub>3</sub>O). Mass spectrum, *m/z* ( $I_{rel}$ , %): 312 (100), 298 (4), 244 (5), 227 (5), 213 (75), 187 (14.5), 174 (32), 159 (12). Found, %: C 80.65; H 9.21. C<sub>21</sub>H<sub>28</sub>O<sub>2</sub>. Calculated, %: C 80.73; H 9.03.

**3-Methoxy-1-methyl-D-homo-8α-estra-1,3,5(10)trien-17a,β-yl acetate (IV)** was synthesized from 0.5 g (1.6 mmol) of **III** as described above for **I**. The product was recrystallized from methanol. Yield 0.45 g (79%), mp 138–141°C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.99 (C<sup>18</sup>H<sub>3</sub>), 2.05 (CH<sub>3</sub>CO), 2.29 (1-CH<sub>3</sub>), 3.75 (CH<sub>3</sub>O), 6.47 (4-H), 6.59 (2-H). Found, %: C 77.61; H 9.14. C<sub>23</sub>H<sub>32</sub>O<sub>3</sub>. Calculated, %: C 77.49; H 9.05.

**3-Methoxy-D-homo-8α-estra-1,3,5(10)-trien-17aβ-yl acetate (XII)** was synthesized according to the procedure described in [25], mp 172.5–173.5°C; published data [25]: mp 172.5–174.0°C. <sup>1</sup>H NMR spectrum, δ, ppm: 0.98 (C<sup>18</sup>H<sub>3</sub>), 1.25 (12α-H), 1.28 (15α-H), 1.46 (16α-H), 1.47 (14α-H), 1.52 (17β-H), 1.58 (11β-H), 1.62 (15β-H), 1.64 (11α-H), 1.66 (12β-H),1.69 (7β-H), 1.71 (17α-H), 1.75 (7α-H), 1.81 (16β-H), 1.88 (8α-H), 2.04 (CH<sub>3</sub>CO), 2.62 (6α-H), 2.64 (9α-H), 2.78 (6β-H), 3.77 (CH<sub>3</sub>O), 4.51 (17αα-H), 6.60 (4-H), 6.72 (2-H), 7.03 (1-H). Found, %: C 77.12; H 8.87. C<sub>22</sub>H<sub>30</sub>O<sub>3</sub>. Calculated, %: C 77.16; H 8.83.

3-Methoxy-6-oxo-D-homo-8a-estra-1,3,5(10)-trien-17aβ-yl acetate (V). A solution of 7.6 g of sodium dichromate dihydrate in a mixture of 90 ml of acetic acid and 45 ml of acetic anhydride was added dropwise to a solution of 4.5 g (0.013 mol) of compound XII in 40 ml of glacial acetic acid. The mixture was stirred for 5 h at 65°C, a solution of 3.7 g of the same oxidant in 20 ml of acetic acid was added, and the mixture was stirred for 6 h at that temperature, poured into 1 l of water, and extracted with diethyl ether. After appropriate treatment, the product was purified by flash chromatography on silica gel, followed by crystallization from methanol. Yield 0.5 g (14%), mp 175-176°C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 1.01 (C<sup>18</sup>H<sub>3</sub>), 1.28 (15α-H), 1.30 (12α-H), 1.43 (16α-H), 1.48 (14α-H), 1.53 (17β-Н), 1.55 (15β-Н), 1.68 (11β-Н), 1.73 (12β-H), 1.73 (17α-H), 1.74 (11α-H), 1.82 (16β-H), 2.04 (CH<sub>3</sub>CO), 2.37 (8a-H), 2.58 (7a-H), 2.69 (7β-H), 2.80 (9α-H), 3.81 (CH<sub>3</sub>O), 4.51 (17aα-H), 7.08 (2-H), 7.17 (1-H), 7.44 (4-H). Found, %: C 74.05; H 8.12. C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>. Calculated, %: C 74.13; H 7.92.

**3-Methoxy-D-homo-8α-estra-1,3,5(10)-triene-6,17a-dione (VI).** A solution of 2.0 g of sodium hydroxide in 18 ml of methanol was added to a solution of 0.7 g (1.96 mmol) of compound V in 25 ml of benzene. The mixture was heated for 6 h under reflux on stirring, cooled to room temperature, and poured into 200 ml of water. Excess alkali was neutralized with 50% acetic acid to weakly acidic reaction, the mixture was extracted with chloroform (3×10 ml), the combined extracts were washed with a 3% solution of sodium carbonate and with water until neutral washings, dried over sodium sulfate, filtered from the drying agent, and evaporated under reduced pressure. The residue was dissolved in 10 ml of anhydrous acetone.
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benzene. The mixture was heated for 6 h under reflux on stirring, cooled to room temperature, and poured into 200 ml of water. Excess alkali was neutralized with 50% acetic acid to weakly acidic reaction, the mixture was extracted with chloroform  $(3 \times 10 \text{ ml})$ , the combined extracts were washed with a 3% solution of sodium carbonate and with water until neutral washings, dried over sodium sulfate, filtered from the drying agent, and evaporated under reduced pressure. The residue was dissolved in 10 ml of anhydrous acetone, 1.7 g of Jones reagent (prepared from 1.0 g of chromium trioxide and 0.7 g of 20% sulfuric acid) was added under vigorous stirring and cooling with an ice-water mixture, and the mixture was stirred for 30 min at room temperature and poured into 100 ml of cold water. The precipitate was filtered on a Schott filter, washed with water until neutral washings, dried under reduced pressure, and recrystallized from methanol. Yield 0.37–0.39 g (60–63%), mp 182–184°C. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 1.20 (C<sup>18</sup>H<sub>3</sub>), 1.49 (15 $\alpha$ -H), 1.66 (16α-Η), 1.71 (14α-Η), 1.77 (11β-Η), 1.79 (12α-Η),  $1.79 (12\beta-H), 1.85 (11\alpha-H), 1.99 (15\beta-H), 2.10$ (16β-Η), 2.26 (17α-Η), 2.47 (8α-Η), 2.62 (17β-Η), 2.70 (7α-H), 2.74 (7β-H), 2.77 (9α-H), 3.80 (CH<sub>3</sub>O), 7.09 (2-H), 7.20 (1-H), 7.45 (4-H). <sup>13</sup>C NMR spectrum,  $\delta_{C}$ , ppm: 130.02 (C<sup>1</sup>), 122.26 (C<sup>2</sup>), 158.53 (C<sup>3</sup>), 108.64  $(C^4)$ , 131.96  $(C^5)$ , 197.70  $(C^6)$ , 37.05  $(C^7)$ , 38.80  $(C^8)$ , 41.21 (C<sup>9</sup>), 140.72 (C<sup>10</sup>), 26.21 (C<sup>11</sup>), 32.57 (C<sup>12</sup>), 47.71 (C<sup>13</sup>), 47.33 (C<sup>14</sup>), 25.08 (C<sup>15</sup>), 26.05 (C<sup>16</sup>), 37.64 (C<sup>17</sup>), 214.99 (C<sup>17a</sup>), 18.83 (C<sup>18</sup>), 55.40 (CH<sub>3</sub>O). Found, %: C 77.01; H 7.75. C<sub>20</sub>H<sub>24</sub>O<sub>3</sub>. Calculated, %: C 76.89; H 7.74.

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