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Synthesis of 6-Oxaestra-1,3,5(10),8,14-pentaenes

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Abstract—The Wendler version of the Torgov–Ananchenko scheme of total steroid synthesis was shown to be applicable to the preparation of 6-oxaestra-1,3,5(10),8,14-pentaenes. Conditions for cyclodehydration of secosteroids thus obtained were found, which ensured isolation of the target compounds in a high yield without using chromatographic purification methods.

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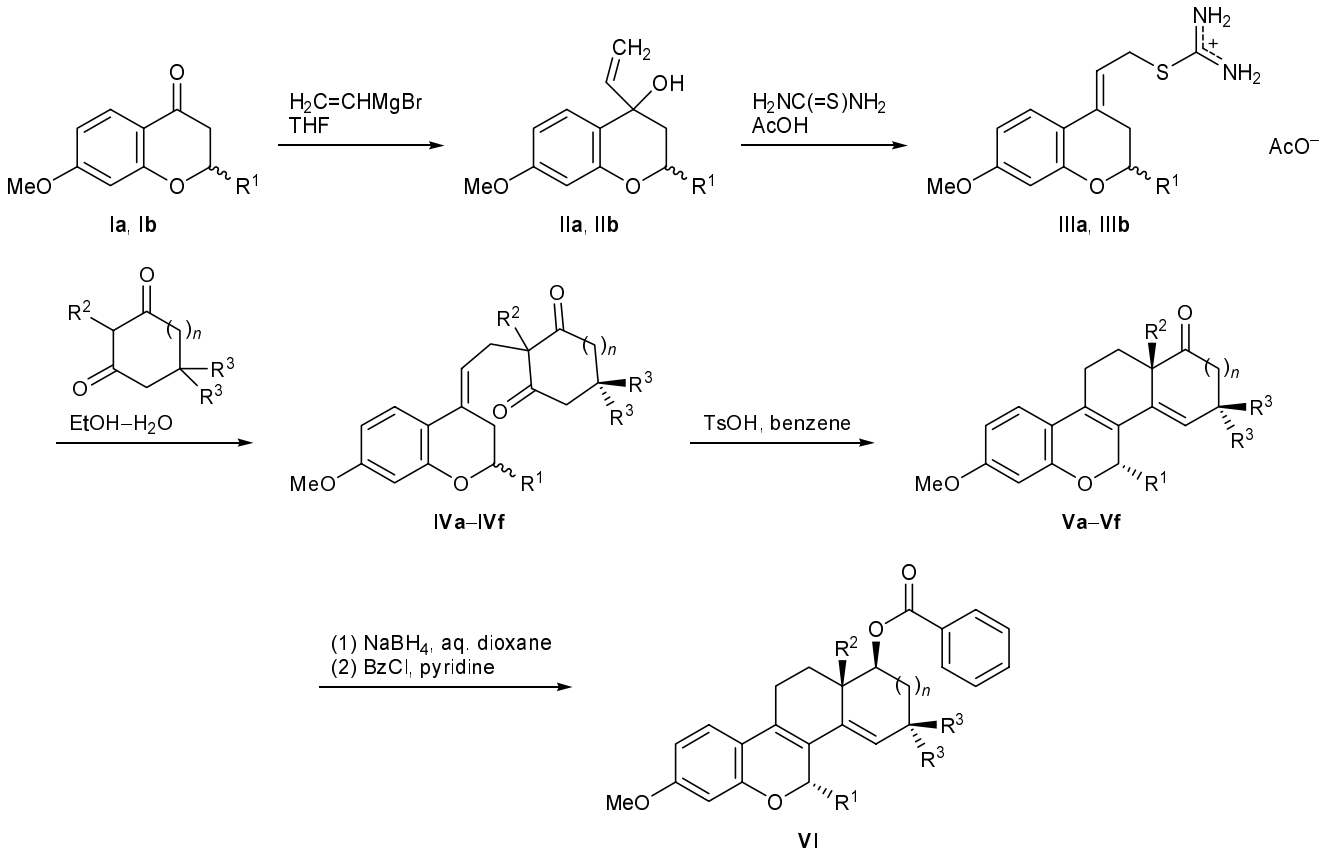
6-Oxa analogs of steroid estrogens exhibit a reduced hormonal activity [1–5], and the relation between their hypolipidemic and uterotropic action may be improved [1–3]. This is a necessary condition for preclinical testing of new potential agents for prophylaxis and treatment of cardiovascular diseases [6]. It is believed that the presence of an oxygen atom in the 6-position may considerably improve metabolism of this group of steroid hormones [7]; therefore, the importance of development of synthetic approaches to such analogs is beyond doubt.

The most widely used synthetic route to 6-oxa analogs of estra-1,3,5(10),8,14-pentaene steroids (**V**) [8–10] is based on the direct condensation of vinylcarbinols with various cyclic 1,3-diones, followed by cyclodehydration of the condensation product. Stereoselective reduction of the double bonds in these compounds gives rise to steroids with a required ring junction [5, 7, 11]. However, this approach is not free from a number of disadvantages. First, secosteroids are formed only in moderate yields; for example, compound **IVb** was isolated in a yield of about 40% [10]. Second, the conditions for cyclodehydration were not optimized. In particular, steroid **Vb** was not isolated with a relatively high yield as reported previously [8–10]: only 24% of 6-oxaestrapentaene **Vb** was obtained from compound **IVb**, while the major product was 3-methoxy-6-oxaestra-1,3,5(10),8(9),15-pentaen-17-one (yield 71%) [7].

We have improved the procedures for the synthesis of 3-methoxy-6-oxa-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17(or 17a)-diones and their subsequent cyclodehydration leading to 6-oxaestra-1,3,5(10),8,14-pentaenes. Secosteroids were obtained through isothiuronium salts **IIIa** and **IIIb** (Scheme 1). We thus succeeded in raising the yields of the target products and simplifying the procedure for their purification, though the application of such approach to the synthesis of 6-oxaestrogens was not always successful [11]. Secosteroids **IVa**–**IVf** were subjected to cyclodehydration by the action of hydrochloric acid in methanol or of *p*-toluenesulfonic acid in benzene. The conditions proposed by us ensured formation of 3-methoxy-6-oxaestra-1,3,5(10),8,14-pentaen-17-ones **Va**–**Vf** as the major products, and there was no need of using preparative chromatography to isolate them (in contrast to [7]).

Of specific interest were estrogen analogs containing an α-methyl group in position *7* due to their enhanced affinity for estrogen receptors [12–14]; therefore, they can be used in the synthesis of modified androgens with improved biological properties [15–17]. In 1971, Dann and co-workers [18] reported that cyclodehydration of 3-methoxy-7-methyl-6-oxa-8(14)-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (**IIIf**) leads to formation of 3-methoxy-7-methyl-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (**Va**); however, orientation of the methyl group on C^7 in the product was not determined. It should be noted that compound **Va** was then converted into 7α-methyl-6-oxaestrone [18]. Catalytic hydrogenation of 7-methylestra-1,3,-5(10),8,14-pentaenes synthesized according to the Torgov–Ananchenko scheme always afforded steroids with α-orientation of the 7-methyl group [19–21]. We presumed that the 7-methyl group in **Va** also occupies the α-position. In order to verify this assumption we examined the structure of cyclodehydration product **Va** in crystal and in solution.

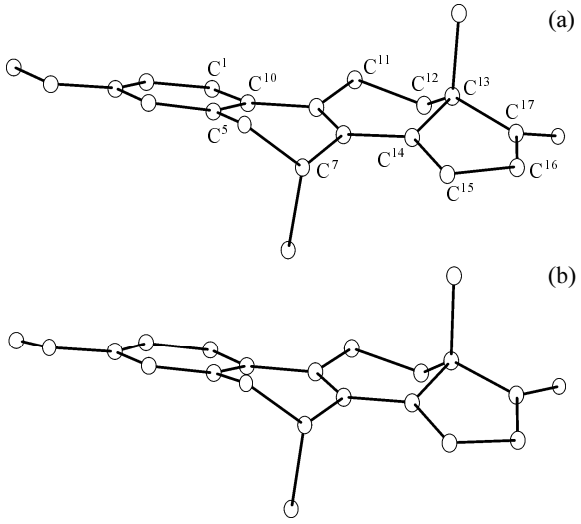
Scheme 1.



I–**III**, R^1 = Me (**a**), H (**b**); **IV**, **V**, R^1 = Me, $R^2 = R^3$ = H (**a**); $R^1 = R^2 = R^3$ = H (**b**); $R^1 = R^3$ = H, R^2 = Me (**c**); $R^1 = R^3$ = H, R^2 = Et (**d**); $R^1 = R^2 = R^3$ = H (**e**); $R^1 = R^2$ = H, R^3 = Me (**f**); **VI**, R^1 = Me, $R^2 = R^3$ = H; n = 0 (**a**–**d**), 1 (**e**, **f**).

The crystalline structure of compound **Va** is characterized by the presence of two molecules in the independent part of a unit cell. Both molecules have similar conformations which may be described as follows. The A ring is planar, and the B and C rings adopt a distorted *half-chair* conformation with pseudoaxial 7α- and 13β-methyl groups and pseudoequatorial 11β-H and 12α-H, respectively. The five-membered ring is a regular 17α-*envelope* where the C^{17}=O carbonyl group occupies the α-side of the steroid skeleton. The B and C ring junction is almost planar. Molecules *A* and *B* (see figure) differ by the position of the methoxy carbon atom with respect to the C^2–C^3 bond (*cis* arrangement in molecule *A* and *trans* in *B*); the C^{3a} atom in *A* lies in the aromatic ring plane, whereas the corresponding atom in molecule *B* deviates from that plane). In addition, the dihedral angles between the *half-chair* base and its bottom part in the B ring of molecules *A* and *B* differ by 4°. In the five-membered ring, the angle between the flap of the *envelope* and its base in molecule *A* is larger by 10° than the corresponding angle in molecule *B* (see table).

Usually, the presence of a double bond system in positions *8*(*9*) and *14*(*15*), i.e., conjugated with the aromatic A ring, strongly reduces hormonal activity of



Crystallographically independent molecules (a) *A* and (b) *B* in a unit cell of 3-methoxy-7α-methyl-6-oxaestra-1,3,5(10),-8,14-pentaen-17-one (**Va**).

Conformational parameters of independent molecules *A* and *B* in the crystalline structure of 3-methoxy-7α-methyl-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (**Va**)

Parameter	Molecule *A*	Molecule *B*
Deviations of atoms from the A ring plane, Å		
O^1	–0.02	–0.08
C^{3a}	–0.04	0.20
O^6 (C^6)	0.02	0.09
C^7	–0.62	–0.51
C^8	–0.14	–0.16
C^9	0.10	0.03
Configuration of the *B* ring (*half-chair*)	7α	6β, 7α
Dihedral angles between planes, deg		
$C^6C^5C^9C^{10}$ and $C^6C^7C^8$	44.3	39.0
$C^8C^9C^{11}C^{12}C^{14}$ and $C^{12}C^{13}C^{14}$	40.9	43.9
$C^{13}C^{14}C^{15}C^{16}$ and $C^{13}C^{16}C^{17}$	23.0	12.9
$C^6C^5C^9C^{10}$ and A ring	3.5	3.2
$C^6C^5C^9C^{10}C^8$ and $C^8C^9C^{11}C^{14}C^{12}$	3.4	7.3
$C^8C^{12}C^{14}C^{13}$ and $C^{14}C^{13}C^{15}C^{17}$	33.8	36.0
Distance O^1–O^2, Å	10.777(5)	10.814(5)

modified compounds [22, 23]. However, the conditions for binding to estrogen receptors for compound **Va** and its analogs having an axial α-methyl group on C^7 may be improved to a considerable extent; this should enhance effects mediated by estrogen receptors. To verify this assumption, we synthesized benzoate **VI** (benzoyl group was introduced to improve the solubility in olive oil which is frequently used as solvent for oral administration of drugs) and examined its effect on experimental osteoporosis in ovariectomized female rats [24]. Model steroid **VI** was administered at a dose of 5 mg/kg daily, i.e., at a dose equipotential to 0.1 mg/kg for 17α-ethynylestradiol (positive control). Compound **VI** showed the same osteoprotective effect as did the reference compound, but its influence on reduction in weight of experimental animals was much weaker (detailed information on the results of that part of the study will be reported elsewhere). Thus our results indicate prospects in searching for compounds possessing osteoprotective activity among 6-oxaestrogen analogs.

EXPERIMENTAL

The purity of all compounds was checked by TLC on Silufol plates using hexane–ethyl acetate (6:1, 4:1, and 3:1) as eluent. The mass spectra were obtained on an MX-1321 instrument (ion source temperature 200–210°C). The NMR spectra were recorded at 295 K on a Bruker DPX-300 spectrometer at a frequency of 300.130 or 75.468 MHz for ^1H and ^{13}C, respectively. The ^1H NMR spectra were obtained from solutions of 5–7 mg of a sample in 0.6 ml of $CDCl_3$, and the ^{13}C NMR spectra, from solutions of 30–50 mg of a sample in the same volume of a solvent. The chemical shifts were measured relative to the solvent signals and were referenced to TMS ($CDCl_3/CHCl_3$ 99.9 : 0.1; δ 7.26, δ_C 76.90 ppm; accuracy ±0.002 and ±0.01 ppm, respectively). Homonuclear ^1H–^1H coupling constants were measured with an accuracy of ±0.02 Hz from the ^1H NMR spectra obtained by additional processing of the free induction signal by the Lorentz–Gauss transformation and direct linear prediction procedure, as well as by enhancement of digital resolution via zero padding.

3-Methoxy-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (Vb). *a*. Compound **IIb** was synthesized from 17 g of 7-methoxychroman-4-one (**Ib**) by the procedure described in [8] and was dissolved in 75 ml of glacial acetic acid. Powdered thiourea, 7.5 g, was slowly added to the solution, the mixture was stirred for 4 h at 22–24°C, 550 ml of diethyl ether was added, and the mixture was left to stand for 8 h at 5°C. The precipitate was filtered off, washed with 100 ml of diethyl ether, and dried in air. We thus obtained 27.4 g (80%) of isothiuronium salt **IIIb** with mp 125–128°C. ^1H NMR spectrum, δ, ppm: 1.88 s (3H), 2.76 m (1H), 2.95 m (1H), 3.83 s (3H), 4.2 m (2H), 6.15 (1H), 6.44 d (1H, J = 2.5 Hz), 6.4 d (1H, J = 8.5, 2.5 Hz), 7.64 d (1H, J = 8.5 Hz). Found, %: C 55.67; H 6.27; N 8.46. $C_{15}H_{20}N_2O_4S$. Calculated, %: C 55.54; H 6.21; N 8.64.

b. A mixture of 20 g of isothiuronium salt **IIIb** and 17 g of 2-methylcyclopentane-1,3-dione in 380 ml of aqueous ethanol (1:1) was stirred for 48 h at 20–22°C. The precipitate was filtered off, dried at room temperature, and dissolved in a minimal amount of benzene. The solution was passed through a column charged with 25 g of silica gel, the column was eluted with benzene, and the eluate was evaporated to isolate 16.1 g (88%) of 3-methoxy-6-oxa-8,14-secoestra-1,3,-5(10),9(11)-tetraene-14,17-dione (**IVb**) with mp 110–111°C; published data: mp 110–111°C [7], 107–111°C [10]. ^1H NMR spectrum, δ, ppm: 1.18 s (3H), 4.14 m (2H), 5.15 m (1H), 6.39 d (1H, J = 2.5 Hz), 6.45 d.d (1H, J = 2.5, 8.5 Hz), 7.34 d (1H, J = 8.5 Hz). Found, %: C 72.15; H 6.83. $C_{18}H_{20}O_4$. Calculated, %: C 71.98; H 6.71.

c. Compound **IVb**, 10 g, was dissolved in 900 ml of benzene, 1.35 g of *p*-toluenesulfonic acid was added, and the mixture was heated for 40 min under reflux in a flask equipped with a Dean–Stark trap. The mixture was cooled, washed with an equal volume of a saturated solution of potassium hydrogen carbonate and with water until neutral reaction, and dried over sodium sulfate. The solvent was removed on a rotary evaporator, and the residue was recrystallized from ethanol. Yield of **Vb** 8.0 g (83%), mp 148–149°C; published data [8, 10]: mp 148–152°C. ^{1}H NMR spectrum, δ, ppm: 1.10 s (3H), 4.75 m (1H), 4.92 m (1H), 5.66 t (1H, J = 2.6 Hz), 6.39 d (1H, J = 2.5 Hz), 6.45 d.d (1H, J = 8.5, 2.5 Hz), 7.07 d (1H, J = 8.5 Hz). Found, %: C 76.47; H 6.55. $C_{18}H_{18}O_3$. Calculated, %: C 76.57; H 6.43.

3-Methoxy-18-methyl-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (Vc). *a*. The condensation of 0.9 g of isothiuronium salt **IIIb** with 0.9 g of 2-ethylcyclopentane-1,3-dione, following the procedure described above in *b*, gave 0.42 g (48%) of 3-methoxy-18-methyl-6-oxa-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (**IVc**) with mp 61.5–63.5°C; published data: mp 63–66°C [8], oily substance [10]. ^{1}H NMR spectrum, δ, ppm: 0.78 m (3H), 2.40 s (2H), 3.75 s (3H), 5.53 m (1H); also, signals from three protons in the aromatic region were present. Found, %: C 72.72; H 7.14. $C_{19}H_{22}O_4$. Calculated, %: C 72.59; H 7.05.

b. Compound **IVc**, 1 g, was subjected to cyclodehydration as described above for **IVb** (*c*). We isolated 0.62 g (65.8%) of compound **Vc** with mp 143–146°C [9]. ^{1}H NMR spectrum, δ, ppm: 0.84 t (3H, J = 7.5 Hz), 1.53 t (2H, J = 7 Hz), 3.72 s (3H), 4.87 d (2H, J = 7 Hz), 5.79 m (1H), 6.43–6.57 m (2H, 2-H, 4-H), 7.12 d (1H, J = 9 Hz). Found, %: C 77.07; H 6.92. $C_{19}H_{20}O_3$. Calculated, %: C 77.00; H 6.80.

18-Ethyl-3-methoxy-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (Vd). Following the above procedure, the condensation of 8 g of isothiuronium salt **IIIb** with 8 g of 2-propylcyclopentane-1,3-dione gave 5.12 g (63%) of 18-ethyl-3-methoxy-6-oxa-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (**IVg**), mp 39–43°C. ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, J = 7 Hz), 2.40 s (4H), 3.75 s (3H), 5.53 m (1H), 6.19–6.41 m (2H), 7.11 d (1H, J = 8.7 Hz). Found, %: C 73.10; H 7.39. $C_{20}H_{24}O_4$. Calculated, %: C 73.15; H 7.37.

Compound **IVd**, 1 g, was subjected to cyclodehydration, and the product was purified by recrystallization from methanol. Yield 0.71 g (75%), mp 92–95°C. ^{1}H NMR spectrum, δ, ppm: 0.83 m (3H), 3.73 s (3H), 4.82 d (2H, J = 9 Hz), 5.7 t (1H, J = 4 Hz), 6.29–6.45 m (2H), 7.11 d (1H, J = 9 Hz). Found, %: C 77.14; H 7.31. $C_{20}H_{22}O_3$. Calculated, %: C 77.39; H 7.14.

3-Methoxy-6-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (Ve). The condensation of 30 g of isothiuronium salt **IIIb** with 25 g of 2-methylcyclohexane-1,3-dione, followed by recrystallization from ethanol gave 23.8 g (78%) of 3-methoxy-6-oxa-D-homo-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17a-dione (**IVe**) with mp 84.5–85.5°C. ^{1}H NMR spectrum, δ, ppm: 1.28 s (3H), 3.74 s (3H), 4.15 m (2H), 5.60 t (1H); also, signals from three protons in the aromatic region were present. Found, %: C 72.56; H 7.13. $C_{19}H_{22}O_4$. Calculated, %: C 72.59; H 7.05.

Compound **IVe**, 10 g, was subjected to cyclodehydration according to the above procedure. After appropriate treatment, the product was recrystallized from ethanol. Yield of **Ve** 7.7 g (81%), mp 158–160.5°C; published data [25]: 158.5–161°C. ^{1}H NMR spectrum, δ, ppm: 1.22 s (3H), 3.82 s (3H), 4.84 m (2H), 5.72 m (1H), 6.44 d (1H, J = 2.5 Hz), 6.64 m (1H, J = 2.5, 8 Hz), 7.20 d (1H, J = 8 Hz). Found, %: C 77.00; H 6.80. $C_{19}H_{20}O_3$. Calculated, %: C 76.88; H 6.84.

3-Methoxy-16,16-dimethyl-6-oxa-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (Vf). The condensation of 4.75 g of isothiuronium salt **IIIb** with 4.5 g of 2,5,5-trimethylcyclohexane-1,3-dione gave 4.08 g (86.6%) of compound **IVf** with mp 84.5–86°C. ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H), 0.99 s (3H), 1.27 s (3H), 3.73 s (3H), 4.16 m (2H), 5.62 m (1H); also, signals from three protons in the aromatic region were present. Found, %: C 73.50; H 7.81. $C_{21}H_{26}O_4$. Calculated, %: C 73.66; H 7.65.

Compound **IVf**, 4 g, was subjected to cyclodehydration according to the above procedure to obtain 3.6 g (95%) of steroid **Vf** with mp 90–92°C [25]. ^{1}H NMR spectrum, δ, ppm: 1.04 s (3H), 1.19 s (3H), 1.25 s (3H), 3.78 s (3H), 4.1 m (2H), 5.62 m (1H); also, signals from three protons in the aromatic region were present. Found, %: C 77.32; H 7.28. $C_{21}H_{24}O_3$. Calculated, %: C 77.39; H 7.14.

3-Methoxy-7α-methyl-6-oxaestra-1,3,5(10),8,14-pentaen-17-one (Va). Compound **IIa** prepared from 20 g of 7-methoxy-2-methylchroman-4-one (**Ia**) as described in [8] was brought into reaction with thiourea in acetic acid to obtain 20.6 g (58.5%) of *S*-[2-(7-methoxy-2-methylchroman-4-ylidene)ethyl]isothiuronium acetate (**IIIa**). mp 127–133°C. ^{1}H NMR spectrum, δ, ppm: 1.34 d (3H, J = 6 Hz), 1.80 s (3H), 3.71 s (3H), 4.10 m (1H), 5.99 t (1H, J = 7.7 Hz), 6.47 d

(1H, J = 2.4 Hz), 6.49 d.d (1H, J = 9, 2.4 Hz), 7.49 d (1H, J = 9 Hz). Found, %: C 56.43; H 6.69; N 8.26. $C_{16}H_{22}N_2O_4S$. Calculated, %: C 56.79; H 6.55; N 8.28.

The condensation of 3.2 g of isothiuronium salt **IIIa** with 3 g of 2-methylcyclopentane-1,3-dione gave 2.75 g (92.5%) of compound **IVa** with mp 99–100°C; published data [11]: mp 99.5–101.5°C. ^{1}H NMR spectrum, δ, ppm: 1.18 s (3H), 1.43 d (3H, J = 6 Hz), 3.80 s (3H), 4.1 m (1H), 5.68 m (1H); also, signals from three protons in the aromatic region were present. Found, %: C 72.47; H 6.90. $C_{19}H_{22}O_4$. Calculated, %: C 72.59; H 7.05.

Compound **IVa**, 1 g, was dissolved in 25 ml of methanol, 1 ml of concentrated hydrochloric acid was added, and the mixture was stirred for 24 h at room temperature. The precipitate was filtered off, washed with cold methanol, and recrystallized from chloroform–methanol. Yield of **Va** 0.65 g (69%), mp 138–139°C. ^{1}H NMR spectrum, δ, ppm: 1.13 s (3H), 1.37 d (3H, J = 6.5 Hz), 3.79 s (3H), 5.10 m (1H), 5.66 m (1H), 6.45–6.51 m (2H), 7.16 d (1H, J = 8.5 Hz). ^{13}C NMR spectrum, δ, ppm: 124.00 (C^1), 106.6 (C^2), 160.6 (C^3), 102.1 (C^4), 152.9 (C^5), 71.2 (C^7), 122.1 (C^8), 126.2 (C^9), 115.3 (C^{10}), 20.7 (C^{11}), 26.3 (C^{12}), 48.3 (C^{13}), 143.2 (C^{14}), 113.6 (C^{15}), 41.4 (C^{16}), 218.4 (C^{17}), 20.3 (C^{18}), 19.8 (C^{7a}). Mass spectrum, m/z (I_{rel}, %): 296 (90), 281 (100), 268 (15), 253 (100), 237 (7), 225 (6), 211 (7.5), 178 (5), 165 (11), 152 (8). Found, %: C 76.92; H 6.86. $C_{19}N_{20}O_3$. Calculated, %: C 77.00; H 6.80.

Colorless transparent crystals of **Va** for X-ray analysis (isometric pseudohexagonal prisms) were obtained from a solution in hexane. The structure was solved by the direct methods and was refined with account taken of anisotropy of thermal oscillations of non-hydrogen atoms. The positions of all hydrogen atoms were calculated from the geometry considerations. Absorption by the crystal was not taken into account. The calculations were performed using CSD [26] and SHELXL-97 software packages [27]. The coordinates and thermal parameters U_{eq} of the base atoms, anisotropic thermal parameters of non-hydrogen atoms, and coordinates of hydrogen atoms are available from the authors. A three-dimensional set of 7338 nonzero independent reflections was acquired on a Bruker SMART 1000 CCD automatic diffractometer. Principal crystallographic data: $C_{19}H_{20}O_3$, M 296.35; space group $P2_1/n$; unit cell parameters: a = 11.1246(11), b = 10.5566(10), c = 26.540(3) Å; α = 90, β = 93.643(3), γ = 90°; V = 3110.5(5) Å^3; Z = 8 (two molecules in the independent part of a unit cell); d_{calc} = 1.266 g/cm^3; absorption coefficient 0.084 mm^{-1}; F(000) = 1264; crystal habit 0.36 × 0.22 × 0.14 mm; Θ range 1.94–28.31°; index range $-14 \le h \le 13$, $-14 \le k \le 11$, $-35 \le l \le 32$; number of reflections (total/independent) 18660/7338 (R_{int} = 0.2033); R = 0.042 (F), wR = 0.1006 (F^2); residual electron density 0.146 Å^{-3}.

17β-Benzoyloxy-3-methoxy-7α-methyl-6-oxaestra-1,3,5(10),8,14-pentaene (VI). Compound **Va**, 1 g, was dissolved in a mixture of 20 ml of dioxane and 2 ml of water, 1 g of sodium tetrahydridoborate was added, and the mixture was stirred until the initial compound disappeared (according to the TLC data; hexane–ethyl acetate, 7:3). Excess reducing agent was decomposed by slowly adding acetic acid until the mixture no longer foamed. After appropriate treatment, the product was dissolved in 5 ml of pyridine, 1.5 ml of benzoyl chloride was added, and the mixture was stirred for 24 h at room temperature and poured into 150 ml of water under vigorous stirring. The precipitate was filtered off, dried in air, and recrystallized from methanol. Yield 1.2 g (85%), mp 151–153°C. Mass spectrum, m/z (I_{rel}, %): 402 (10.5) $[M]^+$, 387 (8.5), 280 (100), 265 (99), 253 (15.5), 105 (92). Found, %: C 77.42; H 6.70. $C_{26}H_{26}O_4$. Calculated, %: C 77.59; H 6.70.

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