Russian Journal of Organic Chemistry, Vol. 40, No. 4, 2004, pp. 506–512. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 4, 2004, pp. 537–543.

Synthesis and Study of Equilenin Derivatives and Modified Analogs

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Received July 17, 2003

Abstract—Modified equilenin analogs were synthesized with a view to examine the relation between the structure and biological properties of steroid estrogens. The ^{1}H and ^{13}C NMR signals of six estra-1,3,5,7,9-pentaenes were completely assigned using homo- and heteronuclear correlation NMR spectroscopy. The structure of equilenin methyl ester was determined by X-ray analysis. Among the synthesized steroids, compounds were found which exhibit hypocholesterinemic activity with no uterotropic and hypertriglyceridemic effects.

Analogs of steroid estrogens possessing hypocholesterinemic activity attract interest from the viewpoint of developing on their base of preparations for treatment and prophylactics of cardiovascular diseases [1]. A necessary conditions for preliminary selection of new compounds for detailed biological studies is the lack of both uterotropic effect (which is considered to be a factor favoring carcinogenesis [2]) and the ability to increase the concentration of triglycerides in blood [3–6].

As model compounds for study of the relations between the structure and biological properties of steroid estrogens we selected analogs of equilenin, taking into account that the latter exhibits no carcinogenic properties [7]. Moreover, equilenin has been proposed to use for prophylactics of mammary gland carcinoma [8]. We have synthesized racemic steroids, keeping in mind that modified estrogens of the L-series are specific estrogen receptor modulators [9–11] and that they may attract a stronger interest from the viewpoint of medicine.

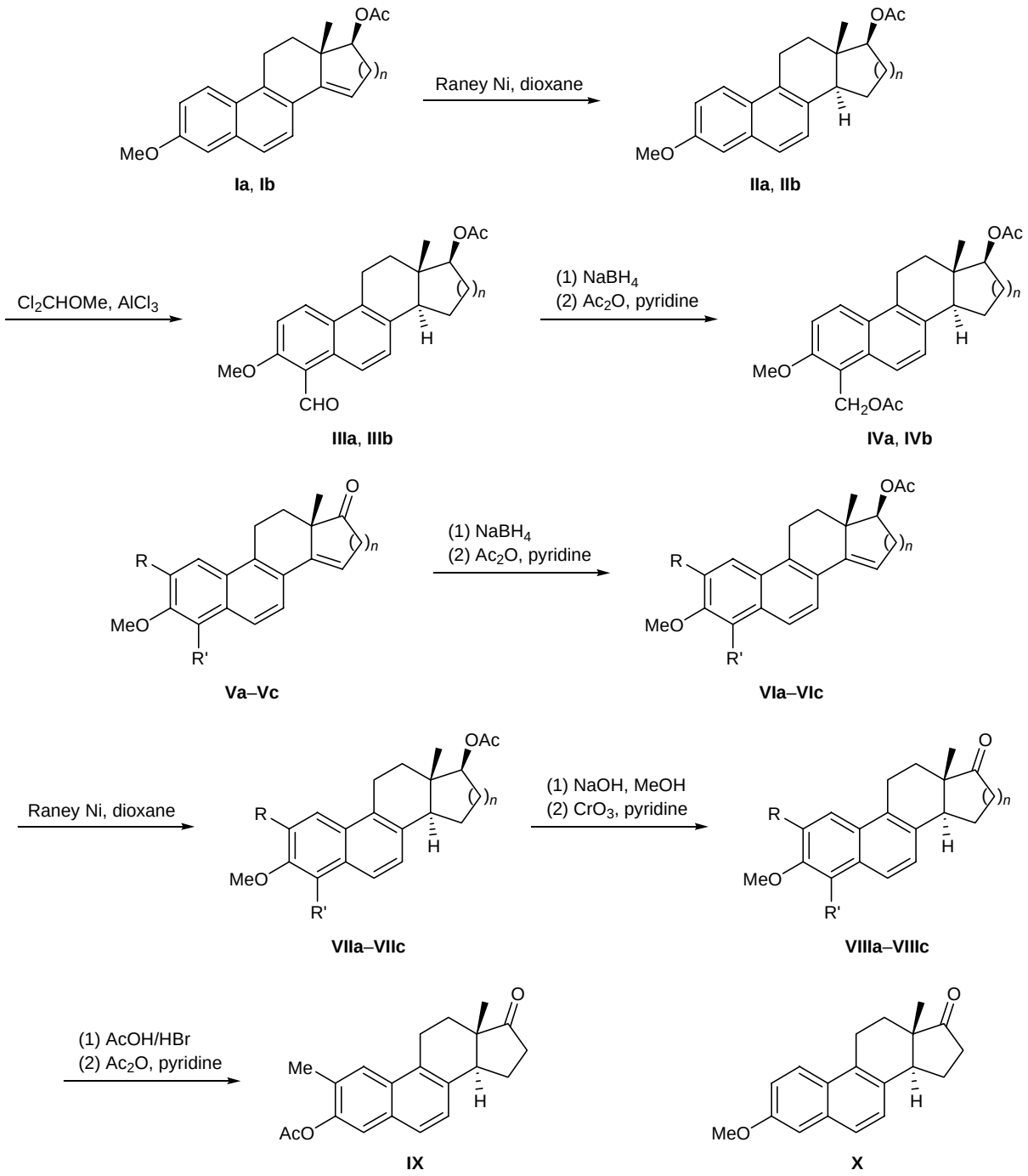
The simplest route to modified equilenin analogs consists of reduction with Raney nickel of estrapentaenes prepared according to Torgov–Ananchenko [12, 13]. The choice of modification, i.e., introduction of substituents into positions *2* and *4* and/or ring D expansion, was dictated by the fact that just in these cases we can expect reduced hormonal action of steroids having a topology related to the natural hormone estradiol [14, 15]. Scheme 1 illustrates the synthesis of model compounds.

Using homo- and heteronuclear correlation techniques (DQF-COSY [16], HSQC [17], COLOC [18], and NOESY [19]), we performed a detailed analysis of scalar and direct (through space) dipole–dipole interactions in the ^{1}H and ^{13}C NMR spectra of six equilenin analogs. No extensive studies in this line were performed previously (as far as we know, complete assignment of the ^{13}C NMR signals of two equilenin derivatives has been reported only in a single publication [20]). The results of signal assignment are given in Tables 1 and 2.

Also, we have found no published data on X-ray diffraction studies of equilenin derivatives. Therefore, we tried to fill this gap by examining the crystalline structure of racemic equilenin methyl ester **X**. The structure was solved by the direct method and was refined with account taken of anisotropy of thermal vibrations of non-hydrogen atoms. The positions of hydrogen atoms were calculated from the geometry considerations. No absorption by the sample was taken into account. The calculations were performed using CSD [21] and SHELXL 97 software packages [22].

Table 3 contains the coordinates and thermal parameters of the basis atoms in molecule **X**. The A and B rings are planar. The methoxy carbon atom is located *trans* with respect to the C^2–C^3 bond. The oxygen atom at C^3 lies almost in the A ring plane, and the methyl carbon atom deviates from that plane by only –0.18 Å. The angle between the A and B ring planes is 2.0°. The C ring is a regular 13β-*half-chair* where the angle between the planes formed by the

Scheme 1.



I–**IV**: *n* = 1 (**a**), 2 (**b**); **V**–**VIII**: R = Me, R' = H, *n* = 1 (**a**); R = Me, R' = H, *n* = 2 (**b**); R = H, R' = Me, *n* = 1 (**c**).

$C^8C^9C^{11}C^{12}C^{14}$ atoms (*chair-bottom*) and $C^{12}C^{13}C^{14}$ (*chair hack*) is 127.5°. The D ring is an almost regular 14α-*envelope* where the angle between the $C^{13}C^{15}C^{16}C^{17}$ (*base*) and $C^{13}C^{14}C^{15}$ (*flap*) planes is 138.7°. On the whole, the molecule is essentially planar: the aromatic ring with the *chair-bottom* plane in the C ring forms an angle of 4.3°, and with the *envelope base* plane in the D ring, 9.0°. The distance between the oxygen atoms at C^3 and C^{17} (which is important for binding with estrogen receptors) is 10.802(5) Å. The corresponding distance in the molecule of estradiol, which is the most active natural

Table 1. Carbon chemical shifts (δ_C, ppm) in the ^{13}C NMR spectra of modified equilenin analogs **IIa**, **IIb**, **VIIa**, **VIIc**, **VIIIb**, and **X**

Carbon atom	**IIa**	**IIb**	**VIIa**	**VIIc**	**VIIIb**	**X**
1	124.7	125.6	124.3	122.1	124.2	125.4
2	118.2	118.2	128.0	113.3	128.1	118.6
3	156.6	156.6	155.8	153.4	156.1	156.8
4	106.4	106.1	105.0	119.6	104.6	106.6
5	133.2	132.8	131.8	132.2	131.7	131.1
6	125.0	124.5	124.0	121.5	124.8	125.4
7	125.0	124.5	124.7	124.7	124.3	124.3
8	133.1	132.5	133.7	132.7	131.4	133.5
9	130.3	130.3	129.5	130.4	129.2	130.8
10	127.2	127.3	127.0	127.3	126.9	127.3
11	24.1	22.7	24.2	24.2	22.8	23.8
12	34.0	33.3	33.9	34.0	29.0	29.0
13	42.4	36.8	42.8	42.3	46.9	47.4
14	46.1	45.0	46.3	46.0	45.4	46.7
15	23.5	24.7	23.4	23.4	23.6	21.8
16	28.2	23.8	31.2	28.2	25.5	36.5
17	81.7	26.2	80.9	81.7	36.8	219.8
17a	–	80.2	–	–	215.5	–
18	11.1	10.4	10.1	11.1	15.6	13.0
2-CH_3		–	–	–	17.1	–
4-CH_3			–	10.6	–	–
CH_3O	55.1	55.1	55.1	56.5	55.0	55.2
CH_3CO	21.0	21.1	–	21.0	–	–
CH_3**C**O	171.1	170.9	–	171.1	–	–

estrogen, is 10.93 Å [23]. The structure of molecule **X** is shown in figure. The obtained X-ray diffraction data can be used for simulation of structures of equilenin complexes with various receptors and enzymes responsible for metabolism of steroids.

Oral administration of compounds **IIb** and **VIIa** in peach oil to ovariectomated rats at a dose of 5 mg/kg per day over a period of 35 days normalizes the concentration of cholesterol in blood serum. Neither **IIb** nor **VIIa** showed uterotropic or hypertriglyceridemic activity. Thus equilenin analogs **IIb** and **VIIa** exhibit better biological properties than most known compounds of this series [24]. Steroids **IIIa**, **IIIb**, **IVa**, **IVb**, and **VIIb** having a substituent in position *4* showed no biological activity. Nevertheless, they may be of interest as starting materials for the synthesis of potential estrone sulfatase inhibitors, for equilenin analogs turned out to be strong inhibitors of that enzyme [25].

EXPERIMENTAL

All the prepared compounds were racemic. Their purity was checked by high-performance liquid chromatography (HPLC) on an Altex chromatograph; gradient elution with acetonitrile–water (80 to 95%), 15 min; columns: A (Lichrosorb RP-18, 5 μm, Merck), B (Ultrasphere ODS, 5 μm, Beckman), and C (ISCO C-8/6.5 μm, 4.6×250 mm).

The mass spectra were recorded on an MKh-1321 spectrometer (ion source temperature 200–210°C). The NMR spectra were obtained at 295 K on a Bruker DPX-300 instrument at 300.130 and 75.468 MHz for ^1H and ^{13}C, respectively. The ^1H NMR spectra were measured from solutions of 5–7 mg of a substance in 0.6 ml of $CDCl_3$, and the ^{13}C NMR spectra were obtained from solutions containing 30–50 mg of a substance in the same volume of a solvent. The chemical shifts were measured relative to TMS using the solvent signals as internal reference ($CDCl_3$–$CHCl_3$, 99.9:0.1; δ 7.26 ppm, δ_C 76.90 ppm; accuracy ±0.01 ppm). The homonuclear coupling constants were determined with an accuracy of ±0.02 Hz from the ^1H NMR spectra processed by the Lorentz–Gauss transformation.

17β-Acetoxy-3-methoxyestra-1,3,5,7,9-pentaene (IIa). To a solution of 2 g of compound **Ia** [26] in 50 ml of dioxane we added 10 g of Raney nickel prepared at 60°C and thoroughly washed from isopropyl alcohol (under a layer of which it was stored). The mixture was stirred for 8 h at 70°C, the catalyst was filtered off, and the filtrate was evaporated on a rotary evaporator. The product was purified by recrystallization from chloroform–ethanol (1:5). Yield 1.1 g (55%), mp 201–203°C. Retention time 8.7 min (column A), purity >99.5%. Found, %: C 77.97; H 7.46. $C_{21}H_{24}O_3$. Calculated, %: C 77.75; H 7.46.

17aβ-Acetoxy-3-methoxy-D-homoestra-1,3,5,7,9-pentaene (IIb) was synthesized from 3.53 g of compound **Ib** [27] as described above for steroid **IIa**. Yield 2.74 g (77%), mp 198–199°C. Retention time 6.7 min (column A), purity >99.5%. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (100) $[M]^+$, 278 (5), 277 (4.5), 263 (12), 249 (2.5), 223 (9.5), 211 (19,5), 197 (5), 171 (9). Found, %: C 78.09; H 7.75. $C_{22}N_{26}O_3$. Calculated, %: C 78.07; H 7.74.

17β-Acetoxy-4-formyl-3-methoxyestra-1,3,5,7,9-pentaene (IIIa). To a solution of 0.85 g of compound **IIa** and 1.5 g of aluminum chloride in 30 ml of nitrobenzene we added 1.3 ml of α,α-dichlorodimethyl ether in 10 ml of nitrobenzene, and the mixture was left to stand for 12 h in a flask capped with a drying tube. Water, 150 ml, was added, the aqueous phase was separated, and nitrobenzene was removed by steam distillation. After appropriate treatment, compound **IIIa** was purified by double recrystallization from chloroform–methanol. Yield 0.45 g (49%), mp 225–230°C. Retention time 8.4 min (column C), purity >99.5%. ^{1}H NMR spectrum, δ, ppm: 0.74 s (3H), 2.11 s (3H), 4.04 s (3H), 4.89 m (1H), 7.28 m (2H), 8.20 d (1H), 9.12 d (1H), 10.85 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 11.1, 21.0, 23.3, 24.2, 28.2, 34.0, 42.3, 46.1, 56.4, 81.5, 112.2, 116.9, 122.9, 126.9, 128.4, 130.2, 130.4, 132.4, 134.4, 170.0. Mass spectrum, *m*/*z* (I_{rel}, %): 352 (100), 309 (2.5), 291 (11), 277 (15), 266 (3.5), 251 (17), 199 (14), 165 (9). Found, %: C 74.89; H 6.96. $C_{22}H_{24}O_4$. Calculated, %: C 74.98; H 6.86.

17aβ-Acetoxy-4-formyl-3-methoxy-D-homoestra-1,3,5,7,9-pentaene (IIIb) was synthesized from 1.6 g of compound **IIb** as described above for **IIIa**. The product was purified by double recrystallization from chloroform–methanol (5:1). Yield 1.1 g (63.5%), mp 241–246°C. ^{1}H NMR spectrum, δ, ppm: 0.83 s (3H), 2.09 s (3H), 4.05 s (3H), 4.75 m (1H), 7.29 d (1H), 7.55 d (1H), 8.27 d (1H), 9.10 d (1H), 10.86 s (1H). ^{13}C NMR spectrum, δ_C, ppm: 10.4, 21.1, 22.9, 23.6, 23.7, 26.2, 33.3, 36.6, 44.9, 56.3, 80.1, 112.1, 116.7, 122.8, 127.0, 128.0, 130.0, 130.4, 132.3, 133.7, 162.9, 170.8, 191.9. Mass spectrum, *m*/*z* (I_{rel}, %): 366 (100), 322 (3.5), 304 (5.5), 291 (11), 277 (3.5), 251 (8.5), 239 (18), 225 (4), 199 (7), 165 (8). Found, %: C 75.49; H 7.01. $C_{23}H_{26}O_4$. Calculated, %: C 75.38; H 7.15.

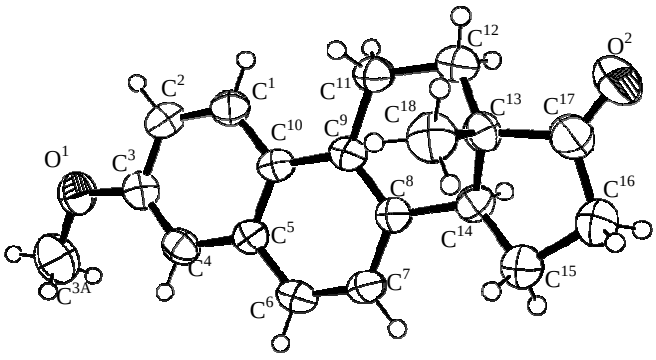
17β-Acetoxy-4-acetoxymethyl-3-methoxyestra-1,3,5,7,9-pentaene (IVa). To a solution of 0.15 g of compound **IIIa** in 10 ml of a 10:1 dioxane–water mixture we added 0.08 g of sodium tetrahydridoborate, the mixture was stirred for 30 min, and excess reducing agent was decomposed with acetic acid. The mixture was diluted with 100 ml of water, and 100 ml of diethyl ether was added. The subsequent treatment of the mixture and acetylation of the product were performed according to standard procedures. Recrystallization from chloroform–ethanol gave 0.075 g (44%) of compound **IVa** with mp 169.5–171.5°C.

Table 2. Proton chemical shifts in the ^{1}H NMR spectra of estra-1,3,5,7,9-pentaenes **IIa**, **IIb**, **VIIa**, **VIIb**, **VIIIa**, and **X**

Hydrogen atom	IIa	IIb	VIIa	VIIb	VIIIa	IX
1	7.87	7.91	7.71	7.85	7.75	7.87
2	7.18	7.18	–	7.28	–	7.18
4	7.13	7.11	7.06	–	7.06	7.13
6	7.59	7.58	7.56	7.83	7.60	7.64
7	7.17	7.40	7.11	7.23	7.37	7.27
11α	3.27	3.20	3.29	3.32	3.27	3.33
11β	3.20	3.08	3.22	3.22	3.12	3.33
12α	1.81	1.67	1.70	1.79	1.83	1.91
12β	2.22	2.03	2.20	2.13	2.37	2.21
14α	2.88	2.69	2.81	2.91	2.94	3.17
15α	2.16	2.55	2.17	2.25	2.51	2.55
15β	1.79	1.38	1.78	1.78	1.89	2.05
16α	2.46	1.64	2.36	2.48	1.90	2.34
16β	1.83	2.08	1.68	1.80	2.33	2.70
17α	4.92	1.87	4.95	4.91	2.80	
17β		1.70			2.38	
17aα		4.75			4.74	
13-CH_3	0.77	0.87	0.71	0.76	1.05	0.81
2-CH_3			2.41		2.44	
4-CH_3				2.56		
CH_3O	3.92	3.92	3.94	3.95	3.95	3.92
CH_3CO	2.11	2.12	2.11	2.11		

Found, %: C 72.63; H 7.26. $C_{24}H_{28}O_5$. Calculated, %: C 72.66; H 7.17.

17aβ-Acetoxy-4-acetoxymethyl-3-methoxy-D-homoestra-1,3,5,7,9-pentaene (IVb) was synthesized from 0.5 g of steroid **IIIb** as described above for **IVa**. Yield 0.37 g (66%), mp 147.5–149.5°C. Retention time 7.3 min (column A), purity 99%. ^{1}H NMR



Structure of the molecule of equilenin methyl ether (**X**) in crystal according to the X-ray diffraction data.

Table 3. Coordinates ($\times 10^4$) and thermal parameters ($Å^2 \times 10^3$) of basis atoms in molecule **X** (U_{eq} is equal to 1/3 of the sum of the projections of the U_{ij} tensor onto the orthogonal axes)

Atom	*x*	*y*	*z*	U_{eq}
O^1	–3982(2)	–3103(1)	–3625(1)	65(1)
O^2	–3810(2)	919(1)	–7506(1)	91(1)
C^1	–4837(3)	–2173(2)	–5025(1)	46(1)
C^2	–4819(3)	–2713(2)	–4550(1)	50(1)
C^3	–3880(3)	–2493(2)	–4069(1)	46(1)
C^{3A}	–3257(3)	–2863(2)	–3095(1)	84(1)
C^4	–3001(3)	–1740(2)	–4070(1)	45(1)
C^5	–3003(3)	–1161(2)	–4560(1)	38(1)
C^6	–2144(3)	–362(2)	–4564(1)	47(1)
C^7	–2168(2)	191(1)	–5035(1)	44(1)
C^8	–3043(3)	–29(2)	–5530(1)	39(1)
C^9	–3914(2)	–811(2)	–5548(1)	38(1)
C^{10}	–3917(3)	–1381(2)	–5055(1)	38(1)
C^{11}	–4822(3)	–1086(1)	–6083(1)	49(1)
C^{12}	–4811(3)	–420(2)	–6592(1)	53(1)
C^{13}	–3301(3)	106(2)	–6608(1)	45(1)
C^{14}	–3123(3)	601(1)	–6034(1)	43(1)
C^{15}	–1859(3)	1301(2)	–6144(1)	58(1)
C^{16}	–2238(3)	1622(2)	–6757(1)	63(1)
C^{17}	–3211(3)	884(2)	–7032(1)	59(1)
C^{18}	–1878(3)	–497(2)	–6743(1)	61(1)

spectrum, δ, ppm: 0.90 s (3H), 2.08 s (3H), 2.13 s (3H), 3.96 s (3H), 4.75 m (1H), 5.67 s (2H); in addition, signals from four protons were present in the aromatic region. ^{13}C NMR spectrum, δ_C, ppm: 10.4, 20.9, 21.1, 22.8, 23.6, 23.7, 26.2, 33.3, 45.0, 56.6, 57.2, 80.1, 112.8, 116.1, 121.1, 125.4, 126.0, 127.4, 130.7, 131.7, 132.6, 155.3, 170.8, 171.3. Mass spectrum, *m*/*z* (I_{rel}, %): 410 (100), 367 (5), 351 (33), 335 (2), 307 (10), 296 (4), 283 (4), 275 (2), 237 (4), 207 (3.5), 191 (3.5), 178 (4), 165 (4), 153 (5.5). Found, %: C 73.01; H 7.47. $C_{25}H_{30}O_5$. Calculated, %: C 73.15; H 7.37.

17β-Acetoxy-3-methoxy-2-methylestra-1,3,-5(10),8,14-pentaene (VIa). A 3-g portion of 3-methoxy-2-methylestra-1,3,5(10),8,14-pentaene (**Va**), synthesized according to Torgov–Ananchenko [28], was reduced with sodium tetrahydridoborate, followed by acetylation with acetic anhydride in pyridine. Recrystallization from methanol gave 2.65 g (76.8%) of compound **VIa** with mp 123.5–124.5°C. ^1H NMR spectrum, δ, ppm: 1.00 s (3H, $C^{18}H_3$), 2.12 s (3H, CH_3CO), 2.22 s (3H, 2-CH_3), 3.85 s (3H, CH_3O), 5.05 d.d (1H, 17-H, $J_1 = J_2 = 8.4$ Hz), 5.49 br.s (1H, 15-H), 6.66 s and 7.10 s (1H each, 2-H, 1-H). Found, %: C 78.01; H 7.75. $C_{22}H_{26}O_3$. Calculated, %: C 78.07; H 7.74.

17β-Acetoxy-3-methoxy-2-methylestra-1,3,5,7,9-pentaene (VIIa). To a solution of 2 g of compound **VIa** in 50 ml of dioxane we added 10 g of Raney nickel, and the mixture was stirred for 8 h at 70°C. After appropriate treatment, the product was recrystallized from chloroform–ethanol (1:5). Yield 0.90 g, mp 172–182°C. Retention time 11.0 min (column A), purity 99.6%. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (100) $[M]^+$, 295 (4), 277 (5), 263 (19.5), 247 (4.5), 237 (14), 225 (7.5), 185 (15.5), 165 (5), 152 (2). Found, %: C 78.01; H 7.87. $C_{22}H_{26}O_3$. Calculated, %: C 78.07; H 7.74.

17aβ-Acetoxy-3-methoxy-2-methyl-D-homoestra-1,3,5(10),8,14-pentaene (VIb) was synthesized from 4.32 g of estrapentaene **Vb** (prepared according to Torgov–Ananchenko [29]) by reduction with sodium tetrahydridoborate in dioxane–water (10:1) and subsequent acetylation with acetic anhydride in pyridine under the conditions recommended in [30]. Recrystallization from chloroform–ethanol (1:4) gave 2.9 g (59%) of compound **VIb** with mp 187–191°C. ^1H NMR spectrum, δ, ppm: 1.08 s (3H, $C^{18}H_3$), 2.11 s (3H, CH_3CO), 2.22 s (3H, 2-H), 3.87 s (3H), 4.85 m (1H, 17-H), 5.78 (1H, 15-H, $J = 3.9$ Hz), 6.69 s (1H, 4-H), 7.16 s (1H, 1-H). Found, %: C 78.58; H 7.95. $C_{23}H_{28}O_3$. Calculated, %: C 78.38; H 8.01.

17aβ-Acetoxy-3-methoxy-2-methyl-D-homoestra-1,3,5,7,9-pentaene (VIIb). Estrapentaene **VIb**, 1.75 g, was converted into steroid **VIIb** as described above for compound **Va**. Recrystallization from chloroform–ethanol (1:5) gave 1.26 g (72%) of compound **VIIb** with mp 191.5–194°C. Mass spectrum, *m*/*z* (I_{rel}, %): 352 (100) $[M]^+$, 309 (1.5), 292 (6), 277 (13), 238 (8), 237 (8), 223 (5.5), 185 (18). Found, %: C 78.22; H 8.19. $C_{23}H_{28}O_3$. Calculated, %: C 78.38; H 8.01.

17β-Acetoxy-3-methoxy-4-methyl-1,3,5,7,9-estrapentaene (VIIc). Compound **Vc** [31], 1.4 g, was reduced with sodium tetrahydridoborate, followed by acetylation with acetic anhydride in pyridine. Acetate **VIc** thus obtained [31] was recrystallized from methanol and treated with Raney nickel as described above for the synthesis of steroid **IIa**. Recrystallization from chloroform–methanol gave 0.90 g (60%) of com-

pound **VIIc** with mp 185–192°C. Mass spectrum, *m*/*z* (I_{rel}, %): 338 (100), 323 (2), 295 (3), 277 (5), 263 (12), 247 (3), 237 (8), 225 (5), 185 (9). Found, %: C 77.93; H 7.88. $C_{22}H_{26}O_3$. Calculated, %: C 78.07; H 7.74.

2-Methylequilenin methyl ester (VIIIa). To a solution of 10 g of acetoxy derivative **VIIa** in 40 ml of benzene we added a solution of 25 g of sodium hydroxide in 350 ml of methanol, and the mixture was heated for 2.5 h under reflux and was poured into water. The oily material was treated with ethyl acetate, and the organic phase was washed with water until neutral reaction and dried over sodium sulfate. The hydrolysis product was dissolved in 50 ml of pyridine, and the Sarett reagent prepared from 5.5 g of chromium(VI) oxide and 100 ml of pyridine was slowly added under vigorous stirring. The mixture was left to stand for 12 h, and excess oxidant was decomposed with methanol. After appropriate treatment [29], the product was recrystallized from chloroform–methanol. Yield 5.9 g (68%), mp 205–210°C. Retention time 7.1 min (column A), 9.31 min (C), purity >99.5%. Mass spectrum, *m*/*z* (I_{rel}, %): 294 (100), 279 (13), 266 (13), 251 (35), 238 (24), 225 (22), 210 (6), 195 (5), 178 (7), 165 (9), 152 (5). ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H), 2.43 s (3H), 3.92 s (3H); signals from four protons were observed in the aromatic region. ^{13}C NMR spectrum, δ_C, ppm: 12.9, 17.2, 21.7, 23.8, 29.0, 36.4, 46.6, 47.4, 55.1, 105.0, 123.1, 124.2, 124.9, 127.0, 128.4, 129.9, 131.9, 132.2, 156.0, 219.9. Found, %: C 81.44; H 7.72. $C_{20}H_{22}O_2$. Calculated, %: C 81.60; H 7.53.

3-Methoxy-2-methyl-D-homoestra-1,3,5,7,9-pentaen-17a-one (VIIIb) was synthesized from 0.97 g of acetate **VIIb** as described above for compound **VIIIa**. Yield 0.7 g (82%), mp 206–210°C. Mass spectrum, *m*/*z* (I_{rel}, %): 308 (100) $[M]^+$, 293 (28), 280 (4), 265 (9.5), 252 (8.5), 237 (15.5), 225 (34), 210 (4), 195 (3.5), 185 (18). Found, %: C 81.67; H 7.92. $C_{21}H_{24}O_2$. Calculated, %: C 81.78; H 7.78.

3-Acetoxy-2-methylestra-1,3,5,7,9-pentaen-17-one (IX). To a solution of 1 g of steroid **VIIIa** in 30 ml of acetic acid we added 15 ml of 48% hydrobromic acid, and the mixture was heated for 5 h under reflux and was then poured into 200 ml of water. The precipitate was filtered off, washed with water until neutral washings, and dried in air. The product was dissolved in a mixture of 20 ml of acetic anhydride and 50 ml of pyridine, and the mixture was left to stand for 72 h at room temperature. After appropriate treatment, recrystallization from ethanol gave 280 mg (25.5%) of steroid **IX** with mp 191–194°C (decomp). Retention time 4.6 min (column A), purity 98.7%. Mass spectrum, *m*/*z* (I_{rel}, %): 322 (26), 280 (100), 265 (9), 252 (10), 237 (20), 224 (15), 223 (14), 211 (15), 195 (6), 178 (6), 165 (8), 152 (5). ^{1}H NMR spectrum, δ, ppm: 0.92 s (3H), 2.35 s (6H), 7.25 d (1H), 7.57 s (1H), 7.62 d (1H), 7.81 s (1H). ^{13}C NMR spectrum, δ, ppm: 13.0, 17.0, 20.7, 21.7, 23.9, 28.9, 36.4, 46.7, 47.3, 119.5, 123.6, 125.0, 125.9, 130.1, 130.3, 131.5, 134.1, 169.3, 219.5. Found, %: C 78.17; H 7.05. $C_{21}H_{22}O_3$. Calculated, %: C 78.23; H 6.88.

Equilenin methyl ether (X) was synthesized from 1.4 g of acetate **IIa** by alkaline hydrolysis and subsequent oxidation with the Sarett reagent under standard conditions [30]. Yield 0.84 g (69%), mp 202–205°C; published data: mp 185°C [32], 187°C [33].

Crystals of **X** suitable for X-ray analysis were obtained from a solution in hexane. Orthorhombic system, space group *Pbca*; unit cell parameters: a = 8.5150(12), b = 14.949(2), c = 23.120(3) Å; α = β = γ = 90°; d_{calc} = 1.270 g/cm^3. The structure was solved by the direct method and was refined in anisotropic approximation for non-hydrogen atoms to R = 0.0438 from reflection intensities measured on a SMART automatic diffractometer [3553 non-zero independent reflections with $I \geq 2\sigma(I)$].

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