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Synthesis and Investigation of Estradiol Receptors Modulators

M. S. Egorov, S. I. Selivanov, and A. G. Shavva

St. Petersburg State University, St. Petersburg, 198504 Russia

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Abstract—New modulators of estradiol receptors were synthesized, 17(γ-alkoxy-3-oxo-8-isoestr-5(10)-enes and the respective D-homoanalogs. Reaction of these compounds with $CuBr_2$ in acetonitrile furnished steroids with aromatic A ring possessing hypocholesterolemic and osteoprotective activity.

Estrogens application in replacement therapy has significant limitations due first of all to the possible carcinogenic effect at prolonged treatment [1–3]. Although a correlation was observed between the estrogen activity of substances and their ability to induce tumor formation [4, 5], there are no definite reasons for a statement that this relation possesses an absolute character. As an example we can cite 2-fluoroestradiol that is not carcinogenic although shows strong estrogen activity [6, 7].

One compound among estrogens, equilenin, is deemed to be noncarcinogenic [8], and although this statement is not sufficiently proved [9], the compound was recommended for preventive treatment against breast cancer [10].

It is presumed that the carcinogenic action originates not from the natural hormone estradiol and its derivatives but the products of their metabolism, first of all 4-hydroxyestradiol and 16α-hydroxyestrone [11]. In this connection a synthesis of modified steroids whose metabolism in this respect would be hampered (at least, hypothetically) appeared interesting .

16α-Hydroxyestrone originates from estrone [11]. It is presumable that 16α-hydroxy-17-ketosteroids would arise in the body to a lesser extent if at C^{17} or C^{17a} (in D-analogs) would be present an alkoxy group. It seemed necessary to establish who this modification will affect the properties of the steroid. For study of biological characteristics we selected as model compounds 8-isoanalogs **I–IV** since the initial member of this series, 8-isoestradiol, possessed weak antiestrogen activity [12].

The target compounds were synthesized by Torgov–Ananchenko [13] scheme modified by Wendler *et al.*[14]. The alkoxy groups were introduced into positions

*17*β and *17*aβ through acetyl derivatives **V–VIII** by Brown reaction [15]. This procedure provides a possibility to prepare along the same scheme both alkoxy and acyloxy derivatives and to carry out a comparative study of biological properties of compounds from both groups. The structure of compounds **I–IV** was derived from the data of mass spectrometry and NMR (see EXPERIMENTAL). Since in [17] was reported that 17β-alkoxy derivatives of 8-isoanalogs of steroid estrogens possessed only estrogen and hypocholesterolemic activity we carried out additional study of their biological characteristics in order to evaluate the prospects of the attempted osteoporosis [17]) showed that steroids **I–IV** administered perorally at a dose of 5 mg /kg of body weight daily are no worse by osteoprotective activity that the corresponding 17β-acetoxy derivatives **V–VIII**. In these compounds also was revealed a hypocholesterolemic activity. Therefore in order to obtain substances with improved relation between the target effect and hormonal activity we attempted a synthesis and study of biological activity of the other 17β- and 17αβ-alkoxy-8-isoestrenes.

The reduction of 8-isoanalogs of estrgens with lithium in liquid ammonia followed by hydrolysis is known [16] to afford a products mixture from which the corresponding 3-oxo-8-isoestr-5(10)enes can be isolated.

3-Oxoestr-5(10)ene fragment is present in the structure of thybolone drug used in clinical practice; the fragment apparently ensures the unique tissue-specific action of the drug [18]. Thybolone similar to estrogens

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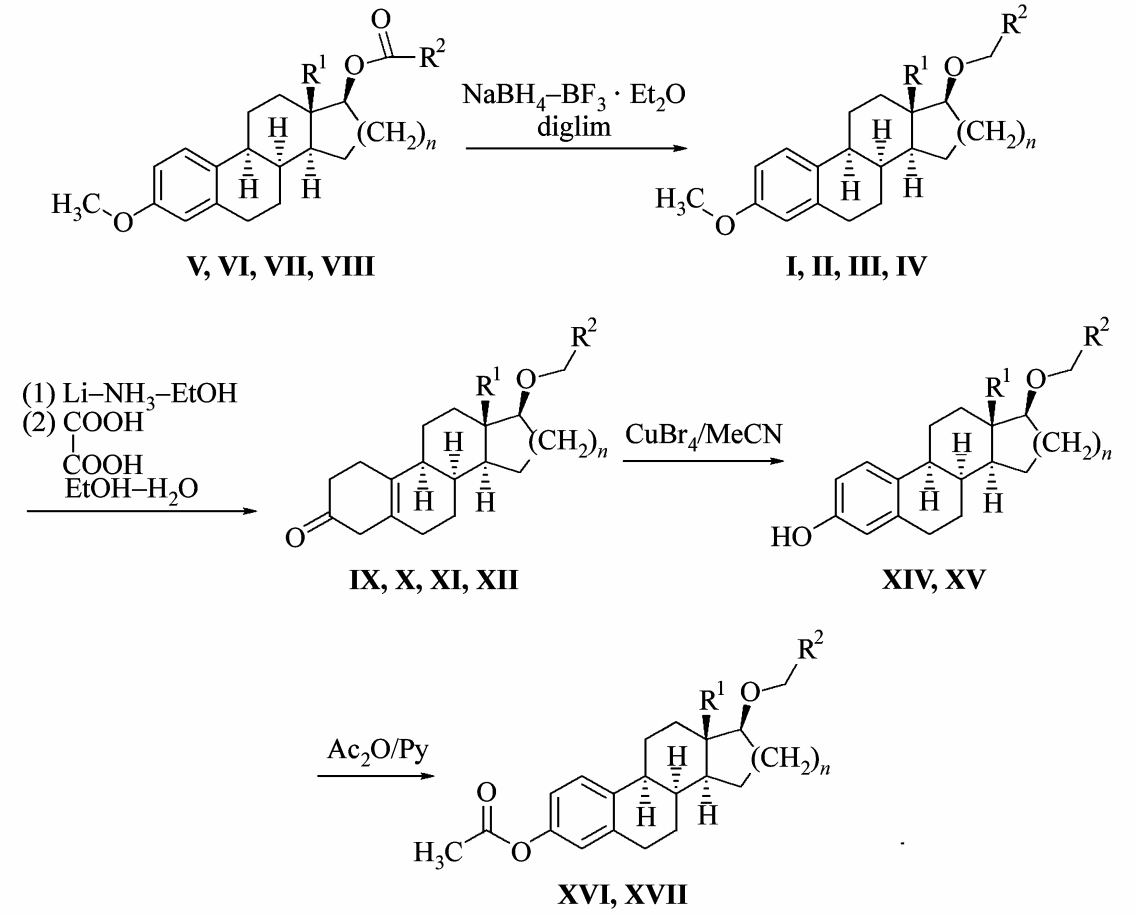
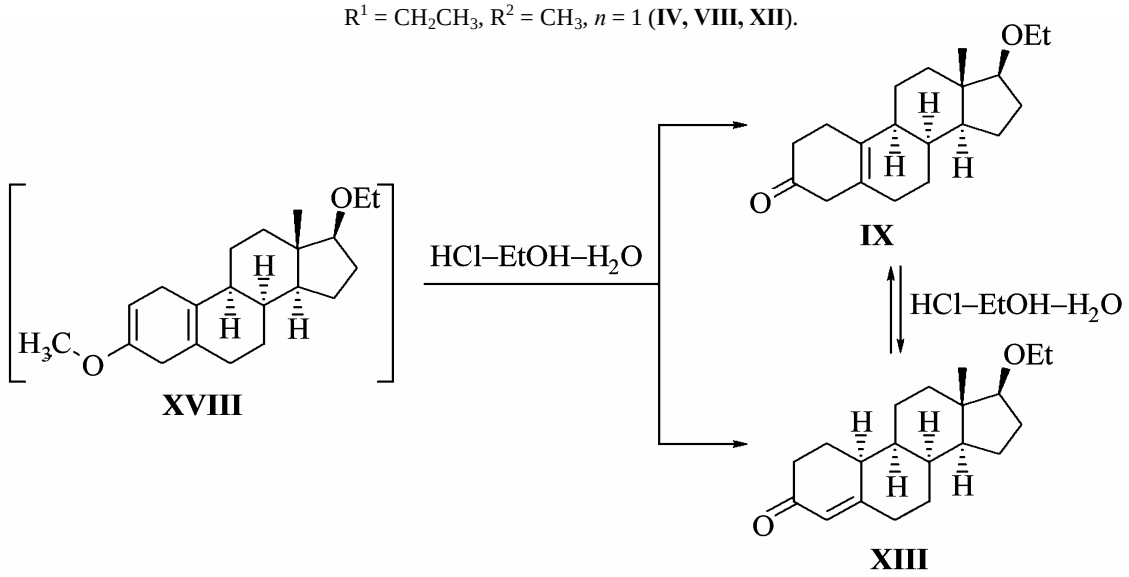
provides osteoprotection and hypocholesterolemia, its carcinogenic level is low, and its activity in breast and endometrial tissues is minimal [19, 20]. Therefore we synthesized 17β- and 17αβ-alkoxy-3-oxo-8-isoestr-5(10)enes (**IX–XII**) starting with estratrienes **I–IV** and using Birch reduction followed by hydrolysis effected obtained by Birch reduction from steroids **V–VII** gave rise only to compounds **I–IV**.



$R^1 = R^2 = CH_3$, $n = 1$ (**I, V, IX, XIV, XVI**); $R^1 = CH_3$, $R^2 = CH_2CH_3$, $n = 1$ (**II, VI, X**); $R^1 = R^2 = CH_3$, $n = 2$ (**III, VII, XI, XV, XVII**); $R^1 = CH_2CH_3$, $R^2 = CH_3$, $n = 1$ (**IV, VIII, XII**).



The structure of 17β-alkoxy-3-oxo-8-isoestr-5(10)-enes and the corresponding D-homoanalog was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The averaging in the spectra of these compounds of the vicinal coupling constants of protons attached to C^{1} with protons H^{2a} and H^{2b} to ~6 Hz value (Fig. 1) resulting in virtually identical multiplet signals of the latter evidences the existence in the solution of compounds in question of a conformational equilibrium in the A ring (Fig. 1). We proved the stability of solutions of 17β-alkoxy-3-oxo-8-isoestr-5(10)-enes in aprotic solvents by an example of compound **IX**. This compound in this respect are unlike thybolone that in a chloroform solution within 24 h isomerizes into a more stable isomer with a C^{4}–C^{5} [double bond 21]. On the contrary, for 8-isoanalogs **IX–XII** the most stable isomer contains C^{5}–C^{10} double bond. For instance, compound **IX** undergoes reversible isomerization into $\Delta^{4(5)}$ derivative **XIII** only when treated with 3 N HCl in ethanol, and the content of isomer **XIII** in the equilibrium mixture is twice smaller than that of $\Delta^{5(10)}$ isomer **IX**.

The structure of 8,10-isoanalog **XIII** was proved by homo- and heteronuclear correlation NMR spectroscopy on ^{1}H and ^{13}C nuclei. The α-orientation of the proton at C^{19} is confirmed by its direct dipole-dipole interaction (NOE) with H^{8a} and H^{9a}. The values of vicinal coupling constants for the protons in the A ring of compound **XIII** indicate that the compound in solution is in conformational equilibrium (Fig. 2a). For the sake of comparison on Fig. 2b, is presented a fragment of the downfield region of the ^{1}H NMR spectrum of the B-nor-D-homo-8,10-isoanalog that exists in solution in a single conformation [22]. As seen, the multiplet structure of signals belonging to protons H^{2a} and H^{2e} of the latter compound are different and possess

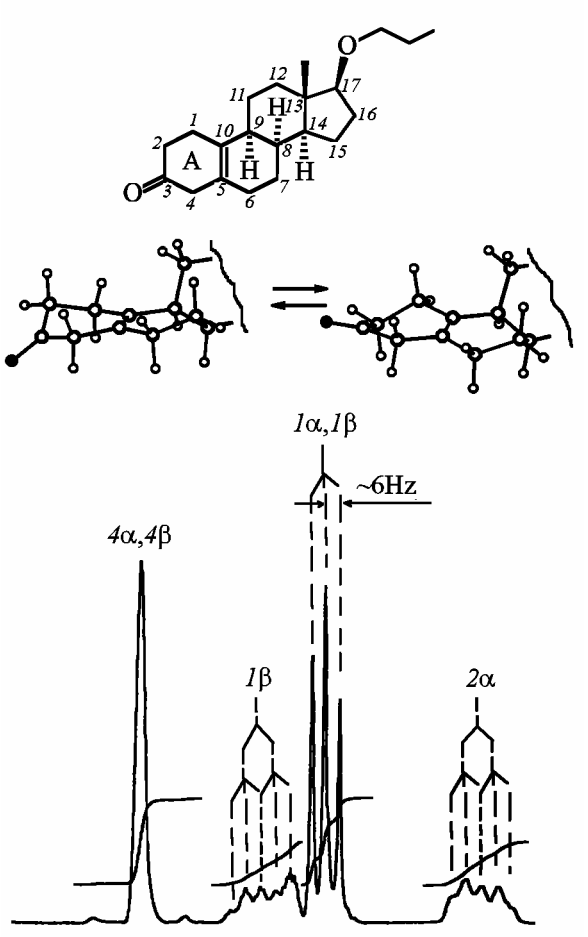


Fig. 1. Typical fragment of the downfield region of ^{1}H NMR spectrum of compounds **IX–XII** (by an example of compound **X**) demonstrating the averaging to 6 Hz of the coupling constants for protons H^{1a} and H^{1b} with protons at C^{2} due to conformational equilibrium existing in the solution of these compounds.

characteristic sets of coupling constants: $^{2}J_{2a,2e}$ 14, $^{3}J_{2a,1a}$ 14.4, $^{3}J_{2a,1e}$ 4.9, $^{3}J_{2e,1a}$ 4.5, $^{3}J_{2e,1e}$ 2.7 Hz. Whereas in compound IX due to equilibrium in solution the multiplets from this pair of protons are similar, and the observed values of vicinal coupling constants are averages between the corresponding constants in A and B conformers. Similar exchange averaging of ^{3}J values to ~6 Hz is observed also for H^{10a} proton.

Biological tests on 75-days-old rats subjected to ovariectomy [17] revealed that alkoxy derivatives with a 5(10) double bond retained the uterotropic and hypocholesterolemic activity, whereas osteoprotection was observed only in steroid **IX**. The notable uterotropic effect of this compound and weight loss in the experimental animals suggest that the activity of the 17β- and 17aβ-alkoxy-8-isoestr-5(10)-enes is mediated by estradiol receptors. In experiment on mice it was established that 3-oxo-17β-ethoxy-8-isoestr-5(10)-ene (**IX**) (at list at short administration) did not show immunodepression in the doses sufficient for osteoprotection and hypocholesterolemic effect. In this respect compound **IX** considerably differs from typical estrogens [23]. The detailed results of investigation of the biological properties of compounds **I–XII** will be published elsewhere.

Aromatization of A ring in compounds **IX–XII** may be considered among the possibilities of preparation of 17β- and 17αβ-alkoxy-8-isoanalogs of estrogens with a free hydrxy group at C^{3} atom.

We showed the possibility of this reaction to occur by treating compounds **IX** and **XI** with $CuBr_2$ in acetonitrile. As a result we obtained in good yield steroids **XIV** and **XV**. Their biological properties are currently under study.

EXPERIMENTAL

The purity of all compounds was checked by TLC on Silufol plates in solvent systems petroleum ether–ethyl acetate (4 : 1, 3 : 1). Mass spectra were measured

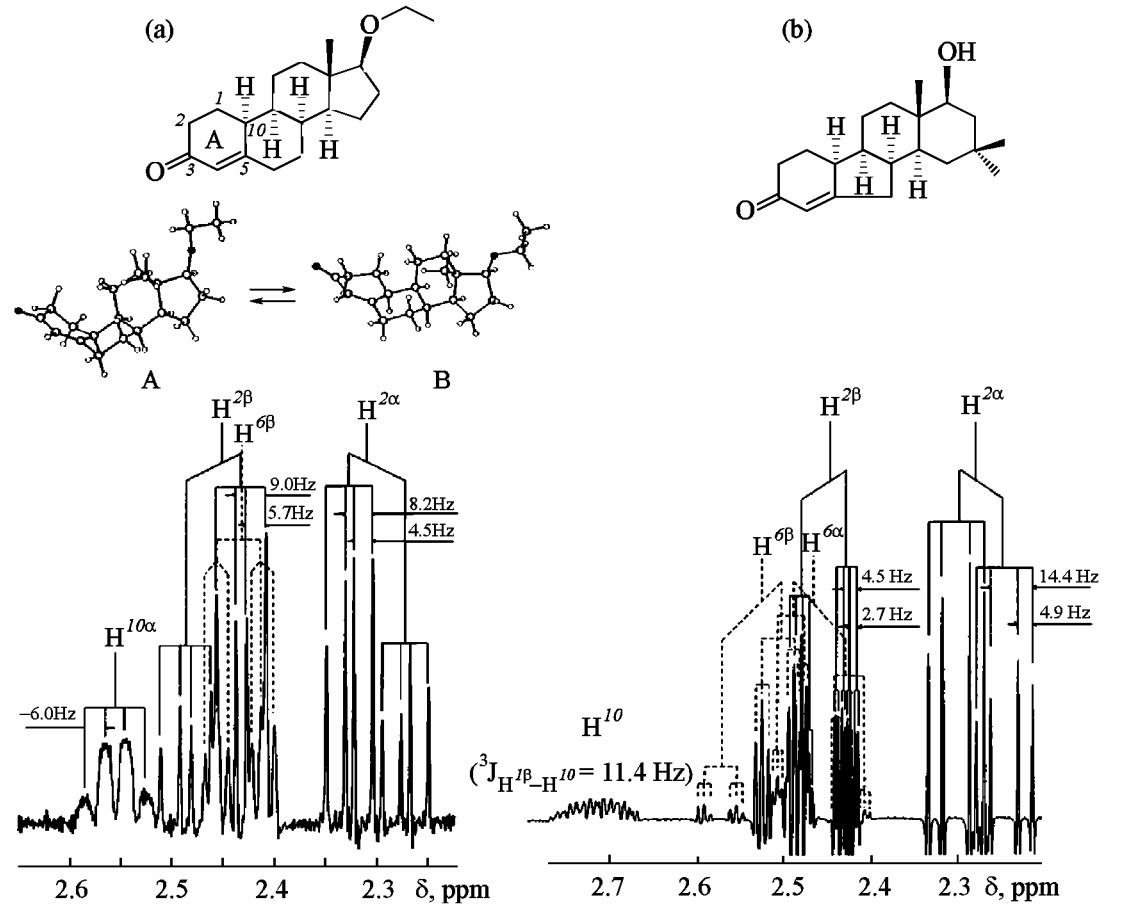


Fig. 2. Fragments of downfield regions of ^{1}H NMR spectra of conformationally nonrigid compound **XIII** (a) and B-nor-D-homo-8,10-isoanalog existing in solution in a single conformation (b).

on MKh-1321 instrument at ionizing chamber temperature 200–210°C. ^{1}H and ^{13}C NMR spectra were registered at 295 K on spectrometer Bruker DPX-300 at operating frequencies 300.130 and 75.468 from solutions in $CDCl_3$ of concentrations 10–15 mg/ml and 60–100 mg/ml respectively. Chemical shifts were measured in δ-scale from the signal of solvent (residual protons in deuterochloroform, at 7.26 ppm, carbon atom at 76.90 ppm).

In steroids **IV, VIII, XII** all chiral centers have *S*-configuration, the other compounds are racemic.

3-Methoxy-17b-ethoxy-8-isoestra-1,3,5(10)-triene (I). To a solution of $NaBH_4$ (1.9 g, 50.2 mmol) in 115 ml of diglyme cooled to −8°C was added dropwise within 2 h at stirring a solution of acetate **V** (6 g, 18.2 mmol) and BF_3 Et_2O (11 ml, 67.4 mmol) in120 ml of THF. The stirring at room temperature continued for 2 h more. On the next day the reaction mixture was treated with 185 ml of 2 N HCl, diluted with 1 l of water, and extracted with chloroform. The organic solutions were combined, dried with sodium sulfate, the solvent was evaporated in a vacuum, anc the residue was applied to a column packed with silica gel 5/40 μ. A gradient elution was performed starting with petroleum ether and finishing with its mixture with ethyl acetate, 3:1. On recrystallization from ethanol we obtained 3.9 g (68%) of substance **I**, mp. 97–99°C. Mass spectrum, *m/z* ($I_{rel.}$, %): 314 (73), 242 (11), 227 (100), 223 (7), 211 (4), 186 (9), 185 (8), 174 (21), 171 (12). ^{1}H NMR spectrum, δ, ppm: 7.05 d (1H, H^1, $^3J_{1,2}$ 8.4 Hz), 6.71 d.d (1H, H^2, $^3J_{2,1}$ 8.4 Hz, $^4J_{2,4}$ 2.7 Hz), 6.60 d (1H, H^4, $^4J_{4,2}$ 2.7 Hz), 3.77 s (3H, OCH_3), 3.57 m (1H, OCH_2), 3.46 m (1H, OCH_2), 3.36 t (1H, H^{17a}, ^3J 8.1 Hz), 1.16 t (3H, $CH_2\underline{CH_3}$, ^3J 7.2 Hz), 0.88 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum, δ, ppm.: 12.94, 15.63, 20.73, 22.10, 27.74, 29.01, 31.40, 37.87, 38.8, 41.46, 42.00, 47.87, 55.07, 65.21, 89.03, 111.95, 113.15, 130.09, 134.00, 137.87, 157.22. Found, %: C 80.23; H 9.60. $C_{21}H_{30}O_2$. Calculated, %: C 80.21; H 9.62.

From the other fractions containing a more polar compound we obtained after recrystallization from a mixture of petroleum ether and ethyl acetate 1.0 g (19%) of 17β-hydroxy-3-methoxy-8-isoestra-1,3,5-triene identified by no depression of melting point in a mixture with an authentic sample.

3-Methoxy-17b-propionyloxyestra-1,3,5(10)-triene (VI). To a solution of 3.2 g of compound **V** in 180 ml of benzene was added a solution of 9 g of NaOH in 75 ml of methanol, and the mixture was boiled on a water bath for 2 h. The reaction mixture was then diluted with 600 ml of water, and the reaction product was extracted into chloroform. After removing the solvent in a vacuum the crystalline residue was dissolved in 15 ml of pyridine, 5 ml of propionic anhydride was added, and the mixture was heated on a water bath for 3 h and left overnight. Then the mixture was poured on 250 g of ice, the precipitated crystals were filtered off, recrystallized from a mixture chloroform-ethanol, 1 : 5. Filtered off again, washed with ethanol, then with 0.5 M HCl, with water, and dried for 2 days. We obtained 3.2 g (96%) of colorless crystals of compound **VI**, mp 134–136°C. ^{1}H NMR spectrum, δ, ppm: 7.09 d (1H, H^1, $^3J_{1,2}$ 8.3 Hz), 6.75 d (1H, H^2, $^3J_{2,1}$ 8.3 Hz), 6.64 s (1H, H^4), 4.67 t (1H, H^{17a}, $^3J_{17a,16}$ 8.5 Hz), 3.80 s (3H, OCH_3), 2.37 q (2H, $OCOCH_2$, ^3J 7.5 Hz), 1.18 t (3H, $CH_2\underline{CH_3}$, ^3J 7.5 Hz), 0.94 s (3H, $C^{18}H_3$). Found, %: C 77.12; H 8.85. $C_{22}H_{30}O_3$. Calculated, %: C 77.16; H 8.77.

3-Methoxy-17b-propoxy-8-isoestra-1,3,5(10)-triene (II) was prepared from propionate **VI** similarly to compound I. Yield 69%, mp 93–95°C (96–98°C [16]). Mass spectrum, *m/z* ($I_{rel.}$, %): 328 (32), 242 (4.5), 227 (100), 213 (4), 200 (3), 185 (5.5), 174 (25), 160 (54), 147 (25). ^{1}H NMR spectrum, δ, ppm.: 7.06 d (1H, H^1, $^3J_{1,2}$ 8.7 Hz), 6.72 d.d (1H, H^2, $^3J_{2,1}$ 8.7, $^4J_{2,4}$ 2.4 Hz), 6.62 d (1H, H^4, $^4J_{4,2}$ 2.4 Hz), 3.78 s (3H, OCH_3), 3.37 m (3H, OCH_2, H^{17a}), 0.93 t (3H, $CH_2\underline{CH_3}$, ^3J 7.2 Hz), 0.90 s (3H, $C^{18}H_3$). ^{13}C NMR spectrun, δ, ppm: 10.58, 12.90, 20.70, 22.07, 23.32, 27.61, 28.98, 31.38, 37.84, 38.82, 41.45, 42.01, 47.82, 55.04, 71.68, 89.08, 111.92, 113.11, 130.06, 113.98, 137.83, 157.18. Found, %: C 80.37; H 9.80. $C_{22}H_{32}O_2$. Calculated, %: C 80.44; H 9.82.

3-Methoxy-17ab-ethoxy-D-homo-8-isoestra-1,3,5(10)-triene (II) was prepared from acetate **VII** similarly to compound **I**. Yield 64%, mp 104–105°C .

Mass spectrum, *m/z* ($I_{rel.}$, %): 328 (72), 300 (4), 282 (4), 240 (3), 227 (100), 213 (8), 199 (4), 187 (4), 160 (41), 147 (14). ^{1}H NMR spectrum, δ, ppm: 7.04 d (1H, H^1, $^3J_{1,2}$ 8.7 Hz), 6.72 d.d (1H, H^2, $^3J_{2,1}$ 8.7, $^4J_{2,4}$ 2.4 Hz), 6.60 d (1H, H^4, $^4J_{4,2}$ 2.4 Hz), 3.78 s (3H, OCH_3), 3.65 m (1H, OCH_2), 3.41 m (1H, OCH_2), 1.18 t (3H, $CH_2\underline{CH_3}$, ^3J 6.3 Hz), 0.91 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum, δ, ppm.: 13.45, 15.61, 21.14, 24.67, 26.09, 27.25, 28.45, 31.63, 38.16, 38.69, 40.53, 41.57, 47.12, 55.04, 65.02, 88.02, 111.97, 113.02, 129.85, 134.38, 137.65, 157.16. Found, %: C 80.34; H 10.04. $C_{22}H_{32}O_2$. Calculated, %: C 80.44; H 9.82.

18-Methyl-3-methoxy-17b-ethoxy-8-isoestra-1,3,5(10)-triene (II) was prepared from acetate **VIII** similarly to compound **I**. Yield 64%, mp 71–73°C. Mass spectrum, *m/z* ($I_{rel.}$, %): 328 (49), 282 (3), 272

(2.5), 256 (11), 241 (100), 228 (4), 213 (7), 174 (24), 173 (26), 160 (44), 159 (24). ^{1}H NMR spectrum, δ, ppm: 7.08 d (1H, H^1, $^3J_{1,2}$ 8.7 Hz), 6.72 d.d (1H, H^2, $^3J_{2,1}$ 8.7, $^4J_{2,4}$ 2.7 Hz), 6.60 d (1H, H^4, $^4J_{4,2}$ 2.7 Hz), 3.77 s (3H, OCH_3), 3.54 m (1H, OCH_2), 3.49 m (1H, OCH_2), 3.37 t (1H, H^{17a}, ^3J 8.1 Hz), 1.17 t (3H, $OCH_2\underline{CH_3}$, ^3J 6.9 Hz), 0.95 t (3H, $C^{18}H_2\underline{CH_3}$, ^3J 7.5 Hz). ^{13}C NMR spectrum, δ, ppm: 9.46, 15.58, 19.50, 21.47, 22.01, 28.18, 29.11, 31.82, 35.19, 38.40, 41.44, 44.00, 48.76, 55.08, 65.67, 90.99, 112.00, 113.10, 130.15, 133.78, 138.06, 157.17. Found, %: C 80.44; H 10.12. $C_{22}H_{32}O_2$. Calculated, %: C 80.44; H 9.82.

3-Oxo-17b-ethoxy-8-isoestr-5(10)-ene (IX). To a solution of steroid I (2.8 g, 8.9 mmol) in 200 ml of THF and 300 ml of liquid ammonia at −60°C was added 3 g (0.432 mmol) of finely cut lithium. After 5 h at the same temperature was slowly added 70 ml of methanol. After common work-up [24] to a solution of reaction products in a mixture of 70 ml of chloroform and 150 ml of ethanol was added a solution of 10 g of oxalic acid in 50 ml of water. The mixture was heated to 50°C and then was left standing at room temperature for 40 min. Then it was poured into 1 l of water, and the reaction product was extracted into chloroform. After common work-up the main reaction product was isolated by crystallization from petroleum ether. We obtained 1.93 g (72%) of steroid **IX**, mp 83–85°C. Mass spectrum, *m/z* ($I_{rel.}$, %): 302 (100), 241 (5), 238 (5), 228 (14.5), 215 (73), 199 (16.5), 185 (6.5), 173 (15.5), 160 (37.5), 148 (19).^{1}H NMR spectrum, δ, ppm: 3.48 m (2H, OCH_2), 3.26 t (1H, H^{17a}, $^3J_{17a,16}$ 8.1 Hz), 2.73 s (2H, H^{4a}, H^{4b}), 2.52 m (1H, H^{2e}), 2.45 t (2H, H^{1a}, H^{1b}, $^3J_{1,2}$ 6.5 Hz), 2.20 m (1H, H^{2a}), 1.16 t (3H, $CH_2\underline{CH_3}$, ^3J 6.9 Hz), 0.85 s (3H, $C^{18}H_3$).^{13}C NMR spectrum, δ, ppm: 12.60, 15.36, 20.01, 21.73, 23.71, 27.40, 28.70, 31.11, 37.42, 38.25, 38.83, 42.14, 43.03, 44.13, 47.31, 64.91, 88.75, 125.82, 132.75, 21.03. Found, %: C 79.26; H 10.16. $C_{20}H_{30}O_2$. Calculated, %: C 79.42; H 10.00.

3-Oxo-17b-propoxy-8-isoestr-5(10)-ene (X) was synthesized from steroid **II** in the same way as compound **IX**. Yield 55%, mp 50–52°C.^{1}H NMR spectrum, δ, ppm: 3.38 m (2H, OCH_2), 3.24 t (1H, H^{17a}, $^3J_{17a,16}$ 8.4 Hz), 2.74 s (2H, H^{4a}, H^{4b}), 2.55 m (1H, H^{2e}), 2.45 t (2H, H^{1a}, H^{1b}, $^3J_{1,2}$ 6.5 Hz), 2.22 m (1H, H^{2a}), 0.90 t (3H, $CH_2\underline{CH_3}$, ^3J 7.2 Hz), 0.85 s (3H, $C^{18}H_3$).^{13}C NMR spectrum, δ, ppm: 10.56, 12.90, 20.25, 21.97, 23.30, 23.94, 27.54, 28.94, 31.36, 37.68, 38.47, 39.06, 42.42, 43.30, 44.37, 47.54, 89.07, 126.05, 133.02, 211.25. Found, %: C 79.95; H 10.04. $C_{21}H_{32}O_2$. Calculated, %: C 79.70; H 10.19.

3-Oxo-17ab-ethoxy-D-homo-8-isoestr-5(10)-ene (XI) was prepared from steroid **III** by the same procedure as compound **IX**. Yield 70%, mp 97–99°C. Mass spectrum, *m/z* ($I_{rel.}$, %): 316 (100), 270 (9), 255 (3.5), 215 (69), 201 (5.5), 197 (7), 187 (3), 173 (7.5), 160 (15), 148 (21). ^{1}H NMR spectrum, δ, ppm: 3.59 m (1H, OCH_2), 3.34 m (1H, OCH_2), 2.70 s (2H, H^{4a}, H^{4b}), 2.69 d.d (1H, H^{17aa}, $^3J_{17aa,17a}$ 3.3 Hz), 2.53 m (1H, H^{2e}), 2.43 t (2H, H^{1a}, H^{1b}, $^3J_{1,2}$ 6.5 Hz), 2.18 m (1H, H^{2a}), 1.10 t (3H, $CH_2\underline{CH_3}$, ^3J 7.1 Hz), 0.86 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum, δ, ppm: 13.40, 15.55, 20.60, 23.31, 24.59, 25.83, 27.11, 28.58, 31.57, 37.80, 39.01, 40.27, 43.20, 44.22, 46.89, 64.89, 87.89, 125.63, 133.02, 211.18. Found, %: C 79.56; H 10.29. $C_{21}H_{32}O_2$. Calculated, %: C 79.70; H 10.19.

18-Methyl-3-oxo-17b-ethoxy-8-isoestr-5(10)-ene (XII) was syntesised from steroid IV by the same way as compound IX. Yield 50%, mp52–53°C. Mass spectrum, *m/z* ($I_{rel.}$, %): 316 (84), 287 (3), 270 (8.5), 241 (11), 215 (13.5), 199 (13.5), 187 (9), 171 (7), 160 (60), 148 (33). ^{1}H NMR spectrum, δ, ppm: 3.52 m (1H, OCH_2), 3.47 m (1H, OCH_2), 3.33 t (1H, H^{17a}, $^3J_{17a,16}$ 8.5 Hz), 2.76 s (2H, H^{4a}, sH^{4b}), 2.55 m (1H, H^{2e}), 2.47 t (2H, H^{1a}, H^{1b}, $^3J_{1,2}$ 6.9 Hz), 2.22 m (1H, H^{2a}), 1.16 t (3H, $OCH_2\underline{CH_3}$, ^3J 6.9 Hz), 0.97 t (3H, $C^{18}H_2\underline{CH_3}$, ^3J 7.2 Hz). ^{13}C NMR spectrum, δ, ppm: 9.46, 15.52, 19.52, 21.00, 21.86, 23.91, 28.08, 28.83, 31.61, 34.86, 38.11, 39.02, 43.45, 44.38, 48.44, 65.61, 90.95, 126.27, 132.82, 211.54. Found, %: C 79.50; H 10.33. $C_{21}H_{32}O_2$. Calculated, %: C 79.70; H 10.19.

3-Oxo-17b-ethoxy-8-isoestr-4(5)-ene (XIII) was prepared from steroid I (2.5 g, 7.95 mmol) similarly to compound **IX** but the hydrolysis of product **XVIII** of Birch reduction was carried out in 159 ml of EtOH and 100 ml of 3 N HCl at 60°C for 1 h. The reaction mixture was poured into 800 ml of water, and the reaction products were extracted into chloroform. After drying and removing of the solvent in a vacuum an oily product was obtained that was subjected to column chromatography on silica gel 5/40 with gradient elution with a mixture of petroleum ether and ethyl acetate. As a result we obtained 500 mg (20%) of the initial substance **I**, 500 mg (21%) of compound **IX** (mp 83–86°C), and 250 mg (11%) of compound **XIII** (mp 63–64°C). ^{1}HNMR spectrum of compound **XIII**, δ, ppm: 5.87 m (1H, H^4), 3.50 m (1H, OCH_2), 3.42 m (1H, OCH_2), 3.24 t (1H, H^{17a}, $^3J_{17a,16}$ 9.0 Hz), 2.55 m (1H, H^{10a}), 2.44 m (1H, H^{2e}, H^{6b}), 2.30 m (1H, H^{2a}), 1.16 t (3H, $CH_2\underline{CH_3}$, ^3J 7.5 Hz), 0.84 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum of

compound **XIII**, δ, ppm: 13.51, 15.55, 19.82, 22.15, 23.90, 25.26, 27.61, 36.00, 36.32, 38.52, 40.30, 41.15, 42.34, 46.76, 48.06, 65.09, 88.78, 124.75, 165.74, 199.87. Found, %: C 79.42; H 10.16. $C_{20}H_{30}O_2$. Calculated, %: C 79.42; H 10.00.

3-Hydroxy-17b-ethoxy-8-isoestra-1,3,5(10)-triene (XIV). To a solution of 1 g (3.31 mmol) of steroid **IX** in 33 ml of acetonitrile under argon atmosphere was added at stirring in one portion 0.890 g (3.68 mmol) of $CuBr_2$. The mixture was stirred for 3 h at room temperature and left overnight. Then the mixture was diluted with 60 ml of water, and 3 ml of 3 N HCl was added. The precipitated colorless crystals were filtered off, washed with wter, and dried. We obtained 0.845 g (85%) of steroid **XIV**, mp152–154°C. Found, %: C 79.82; H 9.36. $C_{20}H_{28}O_2$. Calculated, %: C 79.96; H 9.39. Acetate **XVI** was obtained from compound **XIV** by treating with acetic acid in pyridine under known condition, mp 123-124°C. Mass spectrum of acetate **XVI**, *m/z* ($I_{rel.}$, %): 342 (47.5), 300 (77.5), 255 (30), 228 (22.5), 213 (100), 199 (7), 186 (5), 171(8), 160 (20.5), 159 (20.5), 158 (21), 157 (13), 147 (29). ^{1}HNMR spectrum of acetate XVI, δ, ppm.: 7.13 d (1H, H^1, $^3J_{1,2}$ 8.4 Hz), 6.83 d.d (1H, H^2, $^3J_{2,1}$ 8.4, $^4J_{2,4}$ 2.1 Hz), 6.62 d (1H, H^4, $^4J_{4,2}$ 2.1 Hz), 3.57 m (1H, OCH_2), 3.49 m (1H, OCH_2), 3.33 t (1H, H^{17a}, $^3J_{17a,16}$ 8.4 Hz), 2.29 s (3H, $OCCH_3$), 1.20 t (3H, $CH_2\underline{CH}_3$, ^3J 6.9 Hz), 0.90 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum of acetate **XVI**, δ, ppm: 13.46, 16.12, 21.00, 21.53, 22.58, 28.22, 29.39, 31.58, 38.10, 39.37, 42.29, 42.47, 48.24, 65.72, 89.48, 119.10, 121.76, 130.64, 138.63, 139.82, 148.62, 170.22. Found, %: C 77.11; H 8.85. $C_{22}H_{30}O_3$. Calculated, %: C 77.16; H 8.83.

3-Hydroxy-17ab-ethoxy-D-homo-8-isoestra-1,3,5- (10)-triene (XV) was prepared from steroid **XI** by the same procedure as compound **XIV**. Yield 75%, mp 159–160°C. Found, %: C 80.26; H 9.90. $C_{21}H_{30}O_2$. Calculated, %; C 80.21; H 9.62. Acetate **XVII** was obtained from compound **XV** under the same conditions as steroid **XVI**, 105–107°C. Mass spectrum of acetate **XVII**, *m/z* ($I_{rel.}$, %): 356 (24.5), 314 (100), 268 (8.5), 255 (9), 226 (3), 213 (82.5), 199 (5.5), 185 (3), 171 (2.5), 160 (18.5), 147 (26.5). ^{1}H NMR spectrum of acetate **XVII**, δ, ppm.: 7.10 d (1H, H^1, $^3J_{1,2}$ 8.1 Hz), 6.82 d.d (1H, H^2, $^3J_{2,1}$ 8.1, $^4J_{2,4}$ 2.4 Hz), 6.76 d (1H, H^4, $^4J_{4,2}$ 2.4 Hz), 3.62 m (1H, OCH_2), 3.38 m (1H, OCH_2), 2.27 s (3H, $OCCH_3$), 1.16 t (3H, $CH_2\underline{CH}_3$, ^3J 6.9 Hz), 0.89 s (3H, $C^{18}H_3$). ^{13}C NMR spectrum of acetate **XVII**, δ, ppm: 13.98, 16.12, 21.43, 25.15, 26.58, 27.75, 28.86, 31.82, 38.69, 39.19, 40.75, 42.42, 47.52, 65.55, 88.51, 119.15, 121.64, 130.43, 138.46, 140.22, 148.58, 170.25. Found, %: C 77.47; H 9.11. $C_{23}H_{32}O_3$. Calculated, %: C 77.49; H 9.05.

REFERENCES

1. Barret-Connor, E., *Annu. Rev. Med.,* 1992, vol. 43, p. 239.
2. Compston, J.E., *Clinical Endocrinology,* 1998, vol. 48, p. 389.
3. Gratsianskii, N.A., *Klin. Farmakol. Terap*., 1994, vol. 3, p. 869.
4. Wiese, T.E., Polin, L.A., Palomino, E., and Brooks, S.C., *J. Med. Chem.,* 1997, vol. 40, p. 3659.
5. Schafer, J.I.M., Liu, H., Tonetti, D.A., and Jordan, V.C., *Cancer Res.,* 1999, vol. 59, p. 4308.
6. US Patent 4522758, 1985; *Chem. Abstr.,* 1985, vol. 103, 123790k.
7. Liehr, J.G., *Mol. Pharmacol.,* 1983, vol. 23, p. 278.
8. Oshiro, Y., Balwierz, P.Z., and Piper, C.E., *Environ Mutagen.,* 1986, vol. 8, p. 461; *Chem. Abstr.,* 1986, vol. 105, 18785f.
9. Zhang, F., Chen, Y., Pisha, E., Chen, L., Xiong, Y., van Breemen, R.B., and Bolton, J.L., *Chem. Res. Toxicol.,* 1999, vol. 12, p. 204.
10. US Patent 4937238, 1990; *Ref. Zh. Khim.,* 1991, 21O261P.
11. Lewis, J.S., Thomas, T.J., Kling, C.M., Gallo, M.A., and Thomas, T.J., *Mol. Endocrinol.,* 2001, vol. 27, p. 293.
12. Gonzalez, F.B., Neef, G., Eder, U., Wiechert, R., Schillinger, E. and Nishino, Y., *Steroids,* 1982, vol. 40, p. 171.
13. Torgov, I.V., *Izv. Akad. Nauk SSSR, Ser. Khim.,* 1982, p. 299.
14. Kuo, C.H., Taub, D., and Wendler, N.L., *J. Org. Chem.,* 1968, vol. 33, p. 3126.
15. Pettit, G.R. and Piatak, D.M., *J. Org. Chem.,* 1962, vol. 27, p. 2127.
16. US Patent 3407217, 1969; *Chem. Abstr.,* 1970, vol. 70, 88089q.
17. Kalu, D.N., *Bone and Mineral.,* 1991, vol. 15, p. 175.
18. Kloosterboer, H.J., *J. Steroid Biochem. Molec. Biol.,* 2001, vol. 76, p. 231.
19. Yoshitake, K., Yokota, K., Kasugai, Y., Kagawa, M., and Sukamoto, T., *Bone,* 1999, vol. 25, p. 311.
20. Ederveen, A.G.H. and Kloosterboer, J.H., *J. Bone Miner. Res*., 2001, vol. 16, p. 1651.
21. Xu, H., Liu, X., Cui, Y., Zhao, M., and Chen, X., *Bopuxue Zazhi*., 2000, vol. 17, 17; Chem. Abstr., 2000, vol. 132, 334662g.
22. Egorov M.S., Grinenko E.V., Zorina A.D., Balykina L.V., Selivanov S.I., and Shavva A.G., *Zh. Org. Khim.*, 2001, vol. 37, p. 849.
23. RST Int. Appl. WO 9708188; *Chem. Abstr.,* 1997, vol. 126, 225448x.
24. Rzheznikov V.M., Ananchenko S.N., and Torgov I.V., *Khim. Polim. Soed.,* 1965, no. 2, p. 90.