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Synthesis and Investigation of the Spatial Arrangement of the 17β-Acetoxy-7α,18-dimethyl-3-Methoxy-6-oxaestra-1,3,5(10),8(9)-tetraene

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Abstract—A synthesis was developed of 17β-acetoxy-7α,18-dimethyl-3-methoxy-6-oxaestra-1,3,5(10),8(9)-tetraene. The spatial arrangement of the compound in a crystal and in solution was investigated by means of X-ray diffraction analysis and NMR spectroscopy. The conformation prevailing in solution with the *7*α-methyl group in a quasiaxial position corresponds to the structure of the compound in the crystalline state. The presence of a methyl in the *7*α position is an important factor governing the osteoprotecting activity of steroids with the similar structure.

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The presence of a methyl group in the *7*α position of steroid estrogens is known to enhance the hormonal activity [1–3] whereas introducing a double bond into *8(9)* position decreases this effect [4] and strengthens the antioxidant properties of the modified steroid [4, 5]. 8-Dehydroestrogens and their derivatives are proposed for the use in replacement therapy, for treatment of atherosclerosis and osteoporosis [6, 7], of vasomotor symptoms [8], etc. No data exist on simultaneous action on biological properties of both mentioned modifications of the steroid estrogens.

The planning of research on the synthesis of steroid estrogens with the mentioned modifications and on their biological activity requires the elucidation of specific features in the structure of this group compounds, first of all, the spatial position of the methyl group attached to the C^7 atom.

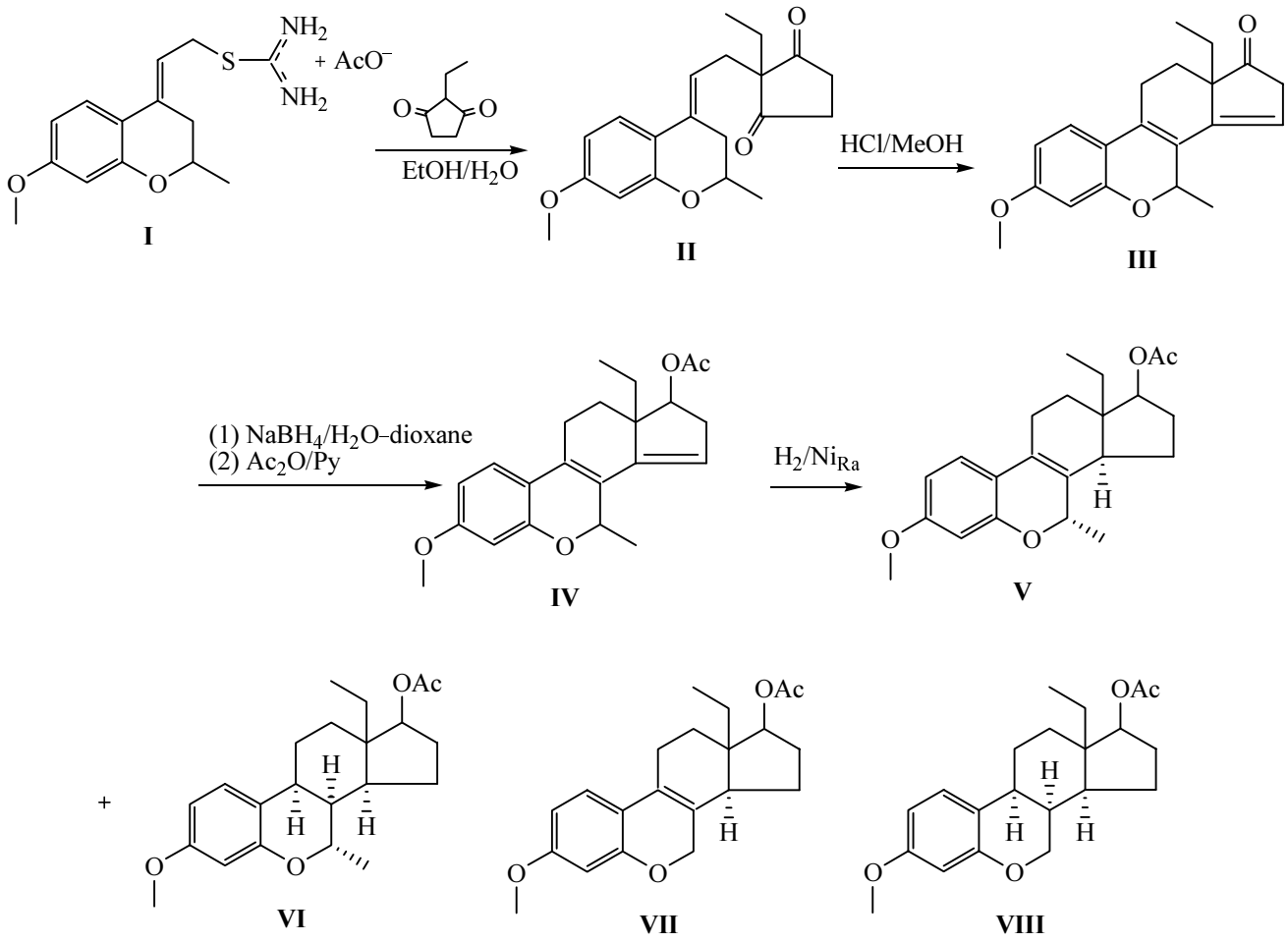
6-Oxaanalogs of estrogens possess better biological activity than their carboanalogs [9, 10] and are easily synthesized [11]. Therefore we selected as model compound for the study of specific structural features of 8-dehydroestrogens with a methyl group on the C^7 atom 17β-acetoxy-7α,18-dimethyl-3-methoxy-6-oxaestra-1,3,5(10),8(9)-tetraene (**V**). We synthesized this steroid by the procedure of Torgov–Ananchenko [12] modified by Wendler [13]. Using the known isothiuronium salt **I** [14] we obtained in a high yield seko compound **II** which by standard procedures was converted into 6-oxaestra-pentaene **IV** [12]. The key stage in the preparation of the target compound **V** was the catalytic hydrogenation of acetate **IV** since the approach of the catalyst to the double bond in the *14*(*15*) position of this steroid is hindered both from the α- and β-side of the molecule. The best results were obtained with Pd/Al_2O_3 as catalyst (see the scheme).

The spatial structure of steroid **V** in a crystal and a solution was elucidated by means of X-ray diffraction analysis and NMR spectroscopy. The data obtained were compared with semiempirical calculations.

The crystal structure was solved by the direct method and refined on the basis of structural factors accounting for the anisotropy of the thermal oscillations of the nonhydrogen atoms till R_1 0.0371, wR_2 0.0965. The hydrogen atoms were placed into the calculated positions. The extinction of X-rays in the crystal was not taken into account (μ 0.84 cm^{-1}). The calculations were carried out using software packages CSD [15] and SHELX-97 [16]. Bond lengths and bond angles are compiled in Tables 1 and 2 respectively.

The carbon skeleton of the molecule 17β-acetoxy-7α,18-dimethyl-3-methoxy-6-oxaestra-1,3,5(10),8(9)-tetraene is flattened (Fig. 1). The conformation of the molecule as a whole may be described as follows: A ring is planar, rings B and C are virtually regular *semichairs*, the substituents at atoms C^7 and C^{13} are located in

Scheme.



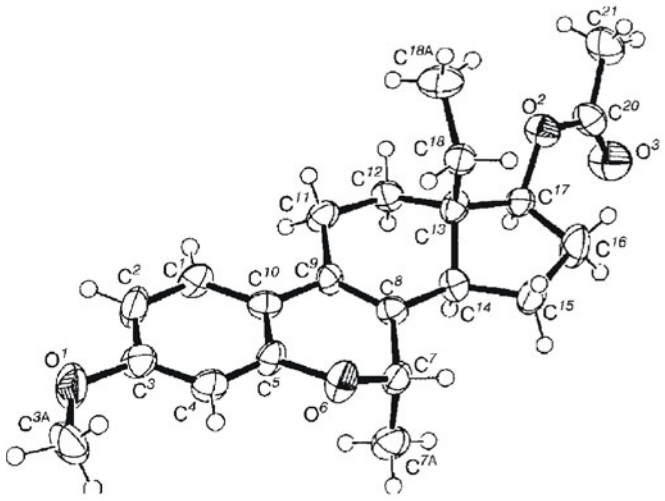


Fig. 1. Spatial arrangement of the molecule of estratetraene **V** according to the X-ray diffraction data.

pseudoaxial positions. The angle between the *semichair* planes for the B ring is 29.9°, for the C ring 53.0°. The D ring is a strongly distorted 13β-*envelop*. The junction of rings A/B is planar, of C/D is 13β,14α-transoid. The carbon from the CH_3O group is located in the *trans*-position with respect to the C^2–C^3 bond and is situated in the plane of the A ring. The ethyl group on the C^{13} atom and the acetyl attached to C^{17} are located in the β-region of the steroid skeleton. Torsion angles characteristic of the main features of the molecule conformation are given in Table 3.

The distance between the oxygen atoms attached to C^3 and C^{17} (important for binding with estrogens receptors) equals 10.853(5) Å, slightly shorter than in the molecule of the natural hormone estradiol (10.93 Å) [17].

The conformation of steroid **V** in solution was derived from the values of torsion angles θ_{HH} and proton–proton

Table 1. Valence bonds lengths in compound **V**

Bond	*r*, Å	Bond	*r*, Å
O^{1}–C^{3}	1.369(5)	C^{8}–C^{9}	1.345(6)
O^{1}–C^{3A}	1.410(7)	C^{8}–C^{14}	1.493(6)
O^{2}–C^{20}	1.365(6)	C^{9}–C^{10}	1.472(6)
O^{2}–C^{17}	1.463(5)	C^{9}–C^{11}	1.517(6)
O^{3}–C^{20}	1.185(5)	C^{11}–C^{12}	1.539(6)
O^{6}–C^{5}	1.392(4)	C^{12}–C^{13}	1.534(6)
O^{6}–C^{7}	1.470(6)	C^{13}–C^{14}	1.519(6)
C^{1}–C^{2}	1.390(7)	C^{13}–C^{17}	1.530(6)
C^{1}–C^{10}	1.390(7)	C^{13}–C^{18}	1.573(6)
C^{2}–C^{3}	1.379(7)	C^{14}–C^{15}	1.559(6)
C^{3}–C^{4}	1.375(6)	C^{15}–C^{16}	1.547(8)
C^{4}–C^{5}	1.376(6)	C^{16}–C^{17}	1.555(6)
C^{5}–C^{10}	1.404(6)	C^{18}–C^{18A}	1.523(5)
C^{7}–C^{7A}	1.485(6)	C^{20}–C^{21}	1.498(7)
C^{7}–C^{8}	1.517(6)		

Table 2. Bond angles φ in compound **V**

Angle	φ, deg	Angle	φ, deg
$C^{3}O^{1}C^{3A}$	120.9(4)	$C^{1}C^{10}C^{9}$	124.2(4)
$C^{20}O^{2}C^{17}$	115.8(3)	$C^{5}C^{10}C^{9}$	119.6(4)
$C^{5}O^{6}C^{7}$	116.9(3)	$C^{9}C^{11}C^{12}$	115.8(3)
$C^{2}C^{1}C^{10}$	120.7(4)	$C^{13}C^{12}C^{11}$	110.8(4)
$C^{3}C^{2}C^{1}$	121.8(4)	$C^{14}C^{13}C^{17}$	99.8(3)
$O^{1}C^{3}C^{4}$	124.8(4)	$C^{14}C^{13}C^{12}$	106.1(3)
$O^{1}C^{3}C^{2}$	117.0(4)	$C^{17}C^{13}C^{12}$	115.2(4)
$C^{4}C^{3}C^{2}$	118.1(5)	$C^{14}C^{13}C^{18}$	110.7(3)
$C^{5}C^{4}C^{3}$	120.3(4)	$C^{17}C^{13}C^{18}$	112.8(4)
$C^{4}C^{5}O^{6}$	117.3(3)	$C^{12}C^{13}C^{18}$	111.4(3)
$C^{4}C^{5}C^{10}$	122.7(4)	$C^{8}C^{14}C^{13}$	114.1(4)
$O^{6}C^{5}C^{10}$	119.7(4)	$C^{8}C^{14}C^{15}$	120.4(4)
$O^{6}C^{7}C^{7A}$	110.9(4)	$C^{13}C^{14}C^{15}$	102.9(3)
$O^{6}C^{7}C^{8}$	111.8(4)	$C^{16}C^{15}C^{14}$	103.7(4)
$C^{7A}C^{7}C^{8}$	111.6(4)	$C^{15}C^{16}C^{17}$	105.0(3)
$C^{9}C^{8}C^{14}$	119.2(4)	$O^{2}C^{17}C^{13}$	109.8(3)
$C^{9}C^{8}C^{7}$	120.2(4)	$O^{2}C^{17}C^{16}$	112.7(3)
$C^{14}C^{8}C^{7}$	120.2(4)	$C^{13}C^{17}C^{16}$	105.0(4)
$C^{8}C^{9}C^{10}$	119.4(4)	$C^{18A}C^{18}C^{13}$	117.2(4)
$C^{8}C^{9}C^{11}$	122.3(4)	$O^{3}C^{20}O^{2}$	124.8(4)
$C^{10}C^{9}C^{11}$	118.2(4)	$O^{3}C^{20}C^{21}$	125.2(5)
$C^{1}C^{10}C^{5}$	116.2(4)	$O^{2}C^{20}C^{21}$	109.7(4)

distances $r_{H–H}$ obtained by measuring respectively the vicinal coupling constants $^{3}J_{H,H}$ and nonstationary nuclear Overhauser effects η_{NOE}. These measurement were carried out after complete assignment of signals in the ^{1}H and ^{13}C NMR spectra of steroid **V** performed by applying the combination of the following homo- and heteronuclear correlation procedures: DEPT-135 [18],

Table 3. Dihedral angles θ in compound **V**

Angle	θ, deg	Angle	θ, deg
$C^{10}C^{1}C^{2}C^{3}$	1.6(8)	$C^{9}C^{11}C^{12}C^{13}$	34.6(5)
$C^{3A}O^{1}C^{3}C^{4}$	0.1(8)	$C^{11}C^{12}C^{13}C^{14}$	–59.4(4)
$C^{3A}O^{1}C^{3}C^{2}$	177.1(5)	$C^{11}C^{12}C^{13}C^{17}$	–168.8(4)
$C^{1}C^{2}C^{3}O^{1}$	179.3(5)	$C^{11}C^{12}C^{13}C^{18}$	61.1(4)
$C^{1}C^{2}C^{3}C^{4}$	–3.4(8)	$C^{9}C^{8}C^{14}C^{13}$	–32.6(5)
$O^{1}C^{3}C^{4}C^{5}$	–179.0(5)	$C^{7}C^{8}C^{14}C^{13}$	154.9(4)
$C^{2}C^{3}C^{4}C^{5}$	4.0(7)	$C^{9}C^{8}C^{14}C^{15}$	–155.7(4)
$C^{3}C^{4}C^{5}O^{6}$	–176.3(4)	$C^{7}C^{8}C^{14}C^{15}$	31.8(6)
$C^{3}C^{4}C^{5}C^{10}$	–2.8(7)	$C^{17}C^{13}C^{14}C^{8}$	179.5(4)
$C^{7}O^{6}C^{5}C^{4}$	–155.8(4)	$C^{12}C^{13}C^{14}C^{8}$	59.6(4)
$C^{7}O^{6}C^{5}C^{10}$	30.5(5)	$C^{18}C^{13}C^{14}C^{8}$	–61.5(4)
$C^{5}O^{6}C^{7}C^{7A}$	83.6(4)	$C^{17}C^{13}C^{14}C^{15}$	–48.2(4)
$C^{5}O^{6}C^{7}C^{8}$	–41.6(5)	$C^{12}C^{13}C^{14}C^{15}$	–168.2(4)
$O^{6}C^{7}C^{8}C^{9}$	30.2(5)	$C^{18}C^{13}C^{14}C^{15}$	70.8(5)
$C^{7A}C^{7}C^{8}C^{9}$	–94.6(5)	$C^{8}C^{14}C^{15}C^{16}$	164.5(4)
$O^{6}C^{7}C^{8}C^{14}$	–157.4(4)	$C^{13}C^{14}C^{15}C^{16}$	36.2(5)
$C^{7A}C^{7}C^{8}C^{14}$	77.8(5)	$C^{14}C^{15}C^{16}C^{17}$	–9.6(6)
$C^{14}C^{8}C^{9}C^{10}$	–179.4(4)	$C^{20}O^{2}C^{17}C^{13}$	168.3(4)
$C^{7}C^{8}C^{9}C^{10}$	–6.9(6)	$C^{20}O^{2}C^{17}C^{16}$	–75.1(5)
$C^{14}C^{8}C^{9}C^{11}$	4.2(6)	$C^{14}C^{13}C^{17}O^{2}$	163.6(3)
$C^{7}C^{8}C^{9}C^{11}$	176.7(4)	$C^{12}C^{13}C^{17}O^{2}$	–83.3(4)
$C^{2}C^{1}C^{10}C^{5}$	–0.3(7)	$C^{18}C^{13}C^{17}O^{2}$	46.2(4)
$C^{2}C^{1}C^{10}C^{9}$	179.0(5)	$C^{14}C^{13}C^{17}C^{16}$	42.3(5)
$C^{4}C^{5}C^{10}C^{1}$	0.9(6)	$C^{12}C^{13}C^{17}C^{16}$	155.3(4)
$O^{6}C^{5}C^{10}C^{1}$	174.2(4)	$C^{18}C^{13}C^{17}C^{16}$	–75.2(4)
$C^{4}C^{5}C^{10}C^{9}$	–178.4(4)	$C^{15}C^{16}C^{17}O^{2}$	–139.6(4)
$O^{6}C^{5}C^{10}C^{9}$	–5.1(6)	$C^{15}C^{16}C^{17}C^{13}$	–20.1(6)
$C^{8}C^{9}C^{10}C^{1}$	173.8(4)	$C^{14}C^{13}C^{18}C^{18A}$	163.6(3)
$C^{11}C^{9}C^{10}C^{1}$	–9.6(6)	$C^{17}C^{13}C^{18}C^{18A}$	–85.6(5)
$C^{8}C^{9}C^{10}C^{5}$	–6.9(6)	$C^{12}C^{13}C^{18}C^{18A}$	45.8(5)
$C^{11}C^{9}C^{10}C^{5}$	169.7(4)	$C^{17}O^{2}C^{20}O^{3}$	–3.8(7)
$C^{8}C^{9}C^{11}C^{12}$	–5.8(6)	$C^{17}O^{2}C^{20}C^{21}$	–177.4(4)
$C^{10}C^{9}C^{11}C^{12}$	177.7(4)		

DQF-COSY [19], J-COSY [20], HSQC with decoupling [21] and without decoupling [22] from ^{13}C nuclei, COLOC [23], NOESY [24], and HOESY [25]. Fig. 2 demonstrates fragments of some among these spectra or their projections and sections used both for assignment of signals and for measuring the coupling constants and NOE.

The chemical shifts values obtained for ^{1}H and ^{13}C signals elucidated the extent of coupling of protons in the ^{1}H NMR spectrum of steroid **V** whose multiplets overlapped in the ^{1}H NMR spectrum (Fig. 2b) and permitted estimation of the corresponding $^{3}J_{H,H}$ and η_{NOE} values. For instance, in the region 2.1–2.4 ppm among the four overlapping signals ($H^{14}\alpha$, $H^{16}\alpha\beta$, $H^{11}\beta$, and $H^{12}\beta$)

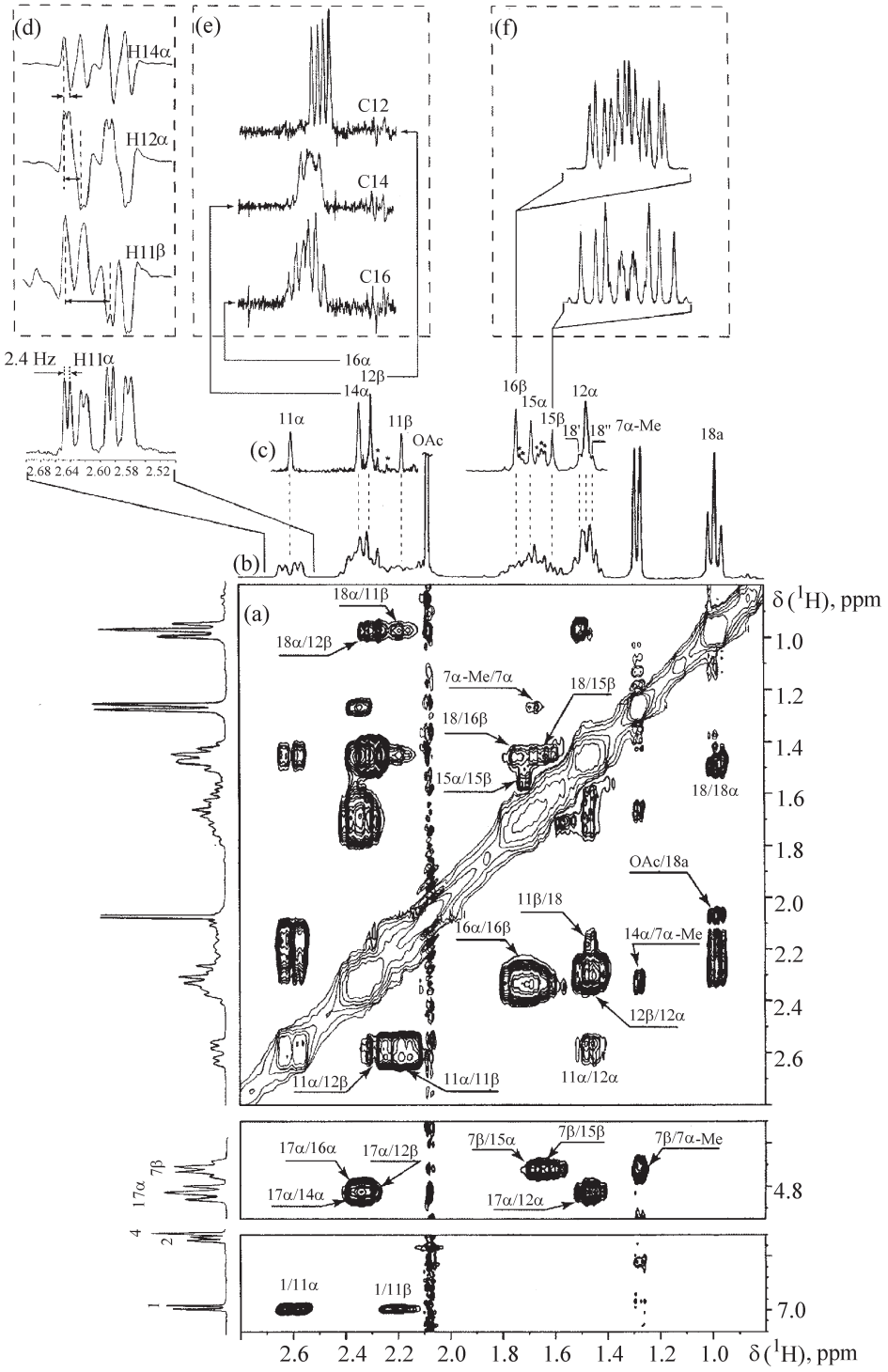


Fig. 2. Fragments of NMR spectra of estratetraene **V**. (a) NOESY (t_m 0.8 s); (b) ^{1}H NMR spectrum; (c) projection on the axis F_2 of J-COSY spectrum after its rotation through 45° corresponding to the ^{1}H NMR spectrum with a wide-band decoupling from protons (additional signals whose appearance is due to strong coupling are marked with asterisk); (d) F_1-sections of cross-peaks of the proton H^{11a} with H^{11b}, H^{12a}, and H^{14a} in the DQF-COSY spectrum (the corresponding active coupling constants are indicated with arrows between the antiphase components of the multiplet); (e) F_1-sections of cross-peaks of HSQC spectrum without decoupling from ^{13}C nuclei for signals C^{16}, C^{14}, and C^{12} in the region of overlapping of the corresponding protons H^{16a}, H^{14a}, and H^{12b} (only high-frequency components are shown for the corresponding antiphase satellite signals $^1\underline{H}$–^{13}C);(f) F_2- sections of signals from protons H^{15b} and H^{16b} in J-COSY spectrum after its turn through 45°.

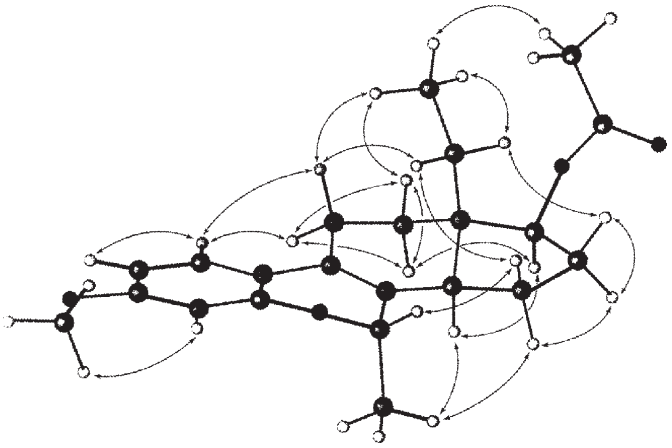


Fig. 3. Spatial arrangement of the molecule of estratetraene **V**. NOE observed in the spectrum NOESY (Fig. 2a) is indicated by arrows.

only the latter two are indirectly coupled, whereas all the three signals located in the range 1.5–1.8 ppm belong to the protons $H^{16\beta\alpha}$, $H^{15\alpha}$, and $H^{15\beta}$ comprising the mutual strongly coupled system. To simplify the analysis of the ^1H NMR spectra of these systems and to estimate the values of coupling constants $^3J_{H,H}$ we used the data of HSQC spectra registered without decoupling from ^{13}C nuclei [22] and of J-COSY spectra [20]. The first of these procedures reduces the degree of coupling between the protons attached to different carbons of the steroid skeleton (Fig. 2e), and the second method is characterized by enhanced resolution with respect to coupling constants (Fig. 2f) and permits obtaining therefrom $^1H\{^1H\}$ NMR spectrum [26] with a wide-band decoupling from protons (Fig. 2c). The spatial α- or β-orientation of the aliphatic protons was established by analysis of cross-peaks in the NOESY spectrum (Fig. 2a) that correspond to the direct dipole-dipole interactions of protons in steroid **V** demonstrated on Fig. 3.

The experimental values of the vicinal coupling constants $^3J_{H,H}^{exp}$ and the corresponding thereto calculated torsion angles θ^{calc} in comparison with the findings of the X-ray diffraction study and the results of geometry optimization for steroid **V** by the semiempirical PM3 method [27] are given in Table 4. In calculating the torsion angles and the values of vicinal coupling constants $^3J_{H,H}^{calc}$ the modified Karplus relationship (1) for substituted ethanes [28] was used.

$$^3J_{H,H} = A + B\mathrm{Cos}\theta + C\mathrm{Cos}2\theta + \mathrm{Cos}\theta[(\Delta S_1 + \Delta S_4) \times \mathrm{Cos}(\theta - 120^\circ) + (\Delta S_2 + \Delta S_3)\mathrm{Cos}(\theta + -120^\circ)] \quad (1)$$

Here $A = 8.17$, $B = -1.96$, and $C = 6.54$ Hz, ΔS_1, ΔS_2, ΔS_3, ΔS_4 are four empirical constants of the substituents in the ethane fragment accounting for their group electronegativity with respect to proton [29]. We used for steroid **V** the values given in [28] for ΔS of the following substituents: *t*-Bu (2.44 Hz), $CH{=}CH_2$ (2.68 Hz), OAc (4.12 Hz), C(O)Et (3.26 Hz), and H (0.00 Hz).

The comparison of values θ^{calc} (NMR) with the respective data from the X-ray analysis and PM3 calculations shows their good correlation (NMR/X-ray data: *R* 0.998, *SD* 5.7; NMR/PM3: *R* 0.997, *SD* 8.5; X-ray data /PM3: *R* 0.998, *SD* 6.4 where *R* is the correlation factor, *SD* is mean square deviation) Consequently, the spatial structure of steroid **V** prevailing in solution is close to its structure in the crystal.

The quantitative estimation of some proton–proton distances r_3 for steroid **V** in solution (Table 5) was derived from NOESY spectra. These distances were calculated using calibration by formula (2) which taking into account the anisotropy of diffusion movements of the molecules in the liquid was as follows:

$$r_{ij} = r^{st}(\sigma_{st}\tau_c^{st}/\sigma_{ij}\tau_c^{ij})^{-6} \quad (2)$$

We set as standard (r^{st}) the distance 2.47 Å between protons H^1 and H^2 obtained from the X-ray diffraction analysis. The rates of cross-relaxation σ_{ij} between protons *i* and *j* was estimated from the plot of the dependence of S_{ij}/S_{ij} on the mixing time τ_m using a linear approximation: $\sigma_{ij} = S_{ij}/S_{ij}\tau_m$ [30] where S_{ij} and S_{ij} are volume integrals of cross-peaks and diagonal peaks respectively in each of the 8 phase-sensitive NOESY spectra, registered at mixing time τ_m 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, and 1.0 s. Therewith the sum of the relaxation delay D1 and the mixing time τ_m in each experiment remained constant: $D1 + \tau_m = 2.2$ s. The correction for the anisotropy of the movement of molecule **V** in solution τ_c^{st}/τ_c^{ij} was calculated basing on the Woessner expression for evaluation of effective correlation time τ_c^{eff} in the case of axially-symmetric molecules [31]. To this end in the conformation obtained from the semiempirical calculations as possessing the largest heat of formation were determined the polar angles β_{ij} for all pairs of proton–proton vectors r_3, and the ratio of the diffusion constants $D_{||}/D_{\perp} = 6.9$ was calculated from the ratio of moments of inertia of this conformation [32].

The comparison or measurements of the proton–proton distances in solution r_3(NOE) with the corresponding data for the crystalline state r_3(X-ray) shows good agreement between these experimental findings

(*R* 0.988, *SD* 0.06) and consequently evidences that the prevailing conformation in solution of estratetra-ene **V** is similar to the spatial arrangement of the compound in the crystal.

The sum of the findings demonstrated the similarity of the steroid **V** conformations in solution and in the crystalline state. In the conformation of steroid **V** calculated by PM3 method which is the closest to the experimentally found the methyl group on the C^7 atom is in a pseudoaxial position.

The importance of this conclusion we tested experimentally on rats subjected to ovarioectomy by the model suggested in [33]. Steroid **V** orally administered in a daily dose of 5 mg per 1 kg of body weight for 35 days showed the osteoprotection effect in contrast to compound **VII** distinguished from **V** only by the absence of the methyl group on the C^7 atom.

This conclusion should be taken in consideration in planning the syntheses of steroids of the similar structure for the presence in the estrogen molecules the of just axial methyl group attached to C^7 atom in the α-region of the molecule enhances the activity of the hormone [34].

The introduction of methyl group into the position 7(α) of 8-isoanalogs of steroid estrogens in conformity to the previously suggested model [35] should reduce the uterotropic and probably osteoprotection activity. This conclusion was confirmed experimentally: Steroid **VIII** in a daily dose of 5 mg per 1 kg of body weight showed osteoprotection activity whereas compound **VI** in the same dose was virtually inactive. The results of investigation of steroids **V–VIII** effect on the development of the osteoporosis will be published elsewhere.

EXPERIMENTAL

The purity of all compounds was tested by TLC on Silufol plates using as eluents mixtures petroleum ether–ethyl acetate, 6:1, 4:1, and 3:1. Mass spectra were measured on MKh-1321 instrument at the ionizing chamber temperature 200–210°C. NMR spectra were registered at 295° K on spectrometer Bruker DPX-300 at operating frequencies 300.130 and 75.468 MHz for ^1H and ^{13}C nuclei respectively. The ^1H NMR spectra were recorded from solutions of 5–7 mg of the compound in 0.6 of ml $CDCl_3$, and for taking ^{13}C NMR spectra were used solutions of 30–50 mg of the substance in the same volume. The chemical shifts are reported with respect to TMS using as internal standards the solvent ($CDCl_3/CHCl_3$ = 99.9/0.1) signals [7.26 (^1H) and 76.90 ppm (^{13}C)] with an accuracy no less than ±0.002 and ±0.005 ppm respectively. Homonuclear coupling constants were measured with an accuracy of ±0.02 Hz from the ^1H NMR spectra obtained after additional processing of the free induction signal by Lorentz–Gauss transform and the procedure of direct linear prediction, and also by enhancing the digital resolution of the spectrum by zeros addition. The correlation spectra were obtained applying the software package for pulse sequences and spectrum processing supplied by Bruker.

Table 4. Experimental and calculated values of vicinal coupling constants $^3J_3$ (Hz) and torsion angles θ_{ij} (deg) in compound **V**

H_i-H_j	$^3J_{H,H}^{exp}$	θ^{calc} (NMR)	θ (PM3)	$^3J_{H,H}^{calc}$ (PM3)	θ (X-ray)	$^3J_{H,H}^{calc}$ (X-ray)
*11*α-*12*α	6.7	–37	–37	6.7	–35	7.0
*11*α-*12*β	<0.5[a]	–67×–81	–78	2.6	–84	2.0
*11*β-*12*α	11.4[b]	160	153	9.9	153	9.9
*11*β-*12*β	6.9	37	38	6.7	33	7.5
*14*α-*15*α	6.9[b]	–23	–44	3.9	–32	5.6
*14*α-*15*β	11.5[b]	–151	–165	12.8	–155	11.9
*17*α-*16*α	6.9	–15	–20	6.2	–17	6.6
*17*α-*16*β	9.2	–148	–139	7.7	–139	7.7
*16*α-*15*α	9.6[b]	13	15	9.5	9.2	9.8
*16*α-*15*β	6.8[b]	–138	–135	5.7	–132	5.1
*16*β-*15*α	2.5[b]	112	104	1.6	113	2.2
*16*β-*15*β	10.2[b]	–6	–16	9.0	–9.8	9.5

[a] The accuracy of evaluation of the coupling constant depended on the spectral line width.

[b] Obtained from the section F1 of HSQC spectrum with accuracy ±0.8 Hz.

7,18-Dimethyl-3-methoxy-6-oxa-8(14)-seko-estra-1,3,5(10),9(11)-tetraene-14,17-dione (II). A mixture of 10 g of isothiuronium salt **I** [14], 9.6 g of 2-methylcyclopentan-1,3-dione, and 280 ml of ethanol–water mixture, 1:1, was stirred for 48 h at 25°C. The precipitate was filtered off, washed on the filter with cold methanol, and dried in a vacuum. Yield 6.97 g (71.6%), mp 55–58°C. ^1H NMR spectrum, δ, ppm: 0.78 t (3H, $C^{18a}H_3$, *J* 7 Hz), 1.40 d (3H, C^7CH_3, *J* 6.5 Hz), 2.64 m (4H, $C^{15}H_2$ and $C^{16}H_2$), 3.77 s (3H, CH_3O), 5.64 m (1H, $C^{11}H$), 6.38 d (1H, C^4H, $J_{2,4}$ 2.4 Hz), 6.50 d.d (1H, C^2H, $J_{1,2}$ 9, $J_{2,4}$ 2.4 Hz), 7.37 d (1H, C^1H, $J_{1,2}$ 9 Hz). Found, %: C 73.09; H 7.46. $C_{20}H_{24}O_4$. Calculated, %: C 73.15; H 7.37.

17β-Acetoxy-7α,18-dimethyl-3-methoxy-6-oxaestra-1,3,5(10),8,14-pentaene (IV). A mixture of 6.9 g of compound **II**, 130 ml of ethanol, and 50 ml of concn. HCl was stirred for 3 h at room temperature, and

Table 5. Experimental and calculated proton–proton distances r_{ij} (Å) in compound **V**

H_i-H_j	r_{ij} (NOE)[a]	β_{ij}, deg	$(\tau_c^{ij}/\tau_c^{st})^{1/6}$	r_{ij} (NOE)[b]	r_{ij} (X-ray)
1-2	2.47	6	1.00	2.47	2.47
*1-11*α	2.19	18	0.97	2.14	2.20
*1-11*β	2.76	32	0.94	2.60	2.49
*12*α-*17*α	2.44	30	0.96	2.34	2.35
*11*α-*11*β	1.95	75	0.89	1.73	1.78
*11*α-*12*α	2.50	30	0.95	2.39	2.34
*12*α-*12*β	2.17	82	0.83	1.81	1.78

[a] Spherical calculation model. [b] Anisotropic calculation model.

then left standing for 24 h at 5°C. Precipitated steroid **III** was filtered off, washed with water till neutral washings, and dried in a vacuum. Compound **III** was dissolved in a mixture of 140 ml of dioxane and 14 ml of water, and 2 g of sodium borohydride was added thereto. The reaction mixture was stirred for 10 h, the excess reductant was decomposed by cautious addition of acetic acid. After the common workup the reaction products were acetylated with acetic anhydride in pyridine [13]. On recrystallization from methanol we obtained 4.8 g (64.5%) of target steroid **IV**, mp 114–116°C. ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, C^{18a}H$_3$, *J* 7.2 Hz), 1.33 d (3H, C^7-CH$_3$, *J* 6.3 Hz), 2.11 s (3H, CH_3CO), 3.78 s (3H, CH_3O), 4.95 m (2H, C^{7}H and C^{17}H), 5.37 s (1H, C^{15}H), 6.42 d (1H, C^{4}H, $J_{2,4}$ 2.4 Hz), 6.47 d.d (1H, C^{2}H, $J_{2,4}$ 2.4, $J_{1,2}$ 8.4 Hz), 7.22 d (1H, C^{1}H, $J_{1,2}$ 8.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 354 (86.5), 339 (100), 294 (80), 279 (95), 267 (22), 251 (25), 239 (5), 225 (4), 211 (4), 178 (4.5), 165 (6.5), 147 (11). Found, %: C 74.44; H 7.57. $C_{22}H_{26}O_4$. Calculated, %: C 74.55; H 7.39.

Catalytic hydrogenation of 17β-acetoxy-7,18-dimethyl-3-methoxy-6-oxaestra-1,3,5(10),8,14-pentaene (IV). *a*. To a solution of 1 g of compound **IV** in 280 ml of benzene was added 1 g of Raney nickel. The hydrogenation was carried out at 100–140°C and a pressure of 100–160 at till the charged volume of hydrogen exceeded about 150 times the amount required for hydrogenation of two double bonds. After the common workup the solvent was removed on a rotary evaporator, and the residue was crystallized from a mixture chloroform–methanol, 1:6. We obtained 0.35 g (34%) of **17β-acetoxy-7α,18-dimethyl-3-methoxy-6-oxa-estra-1,3,5(10),8(9)-tetraene (V)**, mp 169–171.5°C. ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, C^{18}CH$_3$, *J* 7.3 Hz), 1.26 d (3H, C^{7}CH$_3$, *J* 6.4 Hz), 1.45 m (3H, C^{18}H$_2$, C^{12}H$_\alpha$), 1.58 m (1H, C^{15}H$_\beta$), 1.66 m (1H, C^{15}H$_\alpha$), 1.72 m (1H, C^{16}H$_\beta$), 2.06 s (3H, CH_3CO), 2.16 m (1H, C^{11}H$_\beta$), 2.28 d.d (1H, C^{12}H$_\beta$, $J_{12\beta,12\alpha}$ –13.1, $J_{12\beta,11\beta}$ 6.9 Hz) 2.32 m (2H, C^{14}H$_\alpha$, C^{16}H$_\alpha$), 2.58 d.d.d (1H, C^{11}H$_\alpha$, $J_{11\alpha,11\beta}$ –17.1, $J_{11\alpha,12\alpha}$ 6.7, $J_{11\alpha,14\alpha}$ 2.4 Hz), 3.76 s (3H, CH_3O), 4.72 q (1H, C^{7}H$_\beta$, *J* 6.4 Hz), 4.81 d.d (1H, C^{17}H$_\alpha$, $J_{17\alpha,16\alpha}$ 6.9, $J_{17\alpha,16\beta}$ 9.2 Hz), 6.37 d (1H, C^{4}H, $J_{2,4}$ 2.5 Hz), 6.42 d.d (1H, C^{2}H, $J_{2,4}$ 2.5, $J_{1,2}$ 8.5 Hz), 6.97 d (1H, C^{1}H, $J_{1,2}$ 8.5 Hz). ^{13}C{^{1}H} NMR spectrum, δ, ppm: 9.82 (C^{18a}), 18.47 (C^{18}), 19.74 (C^7$\underline{C}$H$_3$), 21.05 ($\underline{C}$H$_3$CO), 21.47 (C^{15}), 22.46 (C^{11}), 28.23 (C^{16}), 29.54 (C^{12}), 43.88 (C^{13}), 45.05 (C^{14}), 55.08 (CH_3O), 72.07 (C^7), 82.12 (C^{17}), 101.99 (C^4), 105.94 (C^2), 115.78 (C^{10}), 122.69 (C^9), 122.88 (C^1), 128.63 (C^8), 152.37 (C^5), 159.70 (C^3), 170.97 (CH_3**C**O). Mass spectrum, *m/z* (I_{rel}, %): 356 (19), 341 (100), 267 (3), 241 (5.5), 201 (4). Found, %: C 74.01; H 7.92. $C_{22}H_{28}O_4$. Calculated, %: C 74.13; H 7.92.

On recrystallization of the residue from methanol we obtained 0.49 g (48.5%) of **17β-acetoxy-7α,18-dimethyl-3-methoxy-6-oxa-8-isoestra-1,3,5(10)-triene (VI),** mp 92–94°C. ^{1}H NMR spectrum, δ, ppm: 0.93 t (3H, C^{18}CH$_3$, *J* 7.5 Hz), 1.48 d (3H, C^{7}CH$_3$, *J* 6.3 Hz), 2.04 s (3H, CH_3CO), 3.74 s (3H, CH_3O), 4.37 m (1H, C^{7}H), 4.71 t (1H, C^{17}H, *J* 8.7 Hz), 6.34 d (1H, C^{4}H, $J_{2,4}$ 2.4 Hz), 6.46 d.d (1H, C^{2}H, $J_{2,4}$ 2.4, $J_{1,2}$ 8.4 Hz), 6.97 d (1H, C^{1}H, $J_{1,2}$ 8.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 358 (100), 343 (10), 299 (6.5), 283 (4.5), 269 (7.5), 257 (4), 227 (4), 215 (4), 202 (12), 189 (6), 187 (6), 175 (29), 161 (41.5), 137 (22). Found, %: C 73.54; H 8.49. $C_{22}H_{30}O_4$. Calculated, %: C 73.71; H 8.44.

b. To a solution of 0.5 g of compound **IV** in 50 ml of THF was added 0.3 g of 5% Pd on alumina; the hydrogenation was carried out till the end of hydrogen absorption. After the common workup the reaction product was recrystallized from methanol to obtain 0.32 g (64%) of target compound **V**. The mixted sample with the compound obtained in the previous experiment melted with no depression of the melting point. The ^{1}H NMR spectra of these substances were identical.

X-ray diffraction study of compound (V). Crystals of steroid V were grown from hexane to obtain colorless flattened pseudohexagonal pellets. The three-dimentional set of 1625 nonzero independent reflections ($I \geq 4\sigma_I$, $\sin\theta/\lambda \leq 0.79$) was obtained at room temperature from a single crystal of the size 0.3×0.15×0.2 mm on an autodiffractometer Syntex P2$_1$ (MOK_α-radiation, graphite monochromator). Crystals monoclinic, space group *P* 2$_1$/*C*, *a* 23.98(1), *b* 8.08(1), *C* 10.54(1) Å, β 110.38(10)°,

Z 4, D_x 1.237 g/cm^3. The results of the analysis are compiled in Tables 1–3. The coordinates of the basis atoms are available from the authors.

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