Russian Journal of Organic Chemistry, Vol. 37, No. 6, 2001, pp. 802–810. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 6, 2001, pp. 849–857.

Synthesis of 19,B-Bisnoranalogs of Steroid Androgens with *cis*-Fused B and C Rings

M. S. Egorov, E. V. Grinenko, A. D. Zorina, L. V. Balykina, S. I. Selivanov, and A. G. Shavva

St. Petersburg State University, St. Petersburg, 198904 Russia

Received July 5, 2000

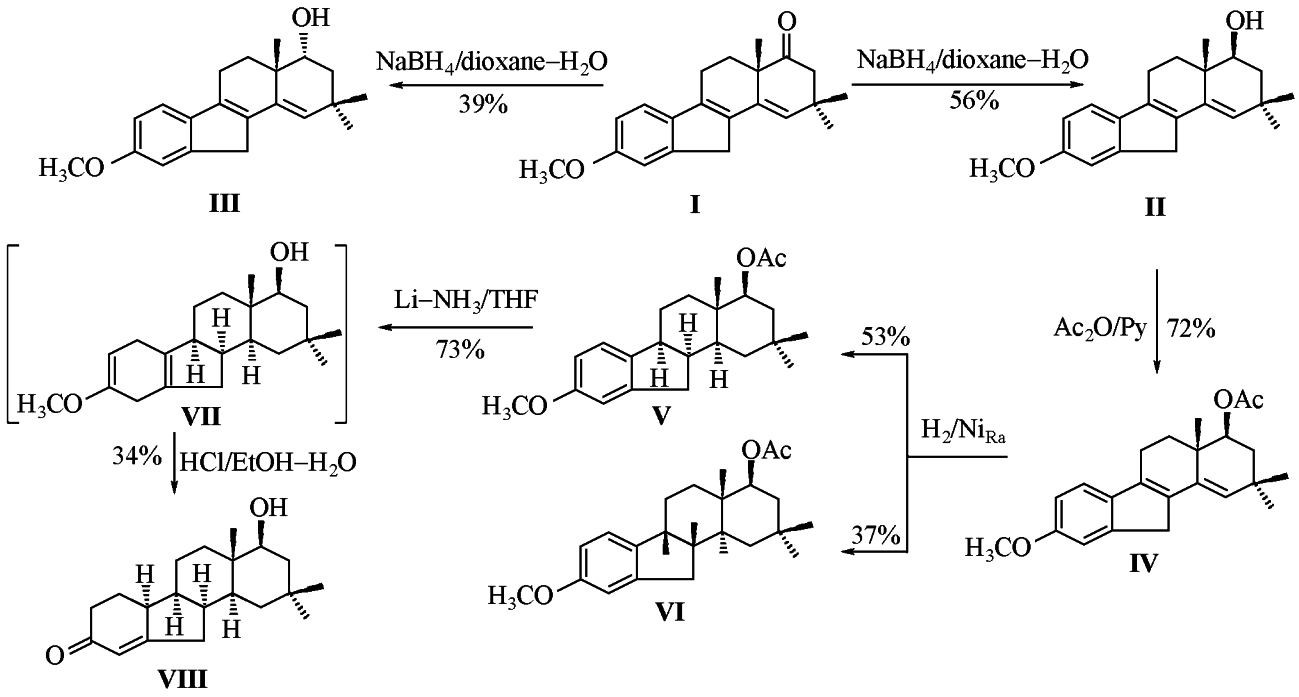
Abstract—Reduction by Birch procedure of 3-methoxy-B-nor-8-isoestra-1,3,5(10)-trienes followed by hydrolysis of reaction products furnished 19,B-bisnor-8,10-isoanalogs of steroid androgens. With the use of the correlation NMR spectroscopy a complete assignment of signals in the ^{1}H and ^{13}C NMR spectra was performed for two representatives of this steroid group, and their prevailing conformations in solution were established.

B-Nor-8-isoanalogs of steroid estrogens may possess more favorable biological properties than the natural hormones [1]. Such compounds from the androgen series were virtually unstudied; only in [2] was reported on Birch reduction of 17β-hydroxy-18-methyl-3-methoxy-B-nor-8-isoestra-1,3,5(10)-triene. The structure of the target steroid was tentatively established as 17β-hydroxy-18-methyl-3-oxo-B-nor-8-isoestr-4-ene. The study of correlation between the structure and biological activity of the new steroid group requires the knowledge of the configuration of the C^{10} centers thereof. This is the aim of the present investigation.

We selected as a model compound 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-8-isoestra-1,3,5(10)-triene that to our knowledge did not possess uterotropic activity at a dose up to 100 mg/kg body weight daily. Since the hormone-binding sites of the receptors for estrogens and androgens are of similar structure [3] we have presumed that the androgen analog synthesized would not possess hormone activity, and therefore we would be able to evaluate the promising properties of these substances effected through the nongenome mechanism.

The synthesis of the target steroid is presented in Scheme 1. The initial 16,16-dimethyl-3-methoxy-17a-

Scheme 1.



1070-4280/01/3706-0802$25.00 © 2001 MAIK "Nauka/Interperiodica"

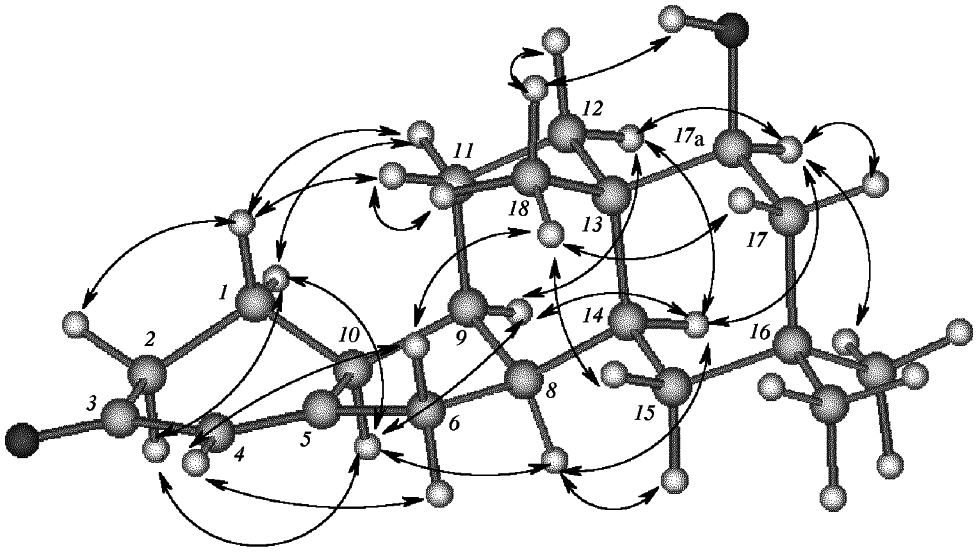


Fig. 1. Spatial structure of 17aβ-hydroxy-16,16-dimethyl-3-oxo-D-homo-B-nor-8,10-isoestr-4-ene (**VIII**). Overhauser effects most important for establishing the conformation are marked with arrows.

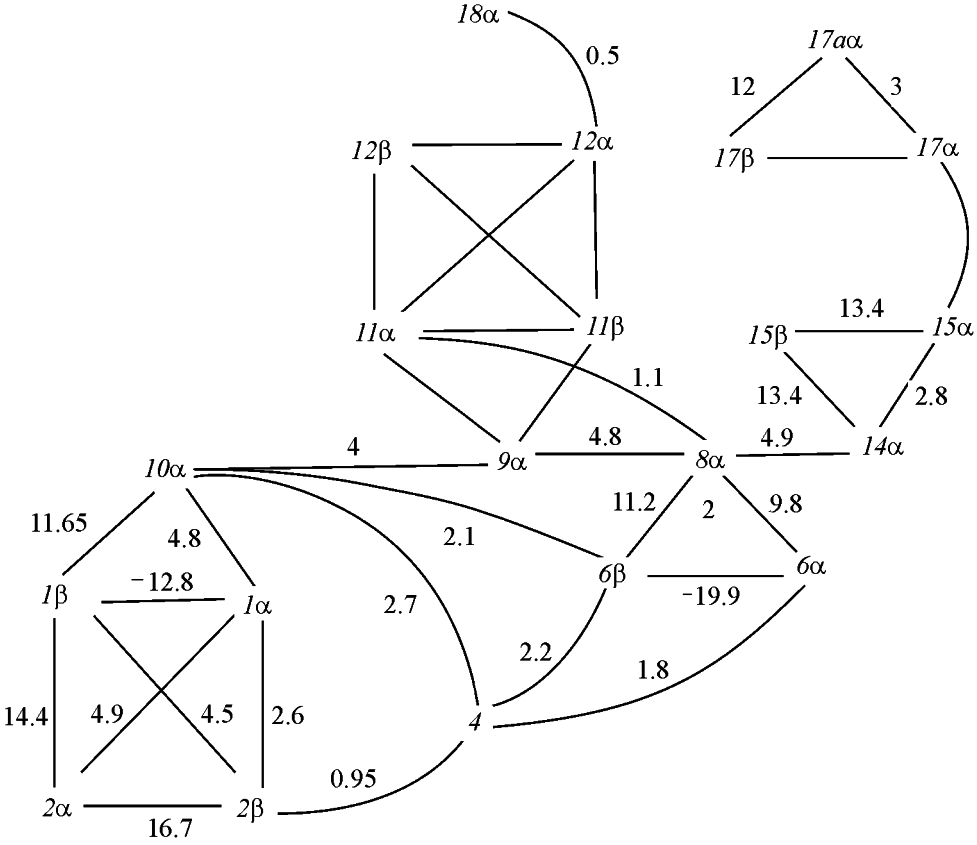


Fig. 2. Scheme of protons spin-spin coupling in the molecule of 17aβ-hydroxy-16,16-dimethyl-3-oxo-D-homo-B-nor-8,10-isoestr-4-ene (**VIII**), and coupling constants (Hz) for proton pairs not included into strongly coupled spin systems.

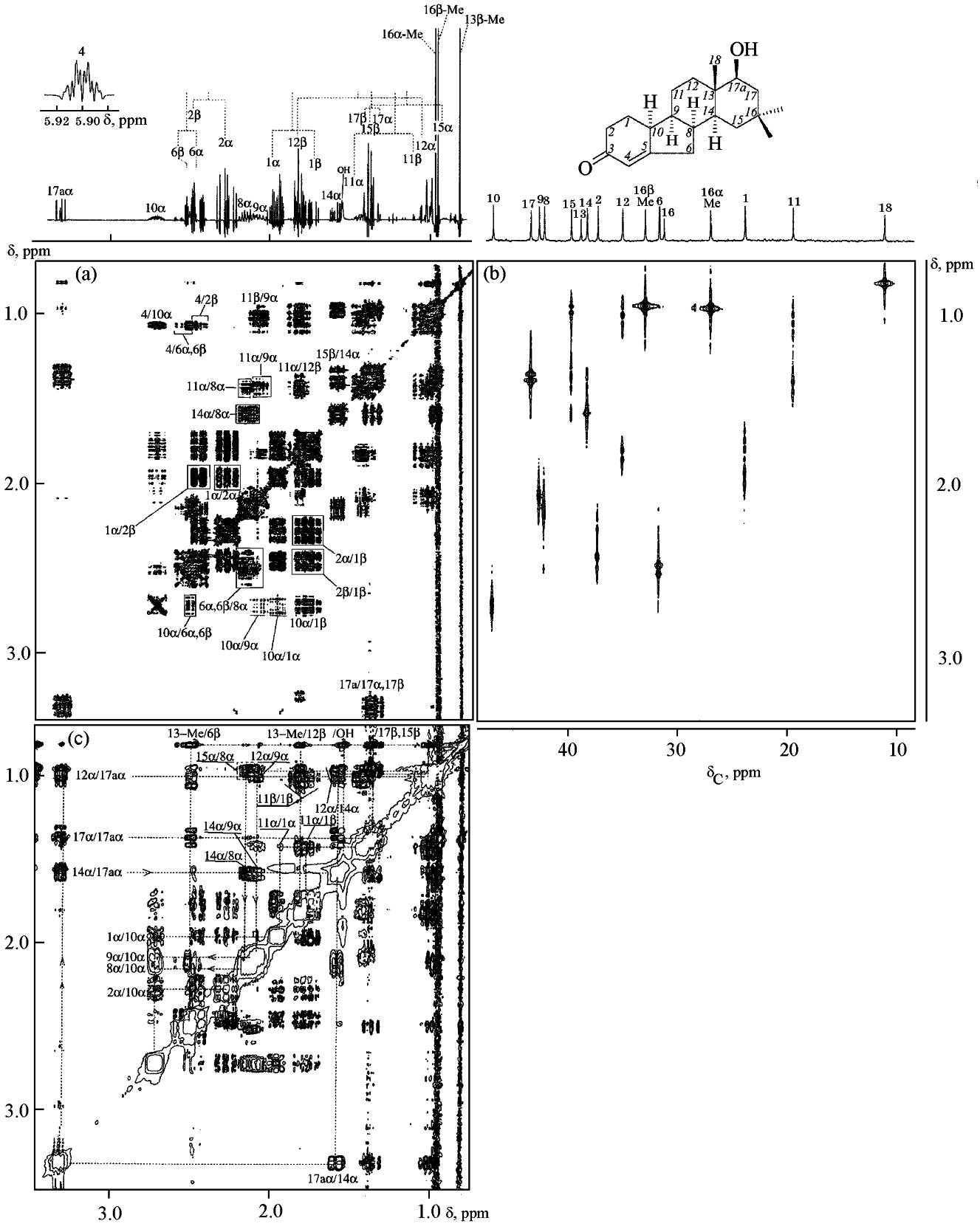


Fig. 3. NMR spectra of 17aβ-hydroxy-16,16-dimethyl-3-oxo-D-homo-B-nor-8,10-isoestr-4-ene (**VIII**), $CDCl_3$, 20°C: (a) COSY-DQF; (b) HETCORR; (c) NOESY.

Table 1. Chemical shifts (δ, ppm) in the ^1H and ^{13}C NMR spectra of 17aβ-hydroxy-16,16-dimethyl-3-oxo-D-homo-B-nor-8,10-isoestr-4-ene (**VIII**), $CDCl_3$, 20°C

Atom	δ_C, ppm	$^1H_\alpha$, δ, ppm		$^1H_\beta$, δ, ppm
C^1	23.86	1.95		1.77
C^2	37.27	2.29		2.45
C^3	199.5		–	
C^4	123.77		5.90	
C^5	174.86		–	
C^6	31.71	2.48		2.51
C^8	42.21	2.14		–
C^9	42.67	2.06		–
C^{10}	46.87	2.72		–
C^{11}	19.49	1.43		1.02
C^{12}	35.03	1.01		1.83
C^{13}	38.86		–	
C^{14}	38.27	1.58		–
C^{15}	39.73	0.96		1.37
C^{16}	31.28	–		–
C^{16}–CH_3	32.99	–		0.95
C^{16}–CH_3	27.02	0.96		–
C^{17}	43.43	1.31		1.41
C^{17a}	76.48	3.31		–
C^{18}	11.13	–	0.81	
C^{17a}–OH	–	–		1.55

oxo-D-homo-B-norestra-1,3,5(10),8,14-pentaene (**I**) was prepared under conditions described in [4], its spectral characteristics were as expected.

The reduction of compound **I** with sodium borohydride afforded alcohols **II** and **III** whose structure was established from mass spectra. In the mass spectrum of steroid **III** is present a peak $[M-18]^+$ indistinguishable in the spectrum of compound **II**. This result is characteristic of steroid alcohols with axial (here α) and equatorial (here β) hydroxy groups respectively [5].

Steroid **IV** was obtained by acetylation of alcohol **II** as described in [4].

The hydrogenation of acetate **IV** on Raney nickel afforded 8-isoanalog **V** in a mixture with 9-isoanalog **VI**. These steroids were completely separated by crystallization from ethanol. The structure of compounds **V** and **VI** was established from the signals in the NMR spectra characteristic of this type compounds [4].

Steroid **V** was reduced under conditions of Birch reaction. The hydrolysis of the intermediate product **VII** by hydrochloric acid in methanol resulted in the target compound **VIII**.

The spatial structure of compound **VIII** (Fig. 1) was proved with the use of NMR spectroscopy. To this end we applied to the assignment of the proton signals correlation spectra COSY-90 [6], COSY-DQF [7], HETCORR [8], COLOC [9], and NOESY [10]. We performed a complete assignment of the signals in the ^1H and ^{13}C NMR spectra, in particular the resonances of eighteen protons in the strong field region 1.0–2.8 ppm (Table 1).

As a result was established the scheme of coupling between protons through the coupling constants, and the values of the coupling constants were determined for the pairs of protons not included into strongly coupled spin systems (Fig. 2).

In establishing the coupling scheme we chose initially the proton signals that were easy to identify: H^4 and H^{17a} at 5.90 and 3.31 ppm (Fig. 3). The first one is not within the spectral interval of the COSY-DQF spectrum on Fig. 3a since in this case the spectral width was taken less than the total spectral range in order to get better resolution. Nevertheless, in this spectrum are present the reflected cross-peaks corresponding to coupling of the H^4 proton with one methine proton at 2.72 ppm and with two methylene groups in the 2.5 ppm region (the number of protons at the respective ^{13}C nuclei has been established from the DEPT-135 and HETCORR spectra). Among methine protons only H^{10} can be coupled with it (^4J 2.7 Hz). Besides this H^{10} proton is coupled with five more protons in the upfield part of the COSY-DQF spectrum (Fig. 3a). The signal of one among them at 2.06 ppm according to DEPT-135 and HETCORR belongs to a methine proton (Fig. 3b). Consequently, this is H^9 proton. The rest four protons originate from two methylene groups (Figs. 3a and 3b, and one of them contains a proton showing Overhauser effect (NOE) with the protons at C^{18} atom (Fig. 3c) and with H^4 (the corresponding cross-peak is outside the spectral region on Fig. 3c). Thus the methylene group in question is at the C^6 carbon atom, and the proton showing NOE with C^{18} atom has β-orientation. The comparison of the cross-peaks in the spectra COSY-DQF and NOESY reveals that the protons of the second methylene group are vicinal with respect to H^{10} and consequently are attached to C^1 atom. Therewith the pseudoaxial proton H^1 possesses three large coupling constants (~11 Hz) with the neighboring protons whereas the pseudoequatorial H^1 has a single large coupling constant. The corresponding cross-peaks unambiguously indicate the position of signals from the protons bonded to C^2 (Figs. 2, 3a). One of the protons shows NOE with H^{10}. Taking into account the interatomic distances the latter is only

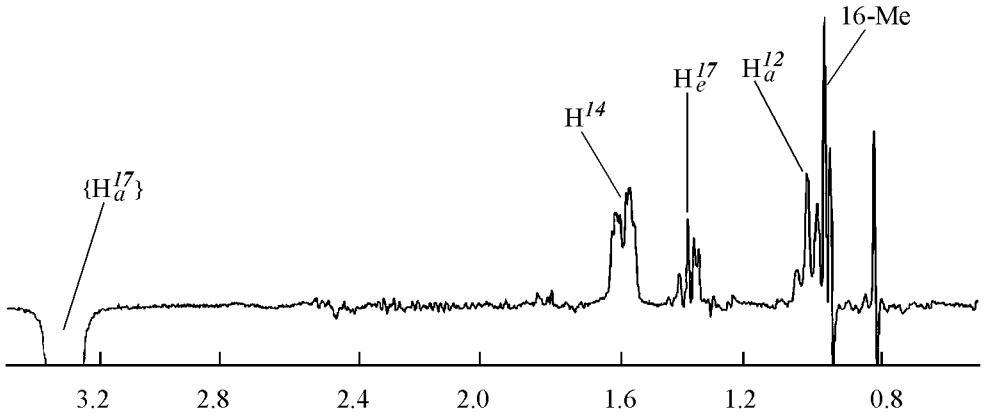


Fig. 4. 1D NOE Difference spectrum of 17aβ-hydroxy-16,16-dimethyl-3-oxo-D-homo-B-nor-8,10-isoestr-4-ene (**VIII**), obtained at irradiation with radiofrequency pulse of H^{17a}_{α}, $CDCl_3$, 20°C.

possible at *syn*-pseudoaxial orientation of the proton with respect to H^{10}. NOE was also observed with H^{10} and two other methine protons (with signals at 2.06 and 2.14 ppm) among the last three. These can be only H^{8}_{α} and H^{9}_{α}. With these protons occurs also NOE with the last methine proton at 1.58 ppm, H^{14}, whose α-orientation is confirmed by its NOE with H^{17a}_{α} at 3.31 ppm (Fig. 3c).

Thus all methine protons including H^{10} are located in the α-region of the molecule. Therefrom follows conformation of the ring A where H^{2}_{α} is pseudoaxial and is in *syn*-orientation with respect of H^{10}, and H^{1}_{α} atom is in pseudoequatorial position. This structure of A ring corresponds to semichair conformation in agreement with the characteristic geminal coupling constant $^{2}J(2\alpha, 2\beta)$ 16.7 Hz [11]. This fact and also the values of the vicinal coupling constants between the protons attached to C^{1} and C^{2} atoms (Fig. 2) evidence that the mentioned conformation of compound **VIII** prevails in solution whereas many Δ^{4}-3-oxo-19-noranalogs of steroid androgens with a six-membered B ring possess considerably more flexible conformation of A ring [11].

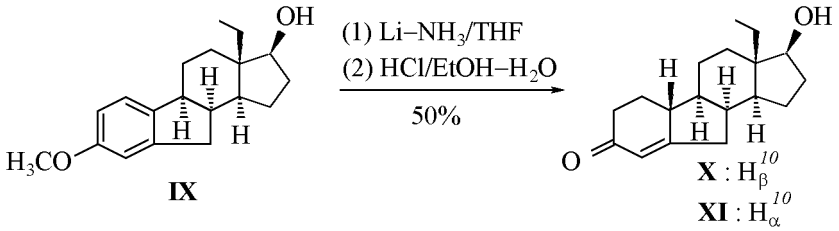
The H^{17a}_{α} proton is coupled only with a pair of protons attached to C^{17} atom, therewith the axial H^{17}_{β} proton at 1.41 ppm is additionally identified as exhibiting NOE with β-$C^{18}H_3$ (Figs. 3a, 3c). At the same time H^{17a}_{α} shows NOE with a proton from another methylene group with which it is not coupled. This proton can be only the axial proton H^{12a}_{α} with the *syn*-orientation with respect to H^{17a}_{α} as is also confirmed by observed therewith a characteristic long-range coupling constant (0.5 Hz) with the protons at C^{18} [12]. The chemical shift of H^{12}_{β} was determined from the HETCORR spectrum (Fig. 3b). The proton pair linked to C^{15} was identified in the ^{1}H spectrum from the presence of coupling constants with H^{14}, therewith the axial proton H^{15}_{β} unlike the equatorial H^{15}_{α} had two large coupling constants (~13 Hz) whereas the second one only a single large constant. The methylene protons at C^{11} atom were identified by the coupling constants with H^{9}_{α} and with protons attached to C^{12}, and the spatial orientation thereof (α or β) was revealed by NOE H^{11}_{β} showed with β-$C^{18}H_3$. Finally, the more downfield of the two methyl groups (0.95 and 0.96 ppm) linked to C^{16} exhibited NOE with H^{17a}_{α} and consequently is located in the α-region (Fig. 4).

Thus in compound **VIII** under consideration the proton H^{10} is located in the α-region of the molecule. Our conclusion is in contrast to that of Rao et al. [2] who has assigned to the H^{10} proton the β-orientation in the hydrolysis product **X** obtained from the steroid **IX** after reduction along Birch reaction (Scheme 2). Since compound **X** differed from the above described steroid **VIII** with α-oriented H^{10} only by the size and substituents in the D ring which is remote from the reaction center we undertook the synthesis of the former in order to establish its spatial structure by NMR means.

The synthesis was carried out in two steps with an overall yield 50% proceeding from 17β-hydroxy-18-methyl-3-methoxy-B-nor-8-isoestra-1,3,5(10)-triene (**IX**) (Scheme 2) that was prepared as in [4].

With the compound **XI** obtained was carried out the assignment of signals in the ^{1}H and ^{13}C NMR spectra and coupling constants determination along the procedure described above for compound **VIII**. Its prevailing conformation in solution was deduced from these data (Table 2, Fig. 5). The homonuclear

Scheme 2.



coupling constants observed in the ^{1}H NMR spectrum thereof are consistent with this structure that is similar in the spatial arrangement of the A, B, and C rings to that of compound **VIII**. For instance, NOE revealed between approached 1,3-*syn*-pseudoaxial protons indicates that the C rings in both compounds and the D ring of compound **VIII** are present in the *chair* conformation. These protons in α- and β-regions of the molecule compose two groups, and in each group they are successively approached to each other. Therewith the H^{10} proton exhibits NOE only with the protons from α-region: with H^2_α (pseudoaxial), H^8_α, H^9_α and H^1_α. Besides the value $^3J(H^{10}_\alpha, H^9_\alpha)$ equal to ~4 Hz (Fig. 2) also is consistent with the α-orientation of the H^{10} proton since if it be located in β-region the expected $^3J(H^{10}_\beta, H^9_\alpha)$ value should be about 14 Hz as for *trans*-diaxial vicinal protons.

Therefore the assumed in [2] β-orientation of the H^{10} proton in the hydrolysis product was erroneous: the obtained steroid had structure **XI** and not **X**.

The data obtained show that the reduction under Birch conditions of 3-methoxy-B-nor-8-isoestra-1,3,5(10)-trienes with no other substituents in the A, B, and C rings followed by hydrolysis effected with HCl gives rise to 3-oxo-B-nor-8,10-isoestr-4-enes notwithstanding the size of the D ring and substituents therein.

Table 2. Chemical shifts (δ, ppm) in the ^{1}H and ^{13}C NMR spectra of 17β-hydroxy-18-methyl-3-oxo-B-nor-8,10-isoestr-4-ene (**XI**), $CDCl_3$, 20°C

Atom	δ_C, ppm	$^1H_\alpha$, δ, ppm		$^1H_\beta$, δ, ppm
C^1	24.00	1.96		1.77
C^2	37.15	2.25		2.43
C^3	199.58		–	
C^4	123.58		5.88	
C^5	175.22		–	
C^6	31.83	2.53		2.70
C^8	39.85	2.45		–
C^9	42.90	2.07		–
C^{10}	46.30	2.74		–
C^{11}	20.68	1.42		0.92
C^{12}	31.98	0.80		2.17
C^{13}	44.35		–	
C^{14}	44.81	1.52		–
C^{15}	18.61	1.46		1.46
C^{16}	30.18	2.07		1.52
C^{17}	83.27	3.65		-
C^{18}	23.44	–	1.49	
C^{18}–CH_3	9.70		0.93	
C^{17}–OH	–	–		1.53

EXPERIMENTAL

Mass spectra were measured on MKh-1321 instrument at ionizing chamber temperature 200–210°C.

The NMR spectra were registered on a spectrometer Bruker DPX-300 at operating frequencies 300.130 and 75.468 MHz for ^{1}H and ^{13}C nuclei respectively. The spectra were recorded from solutions in 0.6 ml of $CDCl_3$ containing 5–7 mg of the substance for ^{1}H spectra and 30–50 mg for ^{13}C spectra.

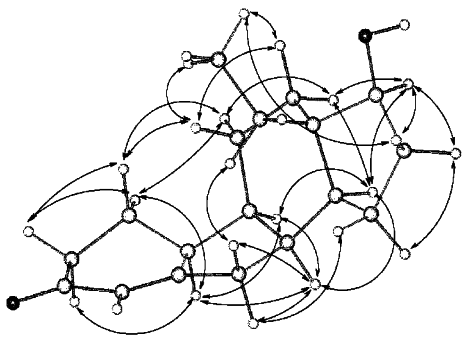


Fig. 5. Spatial structure of 17β-hydroxy-18-methyl-3-oxo-B-nor-8,10-isoestr-4-ene (**XI**). Overhauser effects most important for establishing the conformation are marked with arrows.

The chemical shifts were measured in the δ scale using as internal standard the residual peak of $CHCl_3$ in the solvent (δ 7.26 ppm, δ_C 76.90 ppm). The accuracy was no less than ±0.01 ppm. The homonuclear coupling constants were measured with the accuracy ±0.02 Hz from ^{1}H NMR spectra after the lines were refined by Lorentz-Gauss transformation [13].

All experiments were carried out in a double-channel 5 mm probe, field stabilization on deuterium, standard pulse sequence in the quadrature detection mode. The duration of the π/2 pulse at power parameter *PL* –6 dB was 6.45 μs for ^{1}H and 5.1 μs for ^{13}C nuclei. In the spectra registered with decoupling of protons WALTZ-16 [14] pulse sequence was used.

Always before effecting the Fourier-transform procedure the zeros were supplemented, and apodization was performed. Various weight functions were applied depending on the target of the experiment.

Principal parameters in registration and processing of NMR spectra. ^{1}H NMR: number of points for data sampling *TD* 32K; spectral width *SW* 2.4 kHz; number of scans *NS* 128; relaxation delay *Dl* 3 s; the parameters of Lorentz-Gauss transformations *LB* –2 Hz, *GM* 0.2; supplementing with zeros: *SI* 64 K or 128 K. ^{13}C NMR: *TD* 32 K; *SI* 64 K; *SW* 16.5 kHz; *NS* 512; *D1* 5 s; parameter of the exponential weight function *LB* 3 Hz.

2D COSY-90 [6]: number of points for data sampling *TD*2 512; width *SW1= SW2* 2.4 kHz for each of the 256 t_1-increments; *D*1 3 s; size of the spectra matrix 512 × 512; apodization function along t_1 and t_2 coordinates $\sin(\pi t/t_{max})$; spectrum of the absolute values.

2D COSY-DQF [7]: *TD*2 2 K; *SW*1 = *SW*2 2.4 kHz; *NS* 16 for each of the 512 t_1-increments; *D*1 3 s; phase-sensitive detection with time-proportional phase increase (TPPI); apodization function $\sin(\pi t/t_{max})$. Spectral matrix size 2048 × 1024.

^{13}C-^{1}H-HETCORR [8]: *TD* 1 K; *SW*1 1.2 kHz; *SW*2 3.5 kHz; *NS* 56 for each of the 256 t_1-increments; *D*1 2 s; delay for evolution of direct heteronuclear coupling constant *D*2 3.7 ms, *D*3 2.5 ms; apodization function for t_2 coordinate is exponential (*LB* 3 Hz), for t_1 $\sin(\pi t/t_{max}+ \pi/2)$; the size of spectral matrix for absolute values 1024 × 512.

COLOC [9]: *TD*2 1 K; *SW*1 2.4 kHz; *SW*2 3.5 kHz; *NS* 256 for each of the 128 t_1-increments; *D*1 1 s; delays for evolution of heteronuclear coupling constants ($^nJ_{C-H}$, *n* 2.3): *D*6 62.5 ms, *D*8 41.7 ms. Apodization function $\sin(\pi t/t_{max})$ for time coordinate t_2, and $\sin(\pi t/t_{max}+ \pi/2)$ for t_1; the size of spectral matrix for absolute values 1024 × 512.

NOESY [10]: *TD*2 1 K; *SW*1 = *SW*2 2.4 kHz; *NS* 16 for each of the 256 t_1-increments; *D*1 2 s; mixing time *D*8 0.5 and 1.0 s. Phase-sensitive detection with TPPI; apodization function $\sin(\pi t/t_{max}+ \pi/2)$; spectral matrix size 1024×512.

The purity of all compounds was tested by TLC on Silufol plates in solvent systems petroleum ether–ethyl acetate, 4 : 1 and 3 : 1.

16,16-Dimethyl-3-methoxy-17a-oxo-D-homo-B-norestra-1, 3,5(10),8,14-pentaene (I) was prepared along the procedure from [4]. mp 105–109°C. ^{1}H NMR spectrum (δ, ppm): 1.08 s, 1.23 s and 1.30 s (3H each, methyl groups at D ring), 5.60 s (1H, H^{15}), 6.81 d.d (1H, H^2, $^3J_{2,1}$ 8.1 Hz, $^4J_{2,4}$ 2.4 Hz), 7.01 d (1H, H^4, $^4J_{4,2}$ 2.1 Hz), 7.13 d (1H, H^1, $^3J_{1,2}$ 8.1 Hz). Found, %: C 81.95; H 8.09. $C_{21}H_{24}O_2$. Calculated, %: C 81.78; H 7.84.

Reduction of steroid I with sodium borohydride. To a solution of 5 g (16 mmol) of steroid **I** in 90 ml of dioxane and 9 ml of water was gradually added at stirring 4.5 g (119 mmol) of sodium borohydride. The reaction mixture was stirred for 8 h at 24°C and left overnight. The excess reducing agent was destroyed by cautious addition to the mixture of concentrated acetic acid till the end of foaming. The mixture then was diluted with water, the reaction products were extracted into chloroform, and the extract was dried with sodium sulfate. The solvent was removed on a rotary evaporator, and the residue was subjected to chromatography on silica gel, 5–40 μ, gradient elution in the system petroleum ether–ethyl acetate. The separated substances were crystallized from a mixture petroleum ether–ethyl acetate. The reaction was twice carried out. We obtained 5.55 g of 17aβ-hydroxy-16,16-dimethyl-3-methoxy-D-homo-B-norestra-1,3,5(10),8.14-pentaene (**II**) (55.5%), mp 98–100°C, and 3.9 g of 17aα-hydroxy-16,16-dimethyl-3-methoxy-D-homo-B-norestra-1,3,5(10),8.14-pentaene (**III**) (39%), mp 114–115°C. Mass spectrum of compound **II**, *m/z* (I_{rek}, %): 310 (57), 295 (100), 277 (2), 262 (2), 251 (2), 235 (2), 165 (3.4). Mass spectrum of compound **III**, *m/z* (I_{rel}, %): 310 (60), 295 (100), 292 (3.8), 277 (10), 262 (6), 248 (5.6), 235 (5.8), 209 (5.4), 165 (7.3).

17aβ-Acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-norestra-1,3,5(10),8.14-pentaene (IV). To a solution of 5.55 g (18 mmol) of steroid **II** in 20 ml

of pyridine heated on a boiling water bath was added 50 ml of acetic anhydride. After 4 h the mixture was poured on ice and extracted with chloroform. The extract was washed successively with diluted hydrochloric acid, sodium carbonate solution, and water. The solvent was removed in a vacuum. The product was crystallized from methanol to obtain 4.55 g (72%) of steroid IV, mp 93–95°C. Mass spectrum of compound **IV**, *m/z* (I_{rel}, %): 352 (50), 337 (42), 277 (100), 262 (36), 247 (14), 165 (15), 121 (27). Found, %: C 78.24; H 7.84. $C_{23}H_{28}O_3$. Calculated,%: C 78.38; H 8.01.

Catalytic hydrogenation of steroid IV. A solution of 4.55 g (13 mmol) of steroid IV was subjected to hydrogenation on 10 g of Raney nickel in 270 ml of benzene under hydrogen pressure 50–150 at 60–120°C. On completing the reaction the catalyst was filtered off, the solution was evaporated. By crystallization from 50 ml of ethanol was first obtained 2.45 g (53%) of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-8-isoestra-1,3,5(10)-triene (**V**), mp 125–128°C, and then 1.7 g of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-9-isoestra-1,3,5(10)-triene (**VI**), mp 110–112°C. ^{13}C NMR spectrum (δ_C, ppm) of compound **V**: 11.7, 21.2, 26.6, 26.7, 31.5, 33.0, 33.3, 35.5, 38.0, 38.8, 39.7, 40.0, 44.3, 44.4, 55.3, 78.7, 110.5, 111.6, 123.9, 141.1, 143.9, 158.5, 170.6. Found, %: C 77.3; H 9.45. $C_{23}H_{32}O_3$. Calculated,%: C 77.49; H 9.05. ^{13}C NMR spectrum (δ_C, ppm) of compound **VI**: 10.4, 20.4, 21.1, 26.4, 31.2, 31.8, 33.1, 36.6. 37.4, 37.5, 38.7, 39.4, 41.5, 42.2, 55.3, 78.1, 110.9, 111.1, 122.8, 137.0, 144.7, 158.4, 170.6. Found, %: C 77.65; H 9.44. $C_{23}H_{32}O_3$. Calculated,%: C 77.49; H 9.05.

17aβ-Acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-8,10-isoestr-4-ene (VIII). To a solution of 2.3 g (6 mmol) of steroid **V** in 160 ml of tetrahydrofuran was added at –60°C 300 ml of liquid ammonia. Then at stirring was gradually added 2.5 g (0.357 mol) of finely cut lithium. Four hours later under the same conditions was slowly added 70 ml of anhydrous ethanol. After usual workup [15] the residue was crystallized from a mixture petroleum ether–chloroform. The 1.5 g of colorless crystals of compound **VII** was dissolved in 150 g of ethanol at heating on a boiling water bath, to the solution was added 100 ml of 3 M HCl, the mixture was boiled for 2 h, then poured into 1.2 liter of water, and after the usual workup the residue was crystallized from a mixture hexane–chloroform. We obtained 1.2 g (61%) of steroid **VIII**, mp 180–182°C. ^{1}H and ^{13}C NMR spectra are given in Table 1. Found, %: C 79.44; H 10.22. $C_{20}H_{30}O_2$. Calculated,%: C 79.42; H 10.00.

17β-Hydroxy-18-methyl-3-methoxy-B-nor-8-isoestra-1,3,5(10)-triene (IX) was prepared similarly to compound **V**. mp 138–140°C (publ. mp 148–149°C [2]). ^{1}H NMR spectrum (δ, ppm): 0.94 t (3H, C^{18}–CH_3), 0.95 m (1H, H_α^{12}), 1.23 m (1H, H_β^{11}), 1.60–1.73 m (6H, H^{14}, H_α^{15}, H_β^{15}, H_β^{16}, $2H^{18}$), 1.87 m (1H, H_α^{11}), 2.21 m (2H, H_α^{16}, H_β^{12}), 2.71 m (1H, H_α^{8}), 2.79 m (1H, H^6), 2.95 m (1H, H_α^{9}), 3.11 (1H, H^6), 3.78 t (1H, H_α^{17}), 3.79 (3H, OCH_3), 6.72 d.d (1H, H^2, $^3J_{2,1}$ 8.4 Hz, $^4J_{2,4}$ 2.7 Hz), 6.76 d (1H, H^4, $^4J_{4,2}$ 2.4 Hz), 7.12 d (1H, H^1, $^3J_{1,2}$ 8.1 Hz). ^{13}C NMR spectrum (δ_C, ppm): 9.70, 18.12, 23.60, 27.95, 30.41, 32.18, 33.82, 41.86, 44.29, 44.37, 45.43, 55.26, 83.78, 110.43, 111.95, 124.37, 140.72, 144.14, 158.52.

17β-Hydroxy-18-methyl-3-methoxy-3-oxo-B-nor-8,10-isoestr-4-ene (XI). 0.707 g (2 mmol) of steroid **IX** was reduced under Birch reaction conditions as described for compound **V**. The reaction product was hydrolyzed similarly to compound **VII**. The reaction mixture obtained was subjected to chromatography on a column with a reversed phase sorbent (silica gel–phenyl, 30 μ, prepared along procedure [16]), gradient elution in a system water–acetone. The fractions containing the target product were combined, poured into water, the product was extracted into chloroform, and after a usual workup recrystallized from a mixture ethyl acetate–petroleum ether. We obtained 0.35 g (50%) of steroid XI, mp 136–138°C (cf. [2]: mp 178–179°C). ^{1}H and ^{13}C NMR spectra are presented in Table 2. Found, %: C 78.53; H 9.41. $C_{18}H_{26}O_2$. Calculated, %: C 78.79; H 9.55.

REFERENCES

1. USA Patent 3546292, 1970. *Ref. Zh. Khim.*, 1971, 13N467P.
2. Rao, G.S.R., Subba, and Sundar, N.Sh., *Indian J. Chem.* 1977, vol. 15B, no. 7, pp. 585–588.
3. Ekena, K., Katzenellenbogen, J.A., and Katzenellenbogen, B.S., *J. Biol. Chem.*, 1998, vol. 273, no. 2, pp. 693–699.
4. Krylova, E.B., Martynov, V.F., and Shavva, A.G., *Zh. Org. Khim.*, 1978, vol. 14, no. 12, pp. 2518–2523.
5. Vul'fson, N.C., Zaretskii, V.I., and Zaikin, V.G., *Usp. Khim.*, 1972, vol. 41, no. 2, pp. 272–286.

6. Aue, W.P., Bartholdi, E., and Ernst, R.R., *J. Chem. Phys.*, 1976, vol. 64, no. 5, pp. 2229–2246.
7. Rance, M., Sorensen, O.W., Bodenhousen, G., Ernst, R.R., and Wuthrich, K., *Biochem. Biophys. Res. Commun.*, 1983, vol. 117, no. 2, pp. 479–485.
8. Bax, A. and Morris, G.A., *J. Magn. Res.*, 1981, vol. 42, no. 3, pp. 501–505.
9. Kessler, H., Griesinger, C., Zarbock, J., and Loosli, H.R., *J. Magn. Res.*, 1984, vol. 57, no. 2, pp. 331–336.
10. Jeener, J., Meier, B.H., Bachmann, P., and Ernst, R.R., *J. Chem. Phys.*, 1979, vol. 71, no. 11, pp. 4546–4553.
11. Kirk, Marat, Templeton, J.F., and Sashi, Kumar, *Magnetic resonance in Chemistry*, 1987, vol. 25, no. 1, pp. 25–30.
12. Bhacca, N.S., Gurst, G.E., and Williams, D.H., *J. Am. Chem. Soc.*, 1965, vol. 87, no. 2, pp. 302–307.
13. Ernst, R., Bodenhauzen, G., and Wokaun, A., *Pinciples of Nuclear Magnetic Resonance in One and Two Dimentions*, New York: Oxford University Press, 1987.
14. Shaka, A.J., Keeler, J., and Freeman, R., *J. Magn. Res.*, 1983, vol. 53, no. 2, pp. 313–340.
15. Rzheznikov, V.M., Ananchenko, C.N., and Torgov, I.V., *Khim. Prir. Soed.*, 1965, no. 2, pp. 90–100.
16. Nikolaev, C.V., Novikov, A.G., and Postnov, V.N., *Zh. Fiz. Khim.*, 1991, vol. 65, no. 10, pp. 2683–2686.