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Synthesis and Molecular Structure of D-Homo-B-nor-8α Analogs of Steroidal Estrogens

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Abstract—According to the X-ray diffraction and NMR data, two D-homo-B-nor-8α-analogs of steroidal estrogens in crystal and in solution have similar conformations. The distances between hydrogen atoms in their molecules, calculated *ab initio* and by the PM3 and MM^+ methods, correspond to those found experimentally. These results substantiated docking of the modified estrogens into ligand-binding pockets of various estrogen receptor isoforms with a view to search for compounds with improved biological properties. This was demonstrated using 17,17-dimethyl-D-homo-B-nor-8α-estrone as an example.

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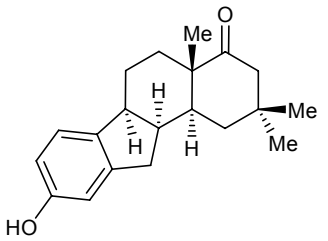
Total syntheses of modified analogs of steroidal estrogens with *cis*-junction of the B and C rings, which exhibit improved biological properties, include at least 10–15 steps [1]. Therefore, the possibility of predicting at least some properties of the targeted compounds is important. In the present article we propose a new approach to preliminary estimation of hormonal activity of D-homo-B-nor-8α analogs of steroidal estrogens mediated by the corresponding nuclear receptors.

It is known that B-nor-8α analogs of steroidal estrogens exhibit much weaker uterotropic activity than do steroids with six-membered B ring [1]. On the other hand, they can retain other biological properties intrinsic to natural hormones. For example, 16,16-dimethyl-D-homo-B-nor-8α-estrone shows immune-suppressing activity, whereas uterotropic action is absent [1]. These data indicate that further experimental studies on such estrogen analogs may be promising. Modified steroidal estrogens possessing the above properties are almost unknown [2]; therefore, information on molecular structure of D-homo-B-nor-8α analogs of steroidal estrogens may be useful in the design of new compounds with changed spectrum of biological activity.

In the first step, structural parameters of model compounds in crystal and in solution are usually compared with those calculated by nonempirical and semiempirical methods [3–6]. As model steroids we selected 16,16-dimethyl-D-homo-B-nor-8α-estrone methyl ether (**I**) for which X-ray diffraction data are available [1] and 1-methoxy-4-methyl-D-homo-B-nor-8α-estra-1,3,5(10)-trien-17a-one (**II**), taking into account that representatives of this stereochemical series with substituents on C^1 and C^4 were not reported.

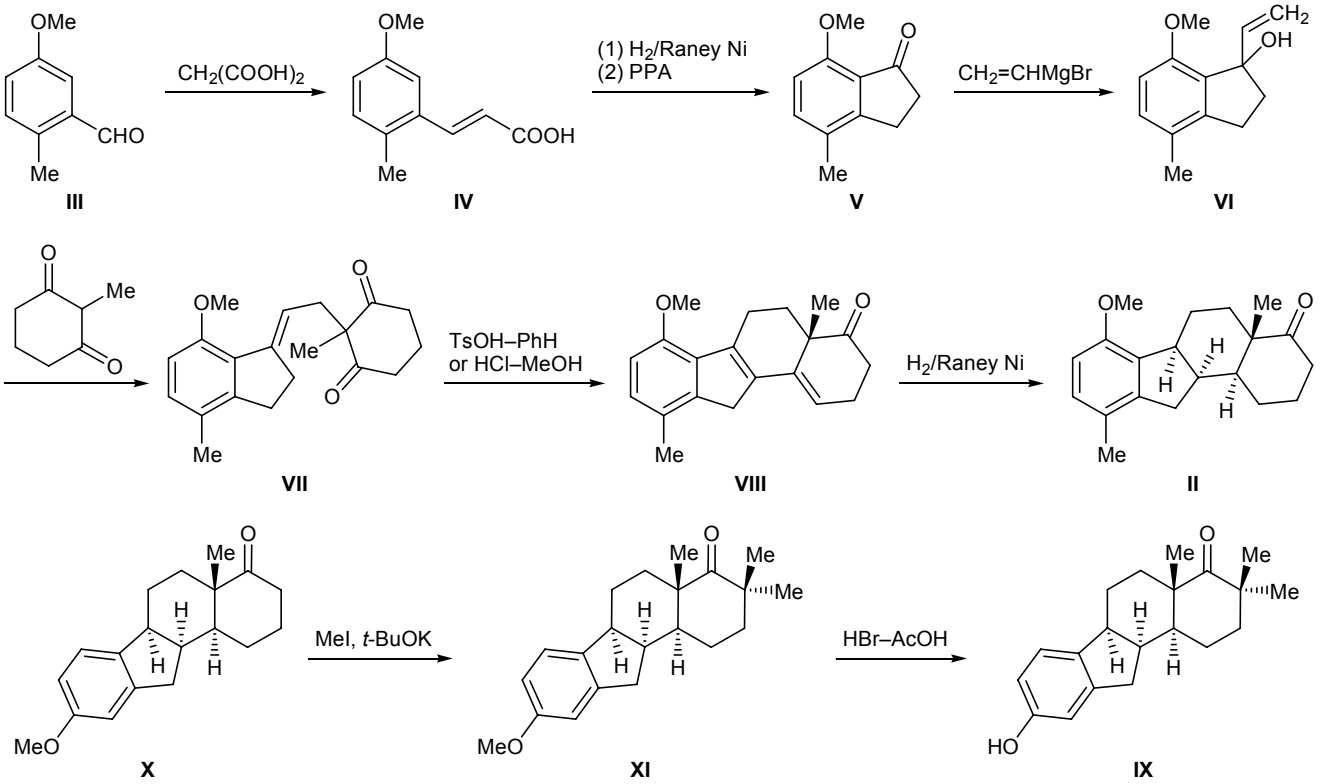


I

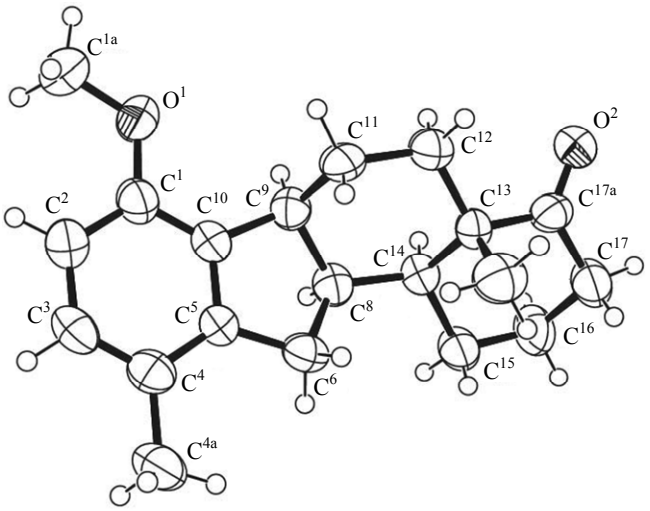
Compound **II** was synthesized as shown in Scheme 1. The syntheses of intermediate products **III**–**VIII** involved no difficulties, and the yields in all steps were consistent with published data for analogous reactions [1, 7]. However, catalytic hydrogenation of estrapentaene **VIII**, followed by oxidation, gave compound **II** in a yield not exceeding 29%, and factors responsible for the poor yield of **II** are not clear.

The steric structure of steroid **II** in crystal and in solution was determined by X-ray analysis and NMR spectroscopy, and the experimental data thus obtained were compared with the results of *ab initio* molecular modeling (6-31G basis set) and semiempirical PM3 and MM^+ calculations [8]. According to the X-ray dif-

Scheme 1.



fraction data, model steroid **II** crystallizes in the triclinic crystal system, and its unit cell contains two independent molecules with fairly similar conformations: the A ring is planar, and the B ring is an almost regular *envelope*. The base of the envelope ($C^5C^{10}C^6C^9$) lies almost in the ring A plane, and the difference between deviations of the flaps of the envelopes in the two independent molecules is equal to 2°. The C and D rings are almost regular *chairs*, and the dihedral angles between their bases ($C^8C^{11}C^{12}C^{14}$ and $C^{13}C^{14}C^{15}C^{17a}$) and the A ring plane are similar. The carbon atoms in the methoxy groups on C^1 in both molecules are oriented *trans* with respect to the C^1–C^2 bond, and they deviate from the ring A plane in opposite directions, by 0.20 Å above the A ring in one molecule, and by 0.11 Å below the A ring in the other. The distances between the oxygen atoms at the A and D rings are equal within the experimental error, 7.374(5) and 7.378(5) Å. One conformer of steroid **II** is shown in figure, and the bond lengths and bond and dihedral angles are available from the authors upon request by e-mail.



Steric structure of steroid **I** molecule according to the X-ray diffraction data.

Analysis of the DQF-COSY, HSQC (without decoupling from ^{13}C nuclei), COLOC, and NOESY spectra with account taken of the data in [9] allowed us to assign all signals in the ^1H and ^{13}C NMR spectra of steroid **II** and estimate distances r_{kl} between protons in molecules **I** and **II** using the calibration technique proposed in [10] with corrections for anisotropy of diffuse molecular motion in liquid [11].

Comparison of the distances between protons in molecules **I** and **II**, estimated by NMR spectroscopy,

Distances (Å) between protons in the molecules of steroids **I** and **II**

Distance	**I**					**II**					
	X-ray	NMR	*ab initio*	PM3	MM^+	X-ray		NMR[a]	*ab initio*[a]	PM3[a]	MM^{+} [a]
						conformer 1	conformer 2				
1–2	2.45	2.29	2.46	2.49	2.44	–	–	–	–	–	–
1–9α	2.85	2.52	2.85	2.84	2.80	–	–	–	–	–	–
1–11α	3.07	2.74	2.98	2.96	2.90	–	–	–	–	–	–
2–3	–	–	–	–	–	2.49	2.47	2.37	2.43	2.45	2.38
4–6α	2.68	2.46	2.75	2.80	2.71	–	–	–	–	–	–
4–6β	3.05	2.82	3.10	3.18	3.03	–	–	–	–	–	–
6α–8α	2.34	2.48	2.35	2.38	2.40	2.32	2.33		2.32	2.38	2.32
6α–15α	2.99	2.74	2.72	2.70	2.88	2.91	2.93		2.91	2.73	2.87
6α–15β	2.80	2.60	2.72	2.76	2.79	2.82	2.83		2.82	2.75	2.83
8α–9α[b]	2.49	2.32	2.34	2.37	2.32	2.58	2.54	2.25	2.31	2.37	2.32
8α–14α	2.27	2.11	2.30	2.30	2.28	2.13	2.17	2.11	2.27	2.29	2.29
8α–15α	2.32	2.36	2.55	2.53	2.53	2.30	2.34	2.50	2.54	2.54	2.54
9α–11α	2.31	2.36	2.40	2.44	2.42	2.32	2.32	2.31	2.36	2.44	2.43
9α–2α	2.46	2.48	2.51	2.73	2.78	2.61	2.58	2.53	2.78	2.73	2.75
9α–14α	2.82		2.88	2.92	2.83	2.80	2.80	2.62	2.86	2.89	2.84
16α–17α	–	–	–	–	–	2.43	2.42	2.46	2.44	2.45	2.44
16β–17β	–	–	–	–	–	2.42	2.42	2.60	2.43	2.45	2.47
17α–17β[c]	1.79		1.78	1.77	1.78	1.79	1.79	1.79	1.75	1.77	1.79

[a] Averaged conformation.

[b] Experimental data are given for a reference distance of 2.32 Å in compound **I** (MM^+), and they correspond to average values of the reduced volume integrals: $(S_{ji}/S_{ii} + S_{ji}/S_{jj})/2$.

[c] Experimental data are given for a reference distance of 1.79 Å in compound **I** (MM^+), and they correspond to average values of the reduced volume integrals: $(S_{ij}/S_{ii} + S_{ij}/S_{jj})/2$.

with the corresponding values determined by X-ray analysis (see table) indicated that conformations of these molecules in solution and in crystal are fairly similar. Various molecular parameters of steroids **I** and **II** (the corresponding data are not given) are consistent with those calculated by the above methods. Therefore, the calculated values can be used to determine geometric parameters of complexes formed by D-homo-B-nor-8α analogs of steroidal estrogens with various macromolecules, including estrogen receptors.

To verify this assumption, docking of various D-homo-B-nor-8α analogs of steroidal estrogens into ligand-binding sites of known isoforms of nuclear estrogen receptors was simulated. It was found that compound **IX** should not bind to these receptors; therefore, it attracts interest from the viewpoint of its biological effect which is not mediated by nuclear estrogen receptors. Steroid **IX** was synthesized by alkylation of methyl ether **X**, followed by deprotection of the hydroxy group on C^3 by acid hydrolysis.

Biological testing of compound **IX** revealed its hypocholesterolemic and cardioprotective effects.* In addition, steroid **IX** displayed immunomodulating activity with no effect on proliferative processes in uterus. The results of biological tests on compound **IX** were given in patent application [12], and they will be reported elsewhere.

EXPERIMENTAL

The purity of all compounds was checked by TLC on Silufol plates using hexane–ethyl acetate mixtures (6:1, 4:1, and 3:1) as eluent. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1321

* The results are available from the authors upon request by e-mail.

instrument (ion source temperature 200–210°C). The NMR spectra were recorded at 295 K on a Bruker DPX-300 spectrometer at 300.130 MHz for ^{1}H and at 75.468 MHz for ^{13}C using $CDCl_3$ as solvent [5–7 (^{1}H) or 30–50 mg (^{13}C) of a substance in 0.6 ml of $CDCl_3$]. The chemical shifts were measured relative to tetramethylsilane by assigning the solvent signals ($CDCl_3$–$CHCl_3$, 99.9 : 0.1) standard values of δ 7.26 ppm and δ_C 76.90 ppm; the accuracy in determination of chemical shifts was ±0.002 (^{1}H) and ±0.01 ppm (^{13}C). Homonuclear spin–spin coupling constants were measured with an accuracy of ±0.02 Hz from the ^{1}H NMR spectra obtained after additional processing of the free induction decay signal using Lorentz–Gauss transformation and direct linear prediction filtering and improvement of the digital spectral resolution by zero padding. The shift correlation spectra were obtained using standard Bruker pulse sequences and processing procedures.

Single crystals of steroid **II** for X-ray analysis were obtained by crystallization from hexane (colorless flattened pseudohexagonal plates). A three-dimensional set consisting of 7167 nonzero independent reflections [$I \geq 4\sigma(I)$] was acquired from a 0.2 × 0.15 × 0.25-mm single crystal on an automatic CCD diffractometer. Triclinic crystal system, space group $P1$-; unit cell parameters: a = 8.412(5), b = 14.362(8), c = 14.566(8) Å; α = 98.490(10), β = 102.340(10), γ = 96.830(11)°; Z = 4; d_{calc} = 1.180 g/cm^3. The structure was solved by the direct method and was refined by F^2 with account taken of anisotropy of thermal vibrations of nonhydrogen atoms. Hydrogen atoms were placed into calculated positions. No correction for absorption was introduced. The calculations were performed using CSD [13] and SHELXL 97 software packages [14]. The coordinates of basis atoms are available from the authors.

7-Methoxy-4-methylindan-1-one (V). 5-Methoxy-2-methylbenzaldehyde (**III**), 50 g, was dissolved in 120 ml of pyridine, 40 g of malonic acid and 0.3 ml of piperidine were added, and the mixture was heated for 8 h on a boiling water bath and poured into 500 ml of dilute (1 : 1) hydrochloric acid. The precipitate was filtered off, washed with water until neutral washings, and dried at room temperature. Yield of compound **IV** 53.2–55.6 g (83–87%).

Acid **IV**, 35 g, was dissolved in 230 ml of isopropyl alcohol, 10 g of Raney nickel was added, and hydrogen was supplied at 100–110°C under a pressure of 100 atm over a period of 1 h. The catalyst was filtered off, the solvent was removed on a rotary evaporator under reduced pressure, and the residue was dissolved in 500 ml of polyphosphoric acid and heated for 1 h at 90–95°C. The mixture was poured under vigorous stirring onto 2 kg of ice and was left to stand for 12 h. The products were extracted into diethyl ether, and the extract was washed thrice with an equal volume of 1 N aqueous potassium hydroxide and then with water until neutral washings and dried over sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate–hexane (1 : 7). Yield 15.4–16.4 g (48–51%), mp 105–107°C. ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, 7-CH_3), 3.93 s (3H, CH_3O), 6.75 d (1H, 6-H, J = 8 Hz), 7.35 d (1H, 7-H, J = 8 Hz). Found, %: C 75.09; H 7.10. $C_{11}H_{12}O_2$. Calculated, %: C 74.98; H 6.87. M 176.21.

1-Methoxy-4-methyl-D-homo-B-nor-8(14)-seco-estra-1,3,5(10),9(11)-tetraene-14,17a-dione (VII). A solution of vinylmagnesium bromide in THF, prepared from 6 g of magnesium [8], was cooled to –15°C, a solution of 10 g of compound **V** in 100 ml of anhydrous THF was added dropwise, and the mixture was stirred for 3 h at –15°C, left to stand for 12 h at room temperature, and then heated for 1 h at 40°C. After appropriate treatment, vinylcarbinol **VI** was brought into condensation with 10 g of 2-methylcyclohexane-1,3-dione in the presence of Triton B as described in [8]. Compound **VII** was isolated by crystallization from methanol. Yield 10 g (56%), mp 93–95°C. ^{1}H NMR spectrum, δ, ppm: 1.30 s (3H, 13-CH_3), 2.19 s (3H, 4-CH_3), 3.85 s (3H, CH_3O), 6.23 m (1H, 11-H), 6.64 d and 6.98 d (1H each, 2-H, 3-H, J = 8 Hz). Found, %: C 76.88; H 7.58. $C_{20}H_{24}O_3$. Calculated, %: C 76.89; H 7.74.

1-Methoxy-4-methyl-D-homo-B-norestra-1,3,5(10),8,14-pentaen-17a-one (VIII). *a*. *p*-Toluenesulfonic acid, 1 g, was added to a solution of 10 g of diketone **VII** in 400 ml of benzene. The mixture was heated for 15 min under reflux, cooled, and passed through a column charged with 100 g of aluminum oxide of activity grade II according to Brockmann. The column was eluted with benzene, the eluate was evaporated, and the residue was crystallized from methanol. Yield 4.75 g (51%), mp 132.5–133.5°C. ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, 18-CH_3), 2.25 s (3H, 4-CH_3), 3.32 m (2H, 6-H), 3.80 s (3H, CH_3O), 5.92 m (1H, 15-H); also, signals from two protons were present in the aromatic region. Found, %: C 81.91; H 7.68. $C_{20}H_{22}O_2$. Calculated, %: C 81.60; H 7.53.

b. A solution of 5 g of compound **VII** in 125 ml of methanol was heated to the boiling point, 5 ml of concentrated hydrochloric acid was added, and the

mixture was heated for 20 min under reflux, quickly cooled, and left to stand for 24 h at 5°C. The precipitate was filtered off, washed on a filter with methanol, and recrystallized from chloroform–methanol (1:8). Yield 2.65–2.75 g (56–58%), mp 133–133.5°C. No depression of the melting point was observed on mixing samples of **VIII** prepared as described in *a* and *b*; their ^{1}H NMR spectra were also identical.

1-Methoxy-4-methyl-D-homo-B-nor-8α-estra-1,3,5(10)-trien-17a-one (II). *a*. A 600-ml steel high-pressure reactor was charged with a solution of 4.75 g of compound **VIII** in 270 ml of benzene, 10 g of freshly prepared Raney nickel [15] (thoroughly washed with benzene) was added, hydrogen was supplied to a pressure of 160 atm, the mixture was heated to 60°C, and stirring was turned on. The hydrogenation process was maintained continuous so that the temperature of the reaction mixture by the end of the process did not exceed 130°C. When 100–120 l of hydrogen was absorbed, the hydrogenation products were oxidized with the Sarett reagent prepared from 5 g of chromium trioxide and 80 ml of pyridine [1]. After appropriate treatment, steroid **II** was purified by recrystallization from chloroform–methanol (1:6). Yield 1.26 g (26%), mp 115–116°C. ^{1}H NMR spectrum, δ, ppm: 6.62 (2-H), 6.94 (3-H), 2.78 (6α-H), 2.84 (6β-H), 2.49 (8α-H), 3.13 (9α-H), 2.08 (11α-H), 1.21 (11β-H), 1.59 (12α-H), 1.73 (12β-H), 1.85 (14α-H), 1.65 (15α-H), 2.01 (15β-H), 1.73 (16α-H), 2.12 (16β-H), 2.27 (17α-H), 2.71 (17β-H), 1.24 (18-H), 2.20 (1-CH_3), 3.80 (CH_3O). ^{13}C NMR spectrum, δ_C, ppm: 153.79 (C^1), 108.26 (C^2), 127.79 (C^3), 125.95 (C^4), 142.34 (C^5), 32.34 (C^6), 44.70 (C^8), 42.02 (C^9), 135.50 (C^{10}), 23.85 (C^{11}), 31.14 (C^{12}), 48.34 (C^{13}), 44.12 (C^{14}), 25.86 (C^{15}), 25.25 (C^{16}), 37.64 (C^{17}), 215.47 (C^{17a}), 17.48 (C^{18}), 17.51 (4-CH_3), 55.05 (CH_3O). Mass spectrum, *m*/*z* (I_{rel}, %): 298 (100) $[M]^+$, 265 (12), 242 (5), 227 (51), 213 (13), 199 (16), 185 (11), 173 (28), 160 (65), 145 (18). Found, %: C 80.67; H 8.67. $C_{20}H_{26}O_2$. Calculated, %: C 80.50; H 8.78.

b. Raney nickel, 5 g, was added to a solution of 4 g of steroid **VIII** in 270 ml of isopropyl alcohol, and the mixture was stirred in a steel high-pressure reactor at 100–110°C under a hydrogen pressure of 100 atm. The mixture was then treated as described above in *a*. Yield 1.18 g (29%), mp 115–116°C. No depression of the melting point was observed on mixing samples of **II** prepared as described in *a* and *b*.

17,17-Dimethyl-D-homo-B-nor-8α-estrone methyl ether (XI). Potassium *tert*-butoxide, 3.3 g, was added to a solution of 1.5 g of compound **X** [7] in 45 ml of anhydrous dioxane. The mixture was stirred until it became homogeneous, 4.0 g of methyl iodide was added in portions, and the mixture was heated for 3 h under reflux, cooled to room temperature, poured into 150 ml of water, and extracted with methylene chloride (4×50 ml). The extracts were combined, washed with 20% acetic acid and then with water until neutral washings, and evaporated, and the residue was recrystallized from methanol. Yield 0.91–0.97 g (55–59%), mp 230–234°C. ^{1}H NMR spectrum, δ, ppm: 7.09 (1-H), 6.70 (2-H), 6.77 (4-H), 2.81 (6α-H), 2.94 (6β-H), 2.58 (8α-H), 2.84 (9α-H), 1.82 (11α-H), 1.28 (11β-H), 1.36 (12α-H), 1.94 (12β-H), 1.92 (14α-H), 1.64 (15α-H), 2.01 (15β-H), 1.68 (16α-H), 1.89 (16β-H), 1.19 (18-H), 1.11 (17α-CH_3), 1.20 (17β-CH_3), 3.78 (CH_3O). ^{13}C NMR spectrum, δ_C, ppm: 123.94 (C^1), 111.74 (C^2), 158.48 (C^3), 110.51 (C^4), 143.55 (C^5), 33.46 (C^6), 45.17 (C^8), 43.81 (C^9), 140.88 (C^{10}), 26.36 (C^{11}), 32.78 (C^{12}), 47.53 (C^{13}), 42.46 (C^{14}), 22.98 (C^{15}), 38.62 (C^{16}), 43.87 (C^{17}), 219.71 (C^{17a}), 18.02 (C^{18}), 28.39 (17α-CH_3), 28.26 (17β-CH_3), 55.25 (CH_3O). Mass spectrum, *m*/*z* (I_{rel}, %): 312 (92) $[M]^+$, 284 (7.5), 240 (13), 228 (47), 213 (46), 199 (13.5), 185 (14.5), 171 (13.5), 160 (32), 146 (100). Found, %: C 80.73, 80.95; H 9.00, 9.05. $C_{21}H_{28}O_2$. Calculated, %: C 80.73; H 9.03. *M* 312.45.

17,17-Dimethyl-D-homo-B-nor-8α-estrone (IX). Compound **XI**, 0.80 g, was dissolved in 35 ml of anhydrous acetic acid, 20 ml of 45% hydrobromic acid was added, and the mixture was heated for 2.5 h on a boiling water bath under stirring, cooled to room temperature, poured into 100 ml of cold water, and extracted with chloroform (3×75 ml). The extract was washed with water until neutral washings, dried over anhydrous sodium sulfate, and filtered, the solvent was removed under reduced pressure, and the residue was crystallized from hexane–dioxane (2:1). Yield 0.36 g (47%), mp 277–281°C. Mass spectrum, *m*/*z* (I_{rel}, %): 298 (100) $[M]^+$, 280 (6), 270 (7), 265 (6), 226 (32), 214 (46), 199 (67), 186 (16), 185 (18), 171 (18), 156 (21), 146 (44), 132 (88). Found, %: C 80.44; H 8.90. $C_{20}H_{26}O_2$. Calculated, %: C 80.49; H 8.78. *M* 298.42.

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