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Molecular Structure and Biological Properties of Some 16,16-Dimethyl-D-homo-B-nor-9β Analogs of Steroid Estrogens

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Abstract—The interproton distances in the molecule of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-9β-estra-1,3,5(10)-triene, determined from the X-ray diffraction data and by ^{1}H NMR spectroscopy, were consistent with those calculated *ab initio* and by the PM3 and MM+ methods. Therefore, MM+ calculations were used to perform docking of a series of D-homo-B-nor-9β-estra-1,3,5(10)-trienes to hormone-binding pocket of estrogen α-receptors, and 16,16-dimethyl-D-homo-B-nor-9-estrone was selected for studying its biological properties. This compound was found to possess cardioprotective activity and no uterotropic effect.

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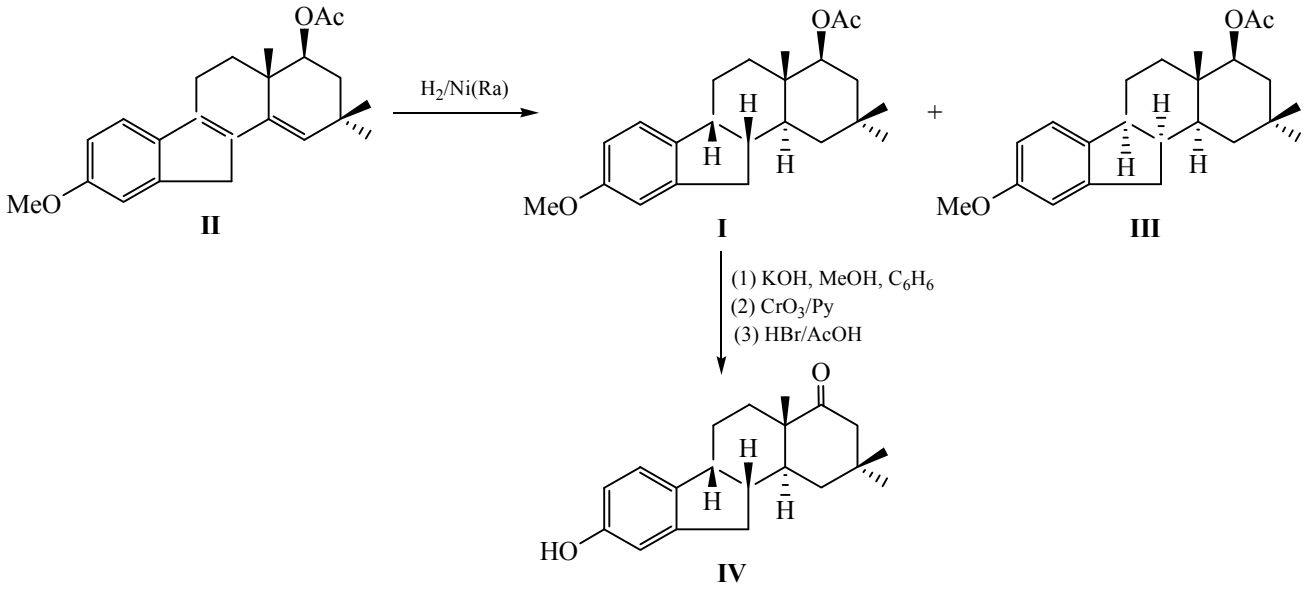
9β-Analogs of steroidal estrogens are characterized by modified spectrum of biological activity as compared to the corresponding natural compounds [1–3]; they are also used as intermediate products in the synthesis of 9β,10α-androgen [4] and 9β,10α-progestagen derivatives [5]. Biological properties of B-nor-9β-estrogens are almost unknown. 18-Methyl-D-homo-B-nor-9β-estrone was reported to exhibit anti-atherosclerotic effect, whereas its uterotropic activity was completely absent [6, 7]. The latter is very important, for in most cases hormone action of estrogens is related to their cancerogenic effect [8].

Schemes of total synthesis of steroidal estrogens include many steps [9], so that the yields of the target products are generally poor. Therefore, much attention is given to selection of compounds for the synthesis and studying biological properties of new steroids. One strategy for the solution of this problem is based on preliminary analysis of the structure of known analogs belonging to one or another stereochemical series in crystal and in solution and calculation of the molecular geometry [10–15]. Comparison of the results makes it possible to choose the simplest procedure for estimation of the efficiency of binding of modified compounds of the given stereochemical series to a ligand-binding pocket in protein, as well as to estimate prospects of their synthesis. No such studies were performed in the series of D-homo-B-nor-9β analogs of steroidal estrogens, and in the present work we tried to fill this gap. As model compound we selected 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-9β-estra-1,3,5(10)-triene (**I**) [16] which was synthesized by catalytic hydrogenation of estrapentaene **II** under the conditions recommended in [17].

The structure of compound **I** was determined by X-ray analysis of its single crystal. The structure was solved by the direct method and was refined with account taken of anisotropy of thermal vibrations of non-hydrogen atoms (see figure). The positions of hydrogen atoms were calculated. Absorption by the crystal was not taken into consideration. The calculations were performed using CSD [18] and SHELXL 97 software packages [19], and the coordinates of atoms and torsion angles are collected in Tables 1 and 2, respectively. The other crystallographic parameters of compound **I** are available from the Cambridge Crystallographic Data Centre (entry no. CCDC 793 120).

Crystals of **I** belong to the triclinic crystal system, and a unit cell includes one independent molecule whose conformation may be described as follows. The A ring is planar, and the B ring is almost regular *envelope*. The *envelope* base $C^5C^{10}C^6C^9$ lies almost in the plane of the A ring, while the flap of the *envelope* deviates from the base plane through a dihedral angle

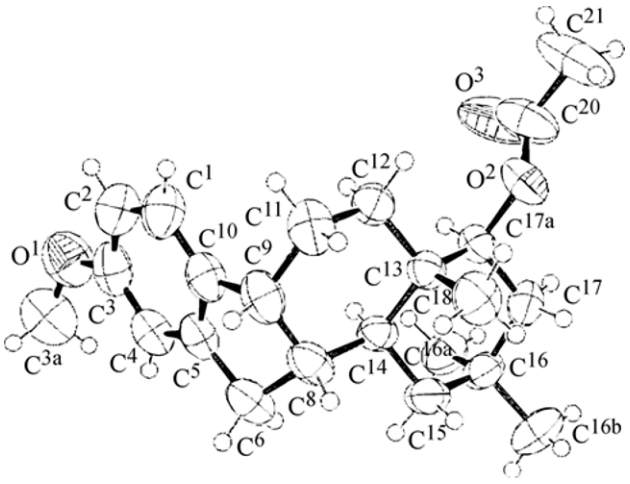


of 38.7(2)°. The C and D rings are almost regular *chairs* whose bases, i.e., $C^8C^{11}C^{12}C^{14}$ and $C^{13}C^{15}C^{16}C^{17a}$, form a dihedral angle of 5.5(1)° and are almost orthogonal to the ring A plane [88.5(1) and 94(1)°, respectively]. The methoxy group is oriented *trans* with respect to the C^2–C^3 bond. The oxygen atom in the methoxy group appears almost in the plane of the A ring, whereas the CH_3O carbon atom is located by 0.32 Å above. The distance between the oxygen atoms at the A and D rings is 8.905(5) Å. Table 3 contains the distances between protons in molecule **I**, calculated on the basis of the X-ray diffraction data.

Complete assignment of signals in the ^1H and ^{13}C NMR spectra of steroid **II** was made by analysis of the DQF-COSY, HSQC (without decoupling from ^{13}C nuclei), COLOC, and NOESY spectra according to [13], and distances between protons in molecle **I** were estimated by the calibration method [20] with corrections for anisotropy of diffusion motion of molecules in liquid [21] (Table 3).

The optimal conformation of steroid **I** was calculated *ab initio* and by the PM3 and MM+ methods [13]. The interproton distances in molecule **I**, determined by X-ray analysis and ^1H NMR spectroscopy, approached the calculated values; therefore, we used the above calculation methods to predict the efficiency of binding of D-homo-B-nor-9β-analogs of steroids to various proteins. Docking of several D-homo-B-nor-9β-estra-1,3,5(10)-trienes to hormone-binding pocket of estrogen α-receptors, which was simulated on the basis of X-ray diffraction data [22], showed that the formation of "productive" complexes is hardly probable because of impossibility for exact matching of oxygen-containing substituents in the A and D rings of steroids with amino acid fragments of the receptor responsible for ligand binding. Therefore, we presumed that steroid **IV** should not exhibit uterotropic effect, which was confirmed experimentally.

The absence of uterotropic activity of modified estrogens is a necessary condition for the design on their base of compounds with different biological properties [23, 24]. Insofar as cardioprotective action of estrogens is not necessarily mediated by their α-receptors [6, 7, 24, 25], we examined the effect of



Structure of the molecule of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-nor-9β-estra-1,3,5(10)-triene (**I**) according to the X-ray diffraction data.

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

Atom	*x*	*y*	*z*	U_{eq}
O^1	8336(3)	3718(2)	5742(2)	104(1)
O^2	6692(2)	–860(2)	1842(2)	74(1)
O^3	7081(3)	–2280(2)	3837(3)	140(1)
C^1	9508(4)	3589(2)	2698(3)	76(1)
C^2	9519(4)	3571(3)	3859(3)	83(1)
C^3	8188(4)	3768(2)	4560(3)	76(1)
C^{3a}	7204(5)	4205(4)	6308(4)	114(1)
C^4	6783(4)	3953(2)	4133(3)	69(1)
C^5	6795(3)	3960(2)	2948(3)	63(1)
C^6	5440(4)	4140(2)	2265(3)	74(1)
C^8	6000(3)	3584(2)	1310(2)	65(1)
C^9	7821(3)	3880(2)	968(2)	66(1)
C^{10}	8133(4)	3784(2)	2223(2)	64(1)
C^{11}	8757(4)	3044(2)	476(3)	74(1)
C^{12}	8124(3)	1608(2)	1323(2)	58(1)
C^{13}	6381(3)	1362(2)	1395(2)	49(1)
C^{14}	5427(3)	2103(2)	2029(2)	50(1)
C^{15}	3666(3)	1841(2)	2176(3)	65(1)
C^{16}	3003(3)	389(2)	3024(3)	61(1)
C^{16a}	2902(3)	–87(3)	4504(3)	74(1)
C^{16b}	1348(3)	224(4)	2851(4)	96(1)
C^{17}	4062(3)	–422(2)	2562(3)	62(1)
C^{17a}	5799(3)	–89(2)	2356(2)	52(1)
C^{18}	6154(4)	1778(3)	–11(2)	74(1)
C^{20}	7331(4)	–1893(3)	2671(4)	93(1)
C^{21}	8276(5)	–2494(4)	1939(5)	139(2)

Table 2. Torsion angles φ in the molecule of steroid **I**

Angle	φ	Angle	φ
$C^{10}C^1C^2C^3$	–1.3(4)	$C^{11}C^{12}C^{13}C^{14}$	–61.0(2)
$C^1C^2C^3C^4$	1.9(4)	$C^{12}C^{13}C^{14}C^{15}$	–177.64(19)
$C^1C^2C^3O^1$	179.6(2)	$C^{17a}C^{13}C^{14}C^{15}$	–60.2(2)
$C^{3a}O^1C^3C^2$	164.7(3)	$C^{18}C^{13}C^{14}C^{15}$	61.0(3)
$C^{3a}O^1C^3C^4$	–17.7(4)	$C^{12}C^{13}C^{14}C^8$	54.5(2)
$C^2C^3C^4C^5$	–1.5(4)	$C^{17a}C^{13}C^{14}C^8$	171.95(17)
$O^1C^3C^4C^5$	–178.9(2)	$C^{18}C^{13}C^{14}C^8$	–66.9(3)
$C^3C^4C^5C^{10}$	0.4(3)	$C^9C^8C^{14}C^{15}$	–171.60(19)
$C^3C^4C^5C^6$	180.0(2)	$C^6C^8C^{14}C^{15}$	74.1(2)
$C^{10}C^5C^6C^8$	18.4(3)	$C^9C^8C^{14}C^{13}$	–44.9(3)
$C^4C^5C^6C^8$	–161.2(2)	$C^6C^8C^{14}C^{13}$	–159.23(18)
$C^5C^6C^8C^{14}$	90.6(2)	$C^{13}C^{14}C^{15}C^{16}$	58.6(3)
$C^5C^6C^8C$	–30.5(2)	$C^8C^{14}C^{15}C^{16}$	–173.2(2)
$C^{14}C^8C^9C^{10}$	–86.8(2)	$C^{14}C^{15}C^{16}C^{16b}$	–167.8(2)
$C^6C^8C^9C^{10}$	31.7(2)	$C^{14}C^{15}C^{16}C^{17}$	–48.5(3)
$C^{14}C^8C^9C^{11}$	40.0(3)	$C^{14}C^{15}C^{16C16a}$	73.2(3)
$C^6C^8C^9C^{11}$	158.5(2)	$C^{16b}C^{16}C^{17}C^{17a}$	165.5(2)
$C^4C^5C^{10}C^1$	0.3(3)	$C^{16a}C^{16}C^{17}C^{17a}$	–75.7(3)
$C^6C^5C^{10}C^1$	–179.4(2)	$C^{15}C^{16}C^{17}C^{17a}$	45.7(3)
$C^4C^5C^{10}C^9$	–178.2(2)	$C^{20}O^2C^{17a}C^{17}$	–103.7(2)
$C^6C^5C^{10}C^9$	2.1(3)	$C^{20}O^2C17^aC^{13}$	131.5(2)
$C^2C^1C^{10}C^5$	0.2(4)	$C^{16}C^{17}C^{17a}O^2$	–176.58(19)
$C^2C^1C^{10}C^9$	178.3(2)	$C^{16}C^{17}C^{17a}C^{13}$	–55.2(3)
$C^{11}C^9C^{10}C^5$	–148.5(2)	$C^{12}C^{13}C^{17a}O^2$	–61.4(2)
$C^8C^9C^{10}C^5$	–21.8(2)	$C^{18}C^{13}C^{17a}O^2$	59.4(2)
$C^{11}C^9C^{10}C^1$	33.2(4)	$C^{14}C^{13}C^{17a}O^2$	–178.10(17)
$C^8C^9C^{10}C^1$	160.0(2)	$C^{12}C^{13}C^{17a}C^{17}$	176.55(19)
$C^{10}C^9C^{11}C^{12}$	74.8(3)	$C^{18}C^{13}C^{17a}C^{17}$	–62.6(2)
$C^8C^9C^{11}C^{12}$	–45.2(3)	$C^{14}C^{13}C^{17a}C^{17}$	59.9(2)
$C^9C^{11}C^{12}C^{13}$	56.6(3)	$C^{17a}O^2C^{20}O^3$	7.0(5)
$C^{11}C^{12}C^{13}C^{17}$	–175.40(19)	$C^{17a}O^2C^{20}C^{21}$	–176.3(3)
$C^{11}C^{12}C^{13}C^{18}$	62.7(3)		

steroid **IV** on several biochemical parameters of rats with alimentary hypercholesterolemia [26]. It was found that no excess cholesterol is transferred into the aorta of experimental animals by the action of analog **IV**. These findings indicated perspectives in further studies on biological properties of steroid **IV** and search for new hypolipidemic and cardioprotective agents among the series of D-homo-B-nor-9β analogs of steroidal estrogens.

Details of the study on biological activity of compound **IV** will be the subject of separate publication.

EXPERIMENTAL

All compounds synthesized in the present work were racemic. Their purity was checked by TLC on Silufol plates using petroleum ether–ethyl acetate (6:1, 4:1, 3:1) as eluent. The mass spectra (electron impact, 70 eV) were recorded on an MKh-1321 spectrometer (ion source temperature 200–210°C). The NMR spectra were measured at 295 K on a Bruker DPX-300 spectrometer at 300.130 and 75.468 MHz for ^1H and ^{13}C, respectively. The ^1H NMR spectra were obtained from solutions of 5–7 mg of a substance in 0.6 ml of

$CDCl_3$, and the ^{13}C NMR spectra, from solutions of 30–50 mg of a substance in the same volume of the solvent. The chemical shifts were determined relative to tetramethylsilane by assigning the solvent signal ($CDCl_3/CHCl_3$ = 99.9/0.1) standard chemical shifts δ 7.26 ppm and δ_C 76.90 ppm with an accuracy of ±0.002 and ±0.01 ppm, respectively. The ^1H–^1H spin–spin coupling constants were determined with an accuracy of ±0.02 Hz from the ^1H NMR spectra obtained by additional Lorentz–Gauss processing of FID signal and direct linear prediction procedure, as well as by enhancing digital spectral resolution via zero padding. The two-dimensional correlation spectra were recorded using Bruker standard pulse sequences and processing programs.

Catalytic hydrogenation of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homo-B-norestra-1,3,5(10),8,14-pentaene (II). Compound **II**, 1 g, was dissolved in 80 ml of benzene, 2 g of Raney nickel (prepared as described in [17]) was added, and hydrogenation was performed at 110–140°C at a hydrogen pressure of 150–200 atm. After appropriate treatment, the products were isolated according to the procedure described in [16]. We isolated 0.384 g (38%) of compound **I**, mp 110–112°C, and 0.545 g (54%) of steroid **III**, mp 125–128°C. The products showed no depression of the melting point on mixing with authentic samples [16].

Steroid **I**. ^1H NMR spectrum, δ, ppm: 7.05 (1-H), 6.72 (2-H), 6.77 (4-H), 2.61 (6α-H), 2.85 (6β-H), 2.19 (8β-H), 3.18 (9β-H), 2.05 (11α-H), 1.94 (11β-H), 1.03 (12α-H), 1.40 (12β-H), 1.01 (14α-H), 1.24 (15α-H), 1.07 (15β-H), 1.39 (17α-H), 1.44 (17β-H), 4.50 (17α-H), 0.92 (18-H), 3.80 (CH_3O), 0.86 (16α-CH_3), 0.95 (16β-CH_3), 2.01 (CH_3CO). ^{13}C NMR spectrum, δ_C, ppm: 122.76 (C^1), 111.12 (C^2), 158.44 (C^3), 110.92 (C^4), 144.27 (C^5), 36.57 (C^6), 41.47 (C^8), 42.25 (C^9), 136.97 (C^{10}), 20.42 (C^{11}), 31.79 (C^{12}), 37.76 (C^{13}), 37.53 (C^{14}), 38.72 (C^{15}), 33.07 (C^{16}), 39.41 (C^{17}), 78.07 (C^{17a}), 10.41 (C^{18}), 26.42 (16α–CH_3), 31.78 (16β-CH_3), 55.27 (CH_3O), 21.07 and 170.56 (17a-$OCOCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 356 (100) $[M]^+$, 296 (9), 281 (9), 267 (4), 240 (12), 213 (22), 199 (6), 159 (26), 146 (36). Found, %: C 77.55; H 9.34. $C_{23}H_{32}O_3$. Calculated, %: C 7.49; H 9.05.

Single crystals of **I** for X-ray analysis were grown from a solution in hexane and were colorless flattened pseudohexagonal plates. Three-dimensional set of 4347 non-zero independent reflections ($I \geq 4\sigma_I$, $\sin\theta/\lambda \leq 0.70$) was acquired at room temperature from a $0.3 \times 0.2 \times 0.2$-mm single crystal on a Syntex $P2_1$ automatic diffractometer (graphite monochromator, MoK_α irradiation). Triclinic crystal system, space group $P\bar{1}$; unit cell parameters: a = 8.726(2), b = 11.773(3), c = 11.817(3) Å; α = 60.89(4)°, β = 78.330(4)°, γ = 89.570(4)°; Z = 2; d_{calc} = 1.146(3) g/cm^3; R_1 = 0.0534.

Table 3. Interproton distances in the molecule of steroid **I**, Å

N_i–H_j	X-Ray	NMR	*Ab initio*	MM+	PM3
1–2	2.458	2.45	2.47	2.45	2.49
1-9β	3.286	3.22	3.29	3.25	3.24
1-11α	2.262	2.21	2.31	2.30	2.24
1-12α	3.173	3.10	3.38	3.07	3.45
4-6α	2.836	2.75	2.80	2.64	2.83
6α-6β	1.810	1.80	1.74	1.81	1.77
6α-8β	2.807	2.88	2.76	2.80	2.80
6α-14α	2.444	2.70	2.62	2.66	2.51
6α-15α	2.073	2.05	2.09	2.12	1.85
6β-8β	2.485	2.36	2.37	2.44	2.40
6β-9β	3.033	2.82	2.86	2.77	3.00
8β-9β	2.453	2.29	2.36	2.44	2.36
8β-15β	2.477	2.49	2.54	2.57	2.49
9β-11α	2.419	2.51	2.56	2.56	2.57
9β-11β	2.204	2.26	2.31	2.40	2.31
11α-11β	1.791	1.78	1.73	1.76	1.76
11α-12α	2.438	2.51	2.45	2.49	2.49
11α-12β	2.476	2.54	2.49	2.50	2.50
12α-12β	1.788	1.80	1.75	1.78	1.77
15α-15β	1.784	1.79	1.74	1.77	1.78
15β-17β	2.747	2.67	2.73	2.77	2.61
17α-17aα	2.394	2.54	2.36	2.49	2.54

Steroid **III**. ^1H NMR spectrum, δ, ppm: 7.05 (1-H), 6.69 (2-H), 6.76 (4-H), 2.67 (6α-H), 2.88 (6β-H), 2.40 (6α-H), 2.89 (9α-H), 1.77 (11α-H), 1.28 (11β-H), 1.18 (12α-H), 1.62 (12β-H), 1.79 (14α-H), 1.10 (15α-H), 1.51 (15β-H), 1.46 (17α-H), 1.49 (17β-H), 4.69 (17α-H), 0.98 ($C^{18}H_3$), 3.78 (CH_3O), 1.07 (16α-CH_3), 1.01 (16β-CH_3), 2.02 (CH_3CO). ^{13}C NMR spectrum, δ_C, ppm: 123.90 (C^1), 111.63 (C^2), 158.44 (C^3), 110.52 (C^4), 143.93 (C^5), 33.29 (C^6), 44.35 (C^8), 44.28 (C^9), 141.06 (C^{10}), 26.62 (C^{11}), 35.53 (C^{12}), 37.97 (C^{13}), 38.78 (C^{14}), 39.68 (C^{15}), 31.49 (C^{16}), 40.02 (C^{17}), 78.71 (C^{17a}), 11.69 (C^{18}), 26.73 (16α-CH_3), 33.00 (16β-CH_3), 55.25 (CH_3O), 21.16 and 170.64 (17a-$OCOCH_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 356 (100) $[M]^+$, 296 (40), 281 (20), 267 (16), 240 (25), 213 (49), 227 (14), 173 (32), 160 (75), 159 (60), 146 (88). Found, %: C 77.49; H 9.24. $C_{23}H_{32}O_3$. Calculated, %: C 77.49; H 9.05.

16,16-Dimethyl-D-homo-B-nor-9β-estrone (IV). A solution of 3 g of sodium hydroxide in 30 ml of methanol was added to a solution of 1 g of compound **I** in 50 ml of benzene, and the mixture was heated for 6 h under reflux with stirring (water bath). The mixture was cooled to room temperature and poured into 200 ml of water, 50% acetic acid was added to weakly acidic reaction, and the mixture was extracted with chloroform (3×20 ml). The extracts were combined, washed with a 5% solution of sodium carbonate and water until neutral washings, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The residue was dissolved in 15 ml of pyridine and treated with the Sarett reagent under standard conditions [13]. The products were dissolved in 25 ml of glacial acetic acid, 15 ml of 45% aqueous HBr was added dropwise, and the mixture was stirred for 2 h on heating on a boiling water bath, cooled to room temperature, poured into 100 ml of cold distilled water, and extracted with chloroform (3×70 ml). The combined extracts were washed with water until neutral washings, dried over anhydrous sodium sulfate, and filtered. The solvent was distilled off under reduced pressure, and the residue was crystallized from hexane–dioxane (2:1). Yield 0.135 g (13%), mp 182–183°C. Found, %: C 80.48; H 8.95. $C_{20}H_{26}O_2$. Calculated, %: C 80.49; H 8.78.

REFERENCES

1. Feyel-Gabanes, T., *C. R. Acad. Sci*., 1963, vol. 257, p. 4075.
2. Gabbard, R.B. and Segaloff, A., *Steroids*, 1983, vol. 42, no. 5, p. 555.
3. Bull, J.R. and de Koning, P.D., *J. Chem. Soc. Perkin Trans. 1*, 2000, no. 6, p. 1003.
4. US Patent no. 3354183, 1967; *Ref. Zh., Khim*., 1969, no. 11N426P.
5. Heidepriem, H., Rufer, C., Kosmol, H., and Schroder, E., *Justus Liebigs Ann. Chem*., 1968, vol. 712, no. 1, p. 155.
6. Ryzhenkov, V.E., Prokop'ev, A.A., Kameneva, I.Yu., Ishchenko, I.V, and Shavva, A.G., *Khim.-Farm. Zh*., 1991, no. 8, p. 47.
7. Shavva, A.G., Zlobina, I.V., Nersisyan, G.G., Matevosyan, I.N., Ryzhenkov, V.E., and Prokop'ev, A.A., USSR Inventor's Certificate no. 1371962, 1987; *Byull. Izobret*., 1988, no. 5.
8. Wiese, T.E., Polin, L.A., Palomino, E., and Brooks, S.C., *J. Med. Chem*., 1997, vol. 40, no. 22, p. 3659.
9. Chapelon, A-S., Moraledo, D., Rodrigues, P., Ollivier, C., and Santelli, M., *Tetrahedron*, 2007, vol. 63, no. 47, p. 11511.
10. Kayser, F., Maes, D., Wyns, L., Lisgarten, J., Palmer, R., Lisgarten, D., Willem, R., Martins, J.C., Verheyden, P., and Biesemans, M., *Steroids*, 1995, vol. 60, no. 10, p. 713.
11. Schönecker, B., Lange, C., Kötteritzsch, M., Güter, W., Weston, J., Anders, E., and Görls, H.J., *J. Org. Chem*., 2000, vol. 65, no. 18, p. 5487.
12. Commodari, F., Sclavos, G., Ibrahimi, S., Khiat, A., and Boulanger, Y., *Magn. Reson. Chem*., 2005, vol. 43, no. 6, p. 444.
13. Belov, V.N., Dudkin, V.Yu., Urusova, E.A., Starova, G.L., Selivanov, S.I., Nikolaev, S.V., Eshchenko, N.D., Morozkina, S.N., and Shavva, A.G., *Bioorg. Khim*., 2007, vol. 33, no. 3, p. 315.
14. Shavva, A.G., Starova, G.N., Selivanov, S.I., and Morozkina, S.N., *Khim. Geterotsikl. Soedin*., 2008, no. 2, p. 202.
15. Morozkina, S.N., Abusalimov, Sh.N., Starova, G.L., Selivanov, S.I, and Shavva, A.G., *Russ. J. Gen. Chem*., 2010, vol. 80, no. 7, p. 1324.
16. Egorov, M.S., Zorina, A.D., Balykina, L.V., Selivanov, S.I., and Shavva, A.G., *Russ. J. Org. Chem*., 2001, vol. 37, no. 6, p. 802.
17. Morozkina, S.N., Nikolaev, S.V., Selivanov, S.I., Ushakov, D.B., and Shavva, A.G., *Russ. J. Org. Chem*., 2008, vol. 44, no. 5, p. 675.
18. Acselrud, L.G., Griun, Yu.N., Zavalii, P.Yu., Pehsky, V.K., and Fundamentsky, V.S., *Collection of Abstracts of XXIIth European Crystallographic Meeting*, Moscow: Nauka. 1989, vol. 3, p. 135.
19. Sheldrick, G.M., *SHELXL 97*, Gottingen, Germany: University of Gottingen, 1997.
20. Selivanov, S.I. and Shavva, A.G., *Bioorg. Khim*., 2002, vol. 28, no. 3, p. 220.
21. Andersen, N.H., Eaton, H.L., and Lai, X., *Mag. Reson. Chem*., 1989, vol. 27, no. 6, p. 515.
22. Brzozowski, A.M., Pike, A.C., Dauter, Z., Hubbard, B.E., Bonn, T., Engstrom, O., Ohman, L., Green, G.L., Gustafsson, J.A., and Carlquist, M., *Nature*, 1997, vol. 389, no. 6652, p. 753.
23. Shavva, A.G., Selivanov, S.I., Starova, G.L., Boronoeva, T.R., Ischenko, I.V., Gluzdikov, I.A., Sharetskii, A.N., Isaeva, V.G., and Surinov, B.P., *Russ. J. Bioorg. Chem*., 2002, vol. 28, no. 3, p. 215.
24. Shavva, A.G., Morozkina, S.N., and Ushakov, D.B., Abstracts of Papers, *21st IUBMB and 12th FAOBMB Int. Congr. of Biochemistry and Molecular Biology*, Shanghai, China, 2009, p. 100.
25. Russian Patent no. 2391351, 2008.
26. Klimov, A.N. and Ryzhenkov, V.E., *Eksperimental'noe izuchenie gipolipidemicheskikh i antiaterosklerotic heskikh sredstv: Metodicheskie rekomendatsii* (Experimental Assays of Hypolipidemic and Antiatherosclerotic Drugs. Methodical Recommendations), Moscow, 1998, p. 6.