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New Analogs of D-Homoequilenine with Substituents in the D Ring

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Abstract—Stereoselectivity of reaction with Raney nickel of D-homoestra-1,3,5(10),8,14-pentaenes containing one or two methyl groups in position *16* was investigated. The reaction direction is governed by the orientation of the substituent at C^{17a}. The signals in the ^1H and ^{13}C NMR spectra of four synthesized compounds were completely assigned. Criteria for evaluation of the character of rings junction in analogs of D-homoequilenine were suggested. 16,16-Dimethyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaen-17a-one was subjected to X-ray diffraction analysis.

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Modified analogs of steroid estrogens lacking considerable uterotropic activity are promising for producing thereof enzymes inhibitors governing the metabolism of steroid hormones. Development of such inhibitors is very timely [1–5].

In continuation of our search for modified steroid estrogens with improved biological properties [6] we synthesized D-homoanalogs of equilenine with one or two methyl groups of C^{16}. The choice of this group compounds was based on findings that 13α-equilenine lacked hormonal activity (at least, under the experimental conditions) [7] and on preliminary estimation of the possibility of formating a "productive" complex between this kind ligands and an α-receptor of estrogens [8]. The calculations were performed using the data on the geometry of a complex between a natural hormone estradiol and the ligand-binding region of the α-receptor of estrogens obtained by X-ray diffraction study [9].

We selected as model compounds steroids **IV**, **XIIa**, and **XIIb** (Schemes 1 and 2), for their structure according to simulation data was poorly compatible with the geometry of the ligand-binding pocket of receptor. For instance, in the complex of 13α-analog **XIIa** with receptor the hydrogen of the methylene group Leu346 is at a distance of 1.85 Å from $H^{11\alpha}$ proton of the ligand, and one of the atoms of the methyl group Ala350 is at a distance of 1.83 A from $H^{11\beta}$ proton. Strong steric interactions are also observed between $C^{18}H_3$ and methyl group Met343, C^{16}-$CH_3(\alpha)$ and methyl group Ile424, hydrogen at C^4 and methine proton Met388. The distance between the oxygen of the keto group of steroid **XIIa** and proton of NH group His524 equals 4.8 A barring the formation between them of a hydrogen bond. The distance between the hydroxy group at C^3 of steroid and oxygen of the carboxy group Glu353 is according to calculations about 3.8 Å , considerably longer than in the complex with the natural hormone estradiol (2.34 Å [7]).

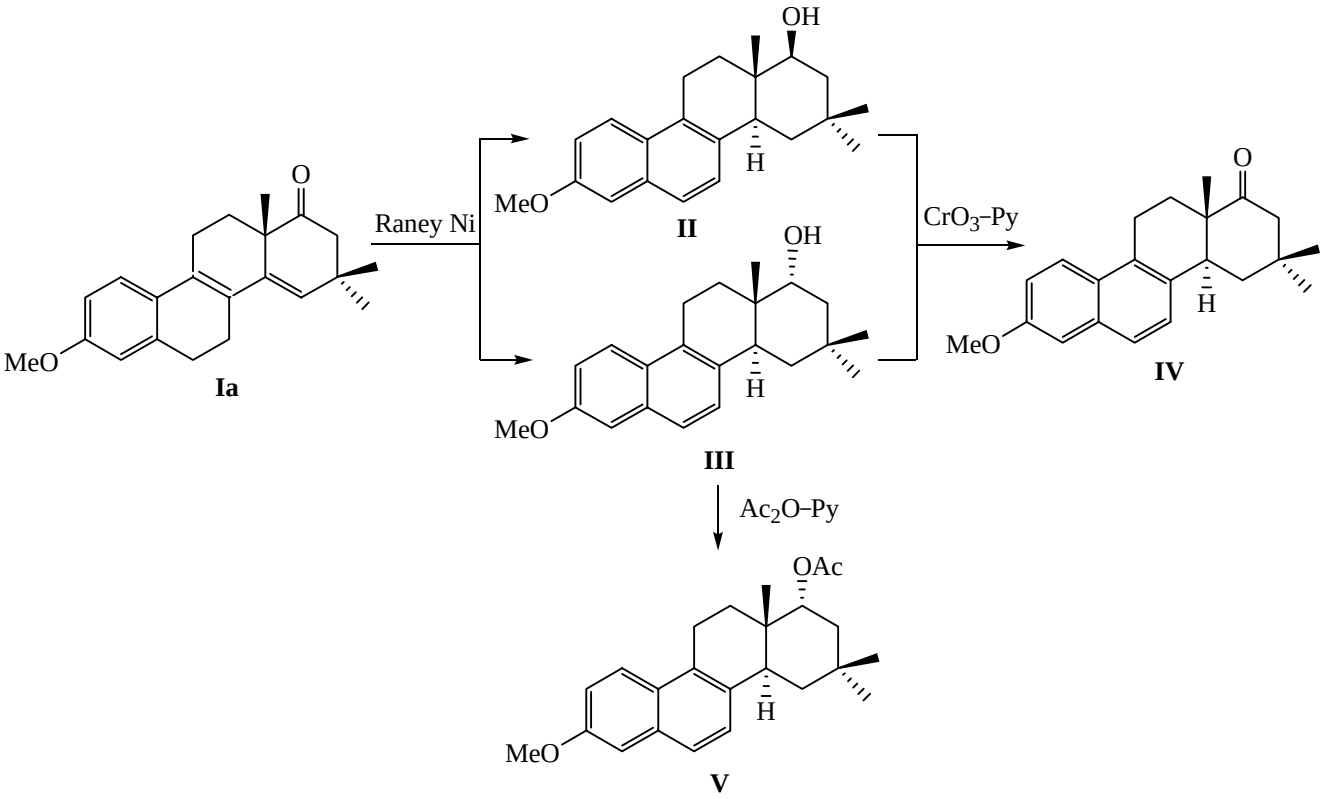
It is presumable that the mentioned inconsistency between the geometry of steroid **XIIa** and the ligand-binding region of receptor can cause low affinity of the compound in question to the receptor resulting in reduced estrogen activity of this steroid.

Analogous conclusions could be reached on molecular simulating ligand-receptor complexes also for steroids **IV** and **XIIb**, and for their antipodes.

We synthesized racemic steroids taking into account that the modified estrogens of l-series were selective hormones [10–12] and, consequently, might attract wide interest in medicine.

Reduction of estrapentaenone (**Ia**) on Raney nickel (Scheme 1) led to the formation of alcohols **II** and **III** with the natural junction of rings whose oxidation with Sarett reagent gave compound **IV**. The reaction of acetate **VIII** with Raney nickel nickel (Scheme 2) resulted in a mixture of compound that we failed to separate by chromatography. The alkaline hydrolysis followed by column chromatography on silica gel made it possible to obtain alcohols of natural **XIII** and 13α-series **XIV** in a ratio 1.8:1, which were converted into the corresponding acetates **XV** and **XVI**.

Scheme 1.



On reducing compounds **Xa** and **Xb** (Scheme 2) on Raney nickel we obtained analogs of D-homoequilenine **XIa** and **XIb** with a *cis*-junction of C and D rings. The hydrolysis of acetates **XIa** and **XIb** followed by oxidation of reaction products with Sarett reagent led to the formation of compounds **XIIa** and **XIIb**.

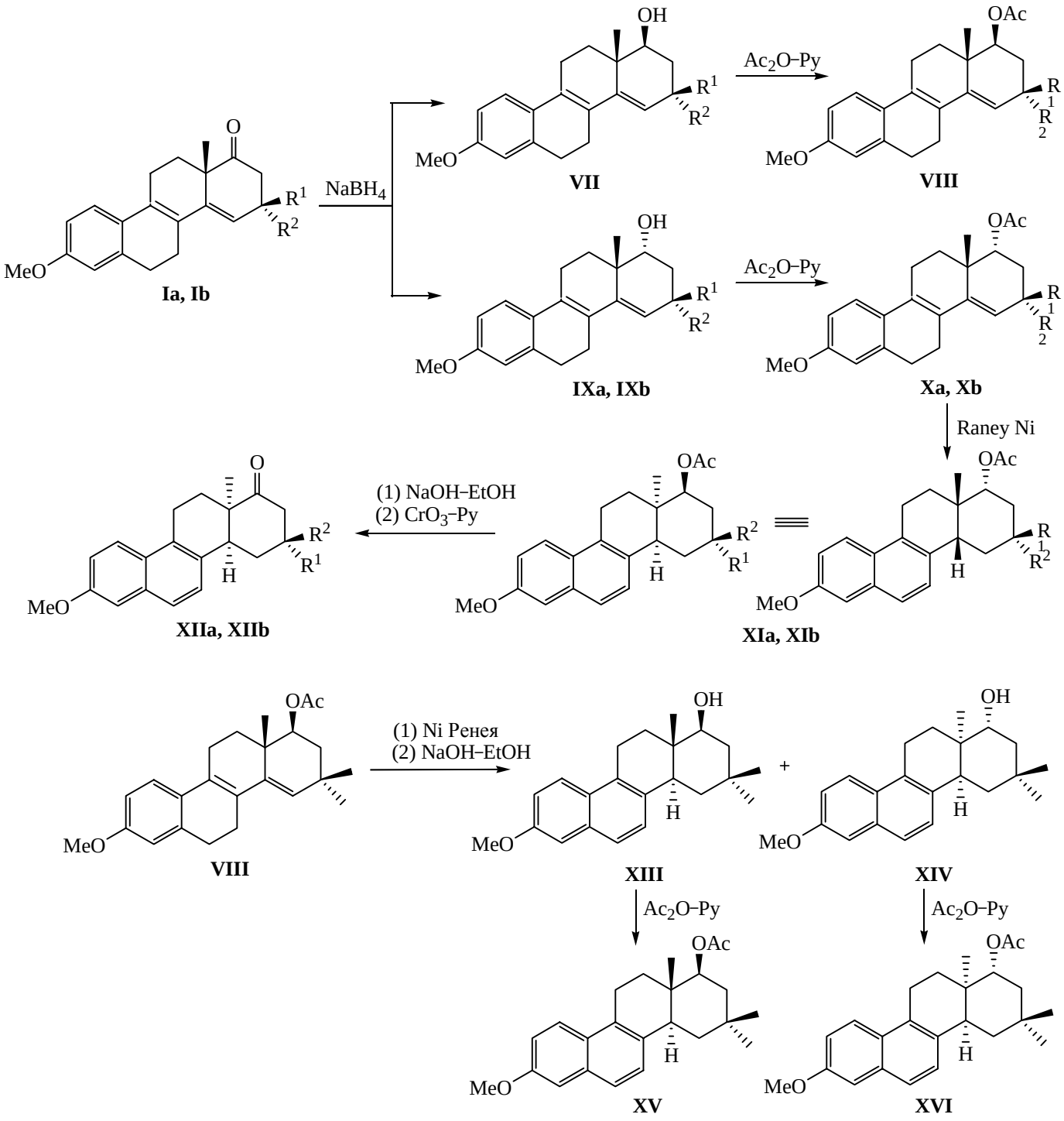
Thus the reaction of Raney nickel with estrapentaenone (**Ia**) led to the formation of compounds belonging to the natural 13β-series. Similar result was observed also with estrapentaenes lacking methyl groups linked to C^{16} [6]. Compound **VIII** possessing an equatorial acetyl group under similar conditions gave rise to a mixture of comparable amounts of steroids **XV** and **XVI**, epimeric at C^{13} atom. With axial acetates **Xa** and **Xb** the reaction proceeded stereoselectively giving D-homo-13α-analogs of equilenine.

The results obtained suggest in the whole that the steric direction of the reaction in question with substrates of similar structure is governed by the orientation of the substituent at C^{17a}.

Only minor number of published data concerned the spatial arrangement of the equilenine analogs in solution [6], and the D-homo-13α-analogs of equilenine were not studied at all. Therefore we performed complete assignment of signals in the ^{1}H and ^{13}C NMR spectra of compounds **V, XIa, XV**, and **XVI** with the help of homo- and heteronuclear correlation methods of NMR (DQF-COSY [15], HSQC [16], COLOC [17], and NOESY [18]). The results of assignment are presented in Table 1. The comparison of the chemical shift values indicates that for compounds with the *trans*-junction of C and D rings the peak of the hydrogen linked to C^7 appears in the region 7.40–7.50 ppm, and for 13α-analogs, at 7.10–7.20 ppm. In the ^{13}C NMR spectra a reliable difference in the chemical shifts was observed for the signals from C^7 and C^8 atoms belonging to compounds with different junction of rings (Table 1). It is therefore possible to suggest the chemical shift values of these atoms in ^{1}H and ^{13}C NMR spectra as a criterium of fast and trustworthy estimation of the ring junction character in analogs of D-homoequilenine.

Inasmuch as no published data existed on X-ray crystallography of D-homo-13α-analogs of equilenine, we carried out X-ray diffraction study of 16,16-dimethyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaen-17a-one (**XIIa**). The structure was solved by the direct method taking into account the anisotropy of thermal

Scheme 2.



I, IX–XII, R^2 = Me, R^1 = Me (**a**), H (**b**); **VII, VIII**, $R^1 = R^2$ = Me.

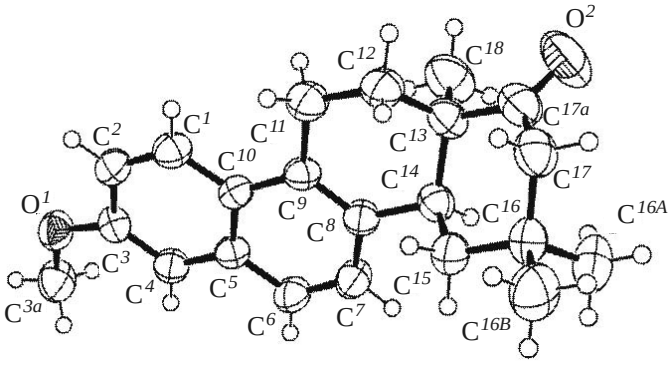
oscillations of nonhydrogen atoms. Hydrogen atoms were located in the calculated positions. The extinction was not taken into account. The calculations were performed using CSD [19] and SHELXL 97 software [20].

The coordinates and thermal parameters of the basis atoms of compound **XIIa** are compiled in Table 2. Conformation of compound **XIIa** is represented in the figure. According to the X-ray diffraction analysis the

Table 1. Chemical shifts of nuclei in the ^{13}C and ^{1}H NMR spectra of compounds **V, XIa, XV**, and **XVI**, δ, ppm

Compd. no.	**V**			**XIa**			**XV**			**XVI**		
Atom no.	C	H^{α}	H^{β}	C	H^{α}	H^{β}	C	H^{α}	H^{β}	C	H^{α}	H^{β}
1	124.64	7.90		124.45	7.88		124.60	7.89		124.39	7.87	
2	118.14	7.16		117.92	7.16		118.20	7.17		117.93	7.17	
3	156.79	–		156.82	–		156.79	–		156.78	–	
4	106.24	7.11		106.65	7.10		106.13	7.11		106.59	7.12	
5	133.82	–		133.21	–		132.80	–		133.17	–	
6	124.95	7.59		125.06	7.54		124.92	7.58		125.11	7.60	
7	124.50	7.47		129.01	7.11		124.33	7.41		128.93	7.18	
8	132.78	–		135.05	–		132.68	–		135.76	–	
9	130.60	–		129.36	–		130.63	–		128.82	–	
10	127.45	–		127.45	–		127.33	–		127.47	–	
11	23.26	3.25	3.13	22.17	3.27	2.95	22.83	3.24	3.10	22.57	3.26	3.06
12	31.46	2.01	1.60	20.26	2.11	1.81	33.39	1.65	2.05	26.32	2.15	1.49
13	35.47	–		35.77	–		36.88	–		34.74	–	
14	35.79	3.26		43.70	2.67		40.70	2.92		40.42	2.90	
15	37.97	2.03	1.39	46.34	1.41	1.55	37.45	2.03	1.39	46.20	1.63	1.45
16	30.83	–		31.81	–		31.60	–		30.67	–	
17	37.92	1.63	1.84	38.85	1.50	1.56	38.95	1.59	1.54	38.10	1.66	1.60
17a	77.90	4.89		77.65	5.08		77.80	4.95		77.90	4.89	
18	15.41	0.84		22.48	0.97		9.77	0.80		20.25	0.93	
16α-Me	28.58	1.17		33.67	0.94		26.58	1.15		33.21	0.88	
16β-Me	34.15	1.06		25.35	1.18		33.27	1.11		27.75	1.18	

angle between the planes of the rings A and B is 0.4°. Carbon atom of the methoxy group is located in the *trans*-position with respect to the C^{2}–C^{3} bond. The oxygen and the carbon of the methoxy group attached to C^{3} lie virtually in the plane of A ring. The C ring is practically a regular *semichair*, the angle between the planes containing atoms $C^{8}C^{9}C^{11}C^{12}C^{14}$ (*seat*) and $C^{12}C^{13}C^{14}$ (*back*) equals 140.5°. D ring is a regular *chair*. The molecule as a whole is nearly planar: The plane of the A and B rings and the plane of the *seat* of the *semichair* in the C ring are at an angle of 7.6°. The distance between the oxygens attached to C^{3} and C^{17} important for binding to the estrogen receptor is 10.795(5) Å. In the estradiol molecule, the most active natural estrogen, this distance amounts to 10.93 Å [21].



Geometry of the molecule of 3-methoxy-16,16-dimethyl-D-homo-13a-estra-1,3,5(10),6,8-pentaen-17à-one (**XIIà**) in a crystall.

Compound **XIIa** can be used further as one among reference substances in the study of binding to various proteins, applying X-ray crystallography to estimation of the efficiency of this binding.

The study on rats of biological action of compounds **IV**, **XIIa**, and **XIIb** demonstrated that at the dose 3 mg/kg body weight these steroids as was expected were not endowed with estrogen action (no effect on the weight of uterus, on induction of progesterone receptors, on the body weight).

EXPERIMENTAL

The purity of all compounds was checked by TLC on Silufol plates in solvent systems petroleum ether–ethyl acetate, 4:1, 3:1. Mass spectra were taken on MKh-1321 device at ionizing chamber temperature 200–210°C. ^{1}H and ^{13}C NMR spectra were registered at 295 K on

a spectrometer Bruker DPX-300 at operating frequencies 300.130 and 75.468 MHz respectively. ^{1}H NMR spectra were recorded from solutions containing 5–7 mg of the substance in 0.6 ml $CDCl_3$, ^{13}C NMR spectra, 30–50 mg of the substance in the same volume. Chemical shifts are reported with respect to TMS, measured from solvent ($CDCl_3$:$CHCl_3$ = 99.9:0.1) signals used for internal reference, 7.26 (^{1}H) and 76.90 ppm (^{13}C).

Reduction of 16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (Ia) on Raney nickel. To a solution of 1 g of compound **Ia** [22] in 25 ml of dioxane was added 5 g of Raney nickel twice washed with dioxane just before the experiment. The reaction mixture was stirred at 70°C for 6 h. The catalyst was filtered off and washed with hot dioxane. The solvent from the combined organic solutions was removed on a rotary evaporator. The residue was subjected to chromatography on a column charged with 20 g of silica gel (5–40 μm), elution with a mixture petroleum ether–ethyl acetate, 6:1. The composition of fractions was controlled by TLC on Silufol plates, eluent petroleum ether–ethyl acetate, 4:1. We obtained 0.1 g (10%) of **16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaen-17aβ-ol (II)**, mp 154–156°C. ^{1}H NMR spectrum, δ, ppm: 0.73 s [3H, C^{16}-CH_3(α)], 0.89–0.93 m (1H), 1.01 s (3H, C$^{18}H_3$), 1.10 s [3H, C^{16}-CH_3(β)], 1.26 s (1H), 1.32–1.70 m (6H), 2.00 d.d (1H), 2.35 d.d (1H), 2.81 d.d (1H), 3.13–3.29 m (2H), 3.66 d.d (1H, C^{17a}H, J_1 5.4, J_2 5.4, 10.1 Hz), 3.94 s (3H, CH_3O), 7.11 d (1H, C^{4}H, J 2.1 Hz), 7.17 d.d (1H, C^{2}H, J_1 8.1, J_2 9.1, 2.2 Hz), 7.41 d (1H, C^{6}H, J 8.7 Hz), 7.58 d (1H, C^{7}H, J 8.7 Hz), 7.92 d (1H, C^{1}H, J 8.13 Hz). Found, %: C 81.65; H 8.65. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

Additionally we obtained 0.16 g (16%) of **16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaen-17aα-ol (III)**, mp 123–133°C. ^{1}H NMR spectrum, δ, ppm: 0.77 s [3H, C^{16}-CH_3(α)], 1.05 s (3H, C$^{18}H_3$), 1.26 s [3H, C^{16}-CH_3(β)], 1.35–1.67 m (5H), 1.87 d.d (1H), 2.08–2.25 m (2H), 3.11–3.34 m (3H), 3.72 s (1H, C^{17a}H), 3.92 s (3H, CH_3O), 7.11 d (1H, C^{4}H, J 2.4 Hz), 7.16 d.d (1H, C^{2}H, J_1 8.3, J_2 2.4 Hz), 7.49 d (1H, C^{6}H, J 8.7 Hz), 7.59 d (1H, C^{7}H, J 8.7 Hz), 7.92 d (1H, C^{1}H, J 8.30 Hz). Mass spectrum, m/z (I_{rel}, %): 324 (96.5), 306 (85), 291 (100), 275 (4.5), 261 (6.8), 250 (16), 235 (11.5), 221 (16), 197 (13), 178 (11.5), 171 (12.5). Found, %: C 81.03; H 8.91. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

16,16-Dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaen-17a-one (IV). To 0.85 g of alcohols **II** and **III** obtained in the previous experiment and dissolved in 10 ml of pyridine was added dropwise at stirring Sarett reagent prepared from 0.7 g of chromium(VI) oxide and 15 ml of pyridine. The reaction mixture was left standing for 24 h, then excess oxidant was decomposed by adding 20 ml of ethanol, the separated precipitate was filtered off, and the filtrate was diluted with 150 ml of water. The reaction products were extracted from the water phase with chloroform (3... 25 ml), combined extracts were washed with dilute hydrochloric acid (3...20 ml), then with water till neutral reaction, and dried with sodium sulfate. The solvent was removed on a rotary evaporator, and the residue was crystallized from a mixture chloroform – ethanol. Yield 0.35 g (43%), mp 202–203°C. ^{1}H NMR spectrum, δ, ppm: 1.01 s [3H, C^{16}-CH_3(α)], 1.02 s (3H, C$^{18}H_3$), 1.23 s [3H, C^{16}-CH_3(β)], 1.57 s (1H), 1.83–2.01 m (2H), 2.09 d.d (1H), 2.17–2.26 m (2H), 2.76 d (1H), 3.08–3.20 m (2H), 3.32 d.d (1H), 3.94 s (3H, CH_3O), 7.12 s (1H, C^{4}H,

Table 2. Coordinates (×10^4) and thermal parameters (Å×10^3) of basis atoms of compound **XIIa**

Atom	x	y	z	U_{eq}[a]
O^1	1916(1)	8395(1)	2163(1)	59(1)
O^2	4648(1)	11842(2)	8691(1)	107(1)
C^1	2514(1)	9824(2)	4598(1)	51(1)
C^2	2190(1)	9547(2)	3711(1)	50(1)
C^3	2261(1)	8458(2)	3040(1)	46(1)
C^{3A}	1975(1)	7418(2)	1420(1)	68(1)
C^4	2647(1)	7600(2)	3287(1)	48(1)
C^5	2985(1)	7848(2)	4209(1)	43(1)
C^6	3390(1)	6983(2)	4480(1)	53(1)
C^7	3718(1)	7298(2)	5354(1)	54(1)
C^8	3672(1)	8500(2)	6017(1)	46(1)
C^9	3282(1)	9354(2)	5778(1)	44(1)
C^{10}	2928(1)	9012(2)	4877(1)	42(1)
C^{11}	3223(1)	10726(2)	6423(1)	62(1)
C^{12}	3599(1)	10863(2)	7416(1)	64(1)
C^{13}	4052(1)	10573(2)	7385(1)	54(1)
C^{14}	4058(1)	8767(2)	6966(1)	49(1)
C^{15}	4069(1)	7310(2)	7665(1)	56(1)
C^{16}	4429(1)	7476(3)	8685(1)	56(1)
C^{16A}	4368(1)	6077(2)	9342(1)	83(1)
C^{16B}	4884(1)	7296(2)	8669(1)	81(1)
C^{17}	4388(1)	9248(3)	9097(1)	64(1)
C^{17a}	4387(1)	10668(3)	8421(1)	68(1)
C^{18}	4147(1)	11946(2)	6762(1)	85(1)

[a] U_{eq} is equal to 1/3 of sum of tensor U_{ij} projection on orthogonal axes.

J 2.1 Hz), 7.18 d.d (1H, C^{2}H, J_1 8.3, J_2 9.3, 2.4 Hz), 7.42 d (1H, C^{6}H, *J* 8.4 Hz), 7.61 d (1H, C^{7}H, *J* 8.4 Hz), 7.91 d (1H, C^{1}H, *J* 8.30 Hz). Mass spectrum, *m/z* (I_{rel}, %): 322 (100), 307 (58), 291 (6.5), 237 (5.5), 233 (17.5), 211 (61), 197 (4.5), 179 (11), 171 (21), 165 (18.5), 153 (8). Found, %: C 81.62; H 8.07. $C_{22}H_{26}O_2$. Calculated, %: C 81.94; H 8.13.

17aα-Acetoxy-16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaene (V). A solution of 0.93 g of compound **III** in 7 ml of pyridine and 5 ml of acetic anhydride was heated on a boiling water bath for 4 h. The reaction mixture was poured on ice, the separated precipitate was crystallized from a mixture chloroform–ethanol, 1:4. Yield 0.91 g (86%), mp 109.5–111.5°C. ^{1}H NMR spectrum, δ, ppm: 0.84 s (3H, C^{18}H$_3$), 1.06 s [3H, C^{16}-CH$_3$(β)], 1.17 s [3H, C^{16}-CH$_3$(α)], 1.37–1.47 m (1H), 1.8–1.96 m (3H), 2.07 s (3H, CH$_3$COO), 2.14–2.25 m (1H), 2.55–2.8 m (5H), 3.92 s (3H, CH$_3$O), 4.89sC (1H, C^{17a}H), 7.11–7.16 m (2H), 7.47 d (1H, C^{7}H, *J* 8.4 Hz), 7.59 d (1H, C^{6}H, *J* 8.4 Hz), 7.90 d (1H, C^{1}H, *J* 8.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 366 (60), 306 (98), 291 (100), 262 (4.5), 256 (15), 235 (10), 221 (8.5), 165 (16). Found, %: C 78.48; H 8.20. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

Reduction of 16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17a-one (Ia). To a solution of 3.3 g of compound **Ia** [22] in 55 ml of a mixture dioxane–water, 10:1, was added gradually at stirring a powder of 1 g of sodium borohydride. After a common workup the reaction products were subjected to chromatography on a column charged with 40 g of silica gel (5–40 μm), elution with a mixture petroleum ether–ethyl acetate, 6:1. The composition of fractions was controlled by TLC on Silufol plates, eluent petroleum ether–ethyl acetate, 4:1. The fractions of the same composition were combined. On removing the solvent the residue was recrystallized from ethanol.

16,16-Dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17aβ-ol (VII). Yield 1.25 g (38%), mp 121–123°C. ^{1}H NMR spectrum, δ, ppm: 0.96 s [3H, C^{16}-CH$_3$(α)], 1.1 s [6H, C^{16}-CH$_3$(β), C^{18}H$_3$], 1.37–1.47 m (1H), 1.61–1.77 m (2H), 2.14–2.25 m (2H), 2.50–2.78 m (5H), 3.69 d.d (1H, C^{17a}H, J_1 4.5, J_2 4.5, 12 Hz), 3.81 s (3H, CH$_3$O), 5.48 s (1H, C^{15}H), 6.74 m (2H, C^{2}H, C^{4}H), 7.25 d (1H, C^{1}H, *J* 7.8 Hz). Found, %: C 81.65; H 8.65. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

16,16-Dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17aα-ol (IXa). Yield 1.58 g (48%), mp 146–147°C. ^{1}H NMR spectrum, δ, ppm: 0.91 s [3H, C^{16}-CH$_3$(α)], 1.1 s [3H, C^{16}-CH$_3$(β)], 1.23 s (3H, C^{18}H$_3$), 1.45–1.52 m (2H), 1.85 m (1H), 1.97 m (1H), 2.08–2.22 m (2H), 2.55–2.82 m (5H), 3.72 t (1H, C^{17a}H, $J_1 = J_2$ = 7 Hz), 3.82 s (3H, CH$_3$O), 5.65 s (1H, C^{15}H), 6.75 m (2H, C^{2}H, C^{4}H), 7.36 d (1H, C^{1}H, *J* 8.3 Hz). Found, %: C 81.52; H 9.29. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

17aβ-Acetoxy-16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaene (VIII) was synthesized similarly to compound **V** from 0.9 g of steroid **VIIa**. Yield 0.86 g (84%), mp 141–143.5°C. ^{1}H NMR spectrum, δ, ppm: 1.03 s [3H, C^{16}-CH$_3$(α)], 1.09 s [3H, C^{16}-CH$_3$(β)], 1.14 s (3H, C^{18}H$_3$), 1.4–1.48 m (1H), 1.67–1.76 m (2H), 1.8–1.92 m (1H), 2.09 s (3H, CH$_3$COO), 2.17–2.22 s (1H), 2.46–2.62 s (3H), 2.74–2.76 m (2H), 3.81s (3H, CH$_3$O), 4.94 d.d (1H, C^{17a}H, J_1 4.5, J_2 4.5, 12 Hz), 5.49 C (1H, C^{15}H), 6.73 m (2H), 7.23 d (1H, C^{1}H, *J* 8.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 366 (100), 351 (44.5), 291 (44.5), 276 (9), 261 (3.5), 233 (3), 178 (3), 171 (6.5), 165 (4.5), 153 (6), 147 (20.5), 145 (13.5).Found, %: C 78.53; H 8.25. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

16α-Methyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaen-17aα-ol (IXb) was synthesized from 3.0 g of compound **Ib** similarly to steroids **VII** and **IXa**. Yield 1.0 g (33%), mp 127–130°C. ^{1}H NMR spectrum, δ, ppm: 1.01 s (3H, C^{18}H$_3$), 1.23 d [3H, C^{16}-CH$_3$(α)], 1.54–1.67 m (3H), 2.05–2.15 m (3H), 2.52–2.80 m (6H), 3.71 t (1H, C^{17a}H), 3.83 s (3H, CH$_3$O), 5.81 s (1H, C^{15}H), 6.74–6.78 m (2H, C^{2}H, C^{4}H), 7.26 d (1H, C^{1}H).

17aα-Acetoxy-16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaene (Xa) was obtained in the same way as compound **V** from 0.93 of compound **IXa**. Yield 0.91 g (86%), mp 100.5–102.5°C. ^{1}H NMR spectrum, δ, ppm: 0.91 s [3H, C^{16}-CH$_3$(α)], 1.03 s [3H, C^{16}–CH$_3$(β)], 1.08 s (3H, C^{18}H$_3$), 1.42–1.47 m (1H), 1.8–1.96 m (3H), 2.04 s (3H, CH$_3$COO), 2.14–2.25 m (1H), 2.55–2.8 m (5H), 3.82 s (3H, CH$_3$O), 4.97 s (1H, C^{17a}H), 5.62 s (1H, C^{15}H), 6.73 m (2H, C^{2}H, C^{4}H), 7.23 d (1H, C^{1}H, *J* 8.3 Hz). Mass spectrum, *m/z* (I_{Otv}, %): 366 (100), 351 (3), 306 (10.5), 291 (10), 276 (13.5), 261 (5), 249 (3), 215 (3), 202 (3), 178 (3.5), 171 (5.5), 165 (4), 153 (7.5), 147 (41), 145 (30). Found, %: C 78.48; H 8.20. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

17aα-Acetoxy-16α-methyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaene (Xb) was obtained in the same way as compound **V** from 0.99 g of steroid

IXb. Yield 1.1 g (98%), mp 150–153°C. ^{1}H NMR spectrum, δ, ppm: 1.01 s (3H, C^{18}H$_3$), 1.18 d [3H, C^{16}–CH$_3$(α)], 1.48–1.53 m (1H), 1.70–1.75 m (1H), 1.82–1.89 m (1H), 2.07 s (3H, CH$_3$COO), 2.19–2.31 m (3H), 2.54–2.61 m (3H), 2.68–2.83 m (3H), 3.83 s (3H, CH$_3$O), 5.99 t (1H, C^{17a}H), 5.81 s (1H, C^{15}H), 6.74–6.77 m (2H, C^{2}H, C^{4}H), 7.26 d (1H, C^{1}H, *J* 8.3 Hz). Found, %: C 78.27; H 8.12. $C_{23}H_{28}O_3$. Calculated, %: C 78.38; H 8.01.

17aβ-Acetoxy-3-methoxy-16,16-dimethyl-D-homo-13α-estra-1,3,5(10),6,8-pentaene (XIa) was prepared from 0.9 g of compound **Xa** similarly to steroids **II** and **III**. Yield 0.44 g (49%), mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 0.94 s [3H, C^{16}-CH$_3$(α)], 0.97 s (3H, C^{18}H$_3$), 1.18 s [3H, C^{16}-CH$_3$(β)], 1.38–1.43 d (1H), 1.47–1.58 m (3H), 1.79–1.86 m (1H), 2.10 s (3H, CH$_3$COO), 2.67 d.d (1H), 2.91–3.04 m (1H), 3.29 d.d (1H), 3.92 s (3H, CH$_3$O), 5.08 d.d (1H, C^{17a}H, J_1 5.7, J_2 5.7, 11.4 Hz), 7.10–7.16 m (3H), 7.26 d (1H), 7.90 d (1H, C^{1}H, $^3J_{HH}$ 8.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 366 (100), 306 (13.5), 291 (31), 277 (4,5), 264 (4.5), 250 (6), 235 (14), 224 (37), 221 (37), 209 (25), 197 (11.5), 184 (7.3), 179 (11.5), 178 (11.5), 171 (10.4), 165 (22), 153 (10). Found, %: C 78.27; H 8.32. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

17aβ-Acetoxy-16β-methyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaene (XIb) was prepared from 0.77 g of compound **Xb** similarly to steroids **II** and **III**. Yield 0.27 g (35%) of compound **XIb**, mp 139.5–140°C. ^{1}H NMR spectrum, δ, ppm: 0.92–0.95 m [6H, C^{18}H$_3$, C^{16}-CH$_3$(β)], 1.11–1.40 m (2H), 1.74–1.90 m (4H), 2.04–2.15 m (4H), 2.51 d.d (1H), 2.87–3.02 m (1H), 3.22–3.41 m (1H), 3.91 s (3H, CH$_3$O), 4.87 d.d (1H, C^{17a}H), 7.11–7.18 m (32H, C^{2}H, C^{4}H, C^{7}H), 7.54 d (1H, C^{6}H), 7.88 d (1H, C^{1}H). Mass spectrum, *m/z* (I_{Otv}, %): 352 (100), 292 (19), 277 (31), 263 (4.5), 249 (6.5), 235 (11), 221 (46), 209 (22), 197 (8.5), 178 (11), 165 (20.5), 152 (7.5). Found, %: C 78.52; H 7.86. $C_{23}H_{30}O_3$. Calculated, %: C 78.38; H 8.01.

16,16-Dimethyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaen-17a-one (XIIa). To a solution of 0.7 g of acetate **XIa** in 35 ml of benzene was added 1.9 g of NaOH in 20 ml of ethanol, the reaction mixture was boiled for 3 h, cooled to room temperature, and poured into 400 ml of water. The benzene layer was separated, the products were extracted from the water layer into chloroform (4×30 ml). The combined organic solutions were dried with sodium sulfate, and the solvent was removed in a vacuum. The crystalline residue was dissolved in 5 ml of pyridine, to the solution obtained was added dropwise at stirring Sarett reagent prepared from 0.4 g of chromium(VI) oxide and 10 ml of pyridine. The reaction mixture was left standing for 24 h, then excess oxidant was decomposed by adding 10 ml of ethanol, and the separated precipitate was filtered off. The filtrate was diluted with 100 ml of 3 N hydrochloric acid and extracted with chloroform (3×25 ml). The organic phase was washed with water till neutral reaction, dried with sodium sulfate, and the solvent was removed in a vacuum. To the oily substance obtained 5 ml of ethanol was added, the separated crystals were filtered off and recrystallized from ethanola. Yield 0.39 g (63%), mp 121–124°C. ^{1}H NMR spectrum, δ, ppm: 1.07 s [3H, C^{16}-CH$_3$(α)], 1.07 C (3H, C^{18}H$_3$), 1.12 s [3H, C^{16}-CH$_3$(β)], 1.62 m (1H), 1.85-2.88 m (2H), 2.19–2.36 m (2H), 2.60 d (1H, C^{14}H), 2.94–3.04 m (2H), 3.32 d.d (1H), 3.94 s (3H, CH$_3$O), 7.15–7.22 m (3H, C^{2}H, C^{4}H, C^{7}H), 7.60 d (1H, C^{6}H, *J* 8.4 Hz), 7.90 d (1H, C^{1}H, *J* 8.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 322 (100), 307 (24), 293 (3.3), 224 (28), 211 (11), 171 (3.9), 165 (7.2), 152 (2.5). Found, %: C 81.83; H 8.54. $C_{22}H_{26}O_2$. Calculated, %: C 81.94; H 8.13.

16β-Methyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaen-17a-one (XIIb) was similarly prepared from 0.2 g of compound **XIb**. Yield 0.13 g (67%), mp 119–120°C. ^{1}H NMR spectrum, δ, ppm: 1.03 d [3H, C^{16}-CH$_3$(β)], 1.11 s (3H, C^{18}H$_3$), 1.50–1.68 m (2H), 1.96–2.11 m (2H), 2.27–2.38 m (3H), 2.80 d.d (1H, C^{14}H), 2.93–3.07 m (1H), 3.29 d.d (1H), 3.92 s (3H, CH$_3$O), 7.12–7.20 m (3H, C^{2}H, C^{4}H, C^{7}H), 7.58 d (1H, C^{6}H), 7.87 d (1H, C^{1}H).

Reaction of 17aβ-acetoxy-16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaene (VIII) with Raney nickel was carried out in the same way as with compound **Ia**. From 0.85 g of compound **VIIIa** we obtained 0.55 g of a mixture of steroids **XIII** and **XIV**, mp 117–119°C. To a solution of 0.54 g of the mixture obtained in 25 ml of benzene was added a solution of 1.3 g of NaOH in 10 ml of methanol. The reaction mixture was boiled on a water bath for 1.5 h. The solution was poured into water, the organic layer was separated, the hydrolysis products were extracted from the water layer into chloroform (4×30 ml). After the usual workup the residue was subjected to chromatography on a column packed with 15 g of silica gel (5–40 μm), elution with a mixture petroleum ether–ethyl acetate, 8:1, 6:1. The composition of fractions was controlled by TLC on Silufol plates, eluent petroleum ether–ethyl acetate, 4:1.

16,16-Dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaen-17aβ-ol (XIII). Yield 0.18 g (38%), mp 150.5–153°C. ^{1}H NMR spectrum, δ, ppm: 0.73 s [3H, C^{16}-CH$_3$(α)], 0.89–0.93 m (1H), 1.01 s (3H, C^{18}H$_3$), 1.10 s [3H, C^{16}-CH$_3$(β)], 1.26 s (1H), 1.32–1.70 m (6H), 2.00 d.d (1H), 2.35 d.d (1H), 2.81 d.d (1H), 3.13–3.29 m (2H), 3.66 d.d (1H, C^{17a}H, J_1 5.4, J_2 5.4, 10.1 Hz), 3.94 s (3H, CH$_3$O), 7.11 d (1H, C^{4}H, *J* 2.21 Hz), 7.17 d.d (1H, C^{2}H, J_1 9.1, J_2 9.1, 2.2 Hz), 7.41 d (1H, C^{7}H, *J* 8.7 Hz), 7.58 d (1H, C^{6}H, *J* 8.7 Hz), 7.92 d (1H, C^{1}H, *J* 9.13 Hz). Found, %: C 81.45; H 8.81. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

16,16-Dimethyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaen-17aβ-ol (XIV). Yield 0.1 g (21%), mp 115–117°C. ^{1}H NMR spectrum, δ, ppm: 0.84 s [3H, C^{16}-CH$_3$(α)], 1.05 s (3H, C^{18}H$_3$), 1.24 s [3H, C^{16}-CH$_3$(β)], 1.46–1.71 m (6H), 2.09–2.19 m (1H), 2.91 d.d (1H), 3.03–3.14 m (1H), 3.26 d.d (1H), 3.73 m (1H, C^{17a}H), 3.94 s (3H, CH$_3$O), 7.13–7.24 m (3H, C^{2}H, C^{4}H, C^{7}H), 7.57d (1H, C^{61}H, *J* 8.4 Hz), 7.89 d (1H, C^{16}H, *J* 9.0 Hz). Found, %: C 81.36; H 8.70. $C_{22}H_{28}O_2$. Calculated, %: C 81.44; H 8.70.

17aβ-Acetoxy-16,16-dimethyl-3-methoxy-D-homoestra-1,3,5(10),6,8-pentaene (XV) was prepared similarly to compound **V** from 0.05 g of steroid **XIII**. Yield 0.04 g (71%), mp 139–141°C. ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, C^{18}H$_3$), 1.11 s [3H, C^{16}-CH$_3$(β)], 1.15 s [3H, C^{16}-CH$_3$(α)], 1.39 t (1H), 1.56–1.71 m (5H), 2.00–2.17 m (5H), 2.92 d (1H), 3.03–3.15 m (1H), 3.23 d.d (1H), 3.92 s (3H, CH$_3$O), 4.94 t (1H, C^{17a}H, $J_1 = J_2$ = 9.3 Hz), 7.12 d (1H, C^{4}H, *J* 2.1 Hz), 7.16 d.d (1H, C^{2}H, J_1 9.0, J_2 2.1 Hz), 7.40 d (1H, C^{7}H, *J* 8.7 Hz), 7.58 d (1H, C^{6}H, *J* 8.7 Hz), 7.89 d (1H, C^{1}H, *J* 9.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 366 (100), 306 (3), 291 (13), 235 (3.5), 221 (7.5), 197 (5.5), 171 (10.5). Found, %: C 78.59; H 8.57. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

17aα-Acetoxy-16,16-dimethyl-3-methoxy-D-homo-13α-estra-1,3,5(10),6,8-pentaene (XVI) was obtained like steroid **V** from 0.08 g of compound **XIV**. Yield 0.08 g (88%), mp 167–169°C. ^{1}H NMR spectrum, δ, ppm: 0.88 s [3H, C^{16}-CH$_3$(α)], 0.93 s (3H, C^{18}H$_3$), 1.18 s [3H, C^{16}-CH$_3$(β)], 1.46–1.54 m (2H), 1.62–1.73 m (3H), 2.10 s (3H, CH$_3$COO), 2.90 d.d (1H), 3.02–3.14 m (1H), 3.26 d.d (1H), 3.94 s (3H, CH$_3$O), 4.90 s (1H, C^{17a}H), 7.13–7.21 m (3H, C^{2}H, C^{4}H, C^{7}H), 7.26 d (1H, C^{6}H, *J* 8.4 Hz), 7.89 d (1H, C^{1}H, *J* 9 Hz). Mass spectrum, *m/z* (I_{rel}, %): 366 (100), 306 (64.5), 291 (61.5), 277 (8.5), 264 (5.5), 250 (7), 235 (11), 224 (20), 209 (13), 197 (6), 171 (8), 165 (11). Found, %: C 78.85; H 8.37. $C_{24}H_{30}O_3$. Calculated, %: C 78.65; H 8.25.

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