ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 5, pp. 675–680. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © S.N. Morozkinaa, S.V. Nikolaev, S.I. Selivanov, D.B. Ushakov, A.G.Shavva, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 5, pp. 685–690.

Catalytic Hydrogenation on Raney Nickel of Estra-1,3,5(10),8,14-pentaenes with Sterically Accessible Double Bonds

S. N. Morozkina, S. V. Nikolaev, S. I. Selivanov, D. B. Ushakov, and A. G. Shavva

St. Petersburg State University, St. Petersburg, 198504 Russia
e-mail: AGShavva@yandex.ru

Received July 10, 2007

Abstract—The catalytic hydrogenation of estra-1,3,5(10),8,14-pentaenes with sterically accessible double bonds in the presence of Raney nickel in 2-propanol at elevated pressure and at heating to 110–120°C resulted in prevailing formation of estrogens 8α-analogs alongside a considerable quantity of estra-5,7,9-trienes. Although the hydrogenation at 45–60°C provided a higher yield of estrogens 8α-analogs, the synthesis of steroids of this group gave better results at hydrogenation in a high purity benzene.

DOI: 10.1134/S1070428008050060

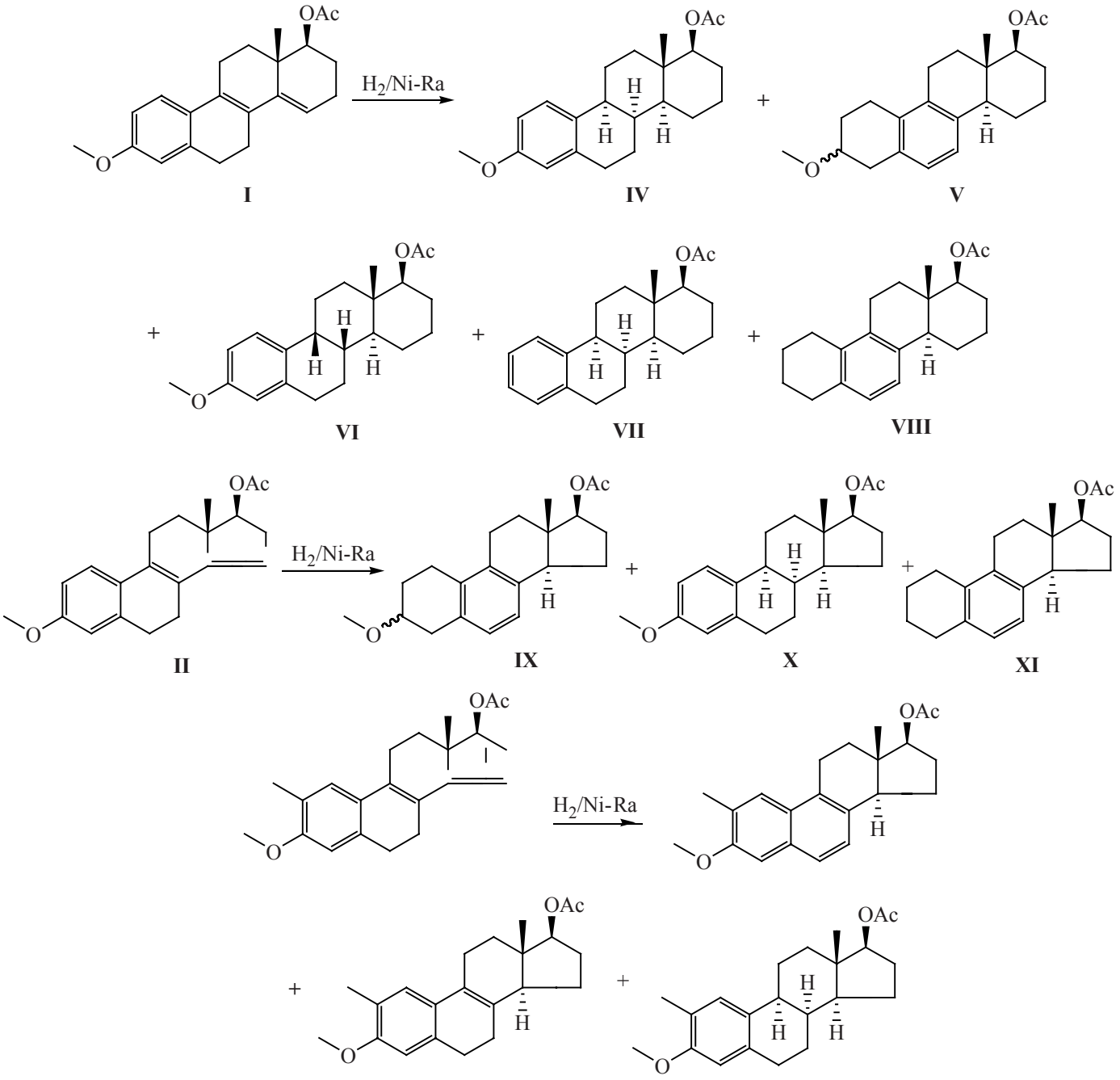
8α-Analogs of the naturally occurring estrogens exhibit a considerable affinity to the corresponding nuclear receptors [1–3] and therefore are promising objects for preparation of new substances with refined biological characteristics [4]. Although these properties are inherent to many steroids of this stereochemical series [5–23] the synthetic procedures for their preparation have not been specially developed. The most common method of preparation of steroids from this class is a catalytic hydrogenation of estra-1,3,5(10),8,14-pentaenes or similar substances containing a double bond in the position *8(9)* [5–32]. The formation of estrogens 8α-analogs is usually ascribed to the easy approach of the catalyst to the α-region of the molecule although this reaction route is unfavorable due to the presence in the forming compounds closely located β-hydrogens at C^{7} and C^{11}, and also of an alkyl group at C^{13} [33]. The yield of target products usually does not exceed 60%, yet the most part of steroids of this group has been synthesized by this method. In particular, in the patent [9] 133 examples are cited of preparation of compounds from this stereochemical series.

Obviously the spatial shielding of the system of conjugated double bonds in the substrate or the existence in the reaction product of additional unfavorable interactions between the substituents would result in decrease in the yield of estrogens 8α-analogs. When under the action of the catalyst a preliminary migration of a double bond is possible the main reaction product might contain the altered junction of the rings that sometimes actually occurs [29]. Besides in some cases (especially when the double bonds are spatially shielded) the *B* ring suffers aromatization that significantly hampers the purification of the target products [24–28].

As a rule the catalytic hydrogenation is carried out in the presence of Pd on some carrier. These catalysts are relatively expensive, therefore attempts have been made to apply the more accessible Raney nickel [15–17]. We started a systematic research on the catalytic hydrogenation of 1,3,5(10),8,14-estrapentaenes in the presence of Raney nickel. The first objects of our study were compounds with a system of conjugated double bonds in positions *8(9),14(15)* sterically accessible for the catalyst.

First problem was to find a solvent suitable for performing the reaction. Inasmuch as an information existed on the hydrogenation of steroids with a double bond in the position *8(9)* in ethanol or a mixed solvent containing ethanol [7, 25, 30–32], we checked the feasibility of applying alcohols to the hydrogenation of analogous substrates on Raney nickel at elevated pressure by examples of compounds **I–III** (see the scheme). The choice of model substances was governed by the potential possibility to use the corresponding estrogens 8α-analogs for the synthesis of products with refined biological action [4]. The catalytic hydrogenation was carried out in 2-propanol for the initial substrates were better soluble in it than in ethanol.

Scheme.



It turned out that the catalytic hydrogenation of a typical Torgov steroid **I** at 110–120°C led to the formation of a complex mixture of substances that was subjected to HPLC to provide compounds **IV–VIII**. Their structure was deduced from mass spectra and ^{1}H and ^{13}C NMR spectra (the procedure of establishing the structure of modified estrogens was described in [34]). Although the 8α-analogs of steroid estrogens formed in relatively high yields the presence of numerous reaction products impeded their purification. The hydrogenation of compound **I** at 45–60°C resulted in the formation of lesser amounts of products of methoxy group hydrogenolysis.

Similar results were obtained also on the hydrogenolysis of steroid **II**: at 110–120°C the yields of estra-5,7,9-trienes and 8α-analog **X** were comparable, at 45–60°C the hydrogenolysis products virtually did not form.

Although the yield of the estrogens of the 8α-series somewhat increased in the process carried out at lower

temperature, the use of 2-propanol as the only solvent for hydrogenation of substrates of similar structure would be limited because of the low solubility of the initial compounds.

Formerly at the Chair of the natural compounds of the Chemical Faculty of Saint-Petersburg State University an efficient synthesis was performed by catalytic hydrogenation of estra-1,3,5(10),8,14-pentaenes on Raney nickel in benzene [13, 14, 35–42]. Taking into account the results of these studies and the findings described above we tested the feasibility of using for the catalytic hydrogenation the Raney nickel thoroughly washed from 2-propanol that was usually used for its storage. It proved that the yield of steroid estrogens 8α-analogs significantly grew, but the reaction should proceed at the temperature not exceeding 80°C; at higher temperature side products formed and hampered the purification of the target substances.

From the compounds synthesized the most interesting biological properties were found in compound **X** exhibiting a high hypocholesteremic action and a considerable osteoprotective effect. The analysis of experimental data on the biological properties of new compounds will be published elsewhere.

EXPERIMENTAL

All compounds synthesized were racemic. Their purity was checked by HPLC on a chromatograph Altex. Mass spectra were taken on MKh-1321 instrument at the ionization chamber temperature 200–210°C and the energy of ionizing electrons 70 eV. ^{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 from solutions in 0.6 ml of $CDCl_3$ of 5–7 mg of compound for registering ^{1}H NMR spectra, 30–50 mg for ^{13}C NMR spectra. Chemical shifts are reported with respect to TMS and have been measured from the signals of the solvent ($CDCl_3$–$CHCl_3$, 99.9:0.1), 7.26 ppm (^{1}H) and 76.90 ppm (^{13}C).

Catalytic hydrogenation of 17aβ-acetoxy-3-methoxy-D-homoestra-1,3,5(10),8,14-pentaene (I). *a*. To a solution of 1 g of compound **I** [43] in 270 ml of 2-propanol was added 3 g of freshly prepared Raney nickel, the hydrogenation was carried out for 1 h at 110–120°C and at the pressure 120 at. After a common workup the reaction products were crystallized from ethanol. We obtained 0.52 g (51%) of **17aβ-acetoxy-3-methoxy-D-homo-8α-estra-1,3,5(10)-triene** (**IV**), mp 172.5–174°C (164–165°C [44]). ^{13}C NMR spectrum, δ, ppm: 129.9 (C^1), 112.0 (C^2), 157.2 (C^3), 113.0 (C^4), 137.5 (C^5), 31.5 (C^6), 21.0 (C^7), 40.2 (C^8), 41.3 (C^9), 134.0 (C^{10}), 28.1 (C^{11}), 37.5 (C^{12}), 37.7 (C^{13}), 46.5 (C^{14}), 24.2 and 25.7 (C^{15} and C^{16}), 27.3 (C^{17}), 81.8 (C^{17a}), 13.5 (C^{18}), 55.0 (CH_3O), 21.1 ($\underline{C}H_3CO$), 170.7 ($CH_3\underline{C}O$). Found, %: C 77.18; H 8.87. $C_{22}H_{30}O_3$. Calculated, %: C 77.16; H 8.83.

The compounds retained in the mother liquor were purified by HPLC on a column Lichrosorb RP-18 5 μm (Merck) with a gradient elution by the mixture acetonitrile–water (80–95%) for 15 min. From the most polar fraction we obtained 0.089 g (9%) of **17aβ-acetoxy-3-methoxy-D-homoestra-5,7,9(10)-triene (V)**, mp 146–149°C (after recrystallization from a mixture ethanol–benzene, 25:1). ^{1}H NMR spectrum, δ, ppm: 0.82 s (3H, $C^{18}H_3$), 2.10 s (3H, $\underline{C}H_3CO$), 3.45 s (3H, CH_3O), 4.62 m (1H, C^3H), 4.68 d.d (1H, H^{17a}, $J_{17\beta H,17a\alpha H}$ 11.1, $J_{17\alpha H,17a\alpha H}$ 4.6 Hz), 6.94 d and 7.05 d (пО 1H, H^6 and H^7, J 8.1 Hz). ^{13}C NMR spectrum, δ, ppm: 10.4, 21.1, 23.1, 23.5, 23.6, 24.5, 26.2, 27.9, 33.4, 35.4, 36.2, 44.9, 55.7, 75.4, 80.2, 123.0, 126.9, 131.7, 133.4, 133.8, 135.3, 162.1, 170.8. Mass spectrum, *m/z* (I_{rel}, %): 342 (49) $[M]^+$, 310 (100), 284 (8), 267 (16), 250 (22), 235 (29), 221 (11), 215 (14), 195 (26), 183 (21), 169 (19), 155 (19). Found, %: C 77.08; H 8.80. $C_{22}H_{30}O_3$. Calculated, %: C 77.16; H 8.83.

The less polar oily fraction (85 mg) contained two components: 20% of steroid **V** and 80% of **17aβ-acetoxy-3-methoxy-D-homo-9β-estra-1,3,5(10)-triene (VI).** ^{1}H NMR spectrum, δ, ppm: 0.97 s (3H, $C^{18}H_3$), 2.04 s (3H, $C\underline{H}_3CO$), 2.94 br.s (1H, H^9), 3.79 s (3H, CH_3O), 4.36 m (1H, H^{17a}), 6.64 d (1H, H^4, *J* 2.5 Hz,), 6.72 d.d (1H, H^2, $J_{2,4}$ 2.5, $J_{1,2}$ 8.6 Hz), 7.23 d (1H, H^1, $J_{1,2}$ 8.6 Hz). ^{13}C NMR spectrum, δ, ppm:127.0 (C^1), 111.8 (C^2), 157.1 (C^3), 113.8 (C^4), 138.5 (C^5), 25.3 (C^6), 25.4 (C^7), 33.3 (C^8), 37.6 (C^9), 130.0 (C^{10}), 23.4 (C^{11}), 31.8 (C^{12}), 38.2 (C^{13}), 39.8 (C^{14}), 23.0 (C^{15}), 23.8 (C^{16}), 26.6 (C^{17}), 81.0 (C^{17a}), 11.4 (C^{18}), 55.1 (CH_3), 20.9 ($\underline{C}H_3CO$), 170.8 ($CH_3\underline{C}O$).

We obtained additionally 175 mg (17%) of compound **IV**, mp 172.5–174°C. Overall yield of steroid **IV** was 68%.

From the fraction with the retention time 10 min by means of crystallization from methanol we isolated 33 mg (4%) of **17aβ-acetoxy-D-homo-8α-estra-1,3,5-(10)-triene (VII),** mp 95–96°C. ^{1}H NMR spectrum, δ, ppm: 0.98 s (3H, $C^{18}H_3$), 2.04 s (3H, $C\underline{H}_3CO$), 4.51 m (1H, H^{17a}), signals of 4 aromatic protons. ^{13}C NMR spectrum, δ, ppm: 13.6 (2C), 21.2 (2C), 24.2, 25.7,

27.3, 28.0, 31.2, 37.6, 37.7, 40.0, 42.0, 46.5, 81.8, 125.4, 125.5, 128.7, 129.1, 136.4, 141.7, 170.8. Mass spectrum, *m/z* (I_{rel}, %): 312 (64) $[M]^+$, 252 (46), 237 (6), 223 (12), 210 (7), 197 (66), 183 (16.5), 169 (14.5), 156 (40), 142 (82), 141 (43), 130 (100). Found, %: C 80.63; H 9.11. $C_{21}H_{28}O_2$. Calculated, %: C 80.73; H 9.03.

From the most polar fraction by means of crystallization from methanol we isolated 78 mg (8%) of **17aβ-acetoxy-D-homoestra-5,7,9-triene (VIII)**, mp 145–147°C. ^{1}H NMR spectrum, δ, ppm: 0.81 s (3H, C^{18}H$_3$), 2.09 s (3H, C$\underline{H}_3$CO), 4.67 d.d (1H, H^{17a}, J_1 11, J_2 4.6 Hz), 6.92 d and 7.04 d (1H each, H^6 and H^7, J 8.1 Hz). ^{13}C NMR spectrum, δ, ppm: 10.4, 21.2, 22.7, 23.0, 23.6, 23.7, 26.2, 26.3, 29.8, 33.5, 36.2, 45.0, 80.3, 122.4, 126.6, 133.8, 134.5, 134.9 (2C), 157.0, 170.9. Mass spectrum, *m/z* (I_{rel}, %): 312 (100) $[M]^+$, 252 (35), 237 (50), 223 (13), 209 (13), 197 (31), 185 (58), 171(8), 155 (13), 143 (16), 141 (14), 129 (15).Found, %: C 80.85; H 9.12. $C_{21}H_{28}O_2$. Calculated, %: C 80.73; H 9.03.

b. The hydrogenation of 0.50 g of compound **I** was performed in 270 ml of 2-propanol at the pressure of 100 at and temperature 45–60°C for 45 min, the reaction products were purified in the same way as in the procedure *a*. We obtained 0.009 g (2%) of compound **V**, mp 144–147°C, 0.035 g (7%) of oily 9β-analog **VI**, and 0.34 g (67%) of steroid **IV**, mp 171–173°C. The respective ^{1}H and ^{13}C NMR spectra were the same as cited above.

c. To a solution of 7.0 g of compound **I** in 270 ml of benzene was added 10 g of freshly prepared Raney nickel W-6 [45] thoroughly washed with benzene. The hydrogenation was carried out at 60–70°C and hydrogen pressure 120–160 at. After consumption of 100–120 l of hydrogen the hydrogenation was stopped, the products were subjected to usual workup, the target compound was isolated by crystallization from methanol, yield 6.55–6.65 g (93–95%), mp 171–173°C. The ^{1}H and ^{13}C NMR spectra of the steroid isolated were identical to those cited above.

Catalytic hydrogenation of 17β-acetoxy-3-methoxy-estra-1,3,5(10),8,14-pentaene (II). *a*. To a solution of 1 g of compound **II** [46] in 270 ml of 2-propanol was added 5 g of Raney nickel, the hydrogenation was carried out for 1 h at 110–120°C and the pressure of 120 at. The reaction products were purified by HPLC on a column Lichrosorb RP-18 5 μm (Merck) with a gradient elution by the mixture acetonitrile–water (80–95%) for 15 min.

From the fraction with the retention time 8.3 min we obtained 0.232 g (23%) of 17β-acetoxy-3-methoxy-estra-5,7,9(10)-triene (**IX**), mp 125–127°C (after recrystallization from methanol). ^{1}H NMR spectrum, δ, ppm: 0.72 s (3H, C^{18}H$_3$), 2.08 s (3H, C$\underline{H}_3$CO), 3.43 s (3H, CH$_3$O), 3.61 m (1H, H^3), 4.82 d.d (1H, H^{17}, J 6.96, 6.90 Hz), 6.83 d and 6.92 d (1H each, H^6 and H^7, J 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 11.2, 21.1, 23.4, 24.5 (2C), 27.8, 28.1, 34.1, 35.5, 41.9, 46.1, 55.7, 75.4, 81.8, 123.3, 126.8, 131.8, 133.5, 133.8, 136.1, 171.2. Mass spectrum, *m/z* (I_{rel}, %): 328 (56) $[M]^+$, 296 (100), 253 (27), 236 (37.5), 221 (47), 210 (17.5), 195 (42), 183 (22), 165 (16.5), 155 (26). Found, %: C 76.69; H 8.71. $C_{21}H_{28}O_3$. Calculated, %: C 76.79; H 8.59.

From the fraction with the retention time 10.5 min we obtained 0.335 g (33%) of 17β-acetoxy-3-methoxy-8α-estra-1,3,5(10)-triene (**X**), mp 112–112.5°C (after recrystallization from methanol). Mass spectrum, *m/z* (I_{rel}, %): 328 (100) $[M]^+$, 285 (2), 268 (14.5), 253 (3), 239 (17), 227 (9), 211 (5.5), 199 (5.5), 186 (41.5), 173 (19.5), 160 (39), 147 (11). Found, %: C 76.73; H 8.64. $C_{21}H_{28}O_3$. Calculated, %: C 76.79; H 8.59.

From the fraction with the retention time 12.8 min we isolated 0.14 g(15%) of 17β-acetoxyestra-5,7,9(10)-triene (**XI**), mp 131–133.5°C (after recrystallization from methanol). ^{1}H NMR spectrum, δ, ppm: 0.73 s (3H, C^{18}H$_3$), 2.10 s (3H, C$\underline{H}_3$CO), 4.84 d.d (1H, H^{17}, $J_{16a,17a} = J_{16\beta,17a} = 6.93$ Hz), 6.81 d and 6.92 d (1H each, H^6 and H^7, J 7.7 Hz). ^{13}C NMR spectrum, δ, ppm: 11.1, 21.1, 22.7, 23.3, 23.4, 24.3, 26.4, 28.1, 30.0, 34.1, 41.9, 46.1, 81.8, 122.7, 126.5, 133.9, 134.5, 134.8, 135.6, 171.1. Mass spectrum, *m/z* (I_{rel}, %): 298 (100) $[M]^+$, 238 (24), 223 (60), 210 (16), 197 (22), 185 (12.5), 165 (5). Found, %: C 80.44; H 8.81. $C_{20}H_{26}O_2$. Calculated, %: C 80.50; H 8.78.

b. The catalytic hydrogenation of 0.5 g of estrapentaene **II** and the purification of the reaction products was performed as in procedure *a*, but the temperature of the process was maintained in the range 45–60°C. We obtained 0.042 g (8%) of steroid **IX**, mp 125–127 °C, 0.29 g (57%) of acetate **X**, mp 112–113°C, and 0.02 g (4%) of compound **XI**, mp 201–203°C (201–203°C [47]).

c. Into a steel pressure reactor of capacity 600 ml was charged a solution of 13 g of estrapentaene **II** in 260 ml of benzene. To the solution 10 g of Raney nickel was added. The catalyst was thoroughly washed with benzene just before the experiment. The hydrogen pressure was increased to 150–180 at.

The reaction mixture was heated to 45–50°C, and then the agitator was started. The temperature was maintained not higher than 90°C without stopping the reaction. After consumption of 100 l of hydrogen the agitator

was stopped, the reaction mixture was cooled to room temperature. The catalyst was filtered off through a glass frit and washed on the filter with 100 ml of benzene, the solutions of the hydrogenation products were combined. The solvents were removed on a rotary evaporator. The residue was recrystallized from methanol. Yield of compound **X** 11.15 g (85%), mp 113.5–115°C. The mixed probe with an authentic sample melted without depression of the melting point. The ^{1}H NMR spectrum of steroid **X** was identical to that of the authentic compound.

Catalytic hydrogenation of 17β-acetoxy-2-methyl-3-methoxyestra-1,3,5(10),8,14-pentaene (III). To a solution of 0.50 g of compound **III** [46] in 270 ml of 2-propanol was added 0.5 g of Raney nickel, the hydrogenation was carried out at 45–65°C and the pressure of 100–105 at for 1 h. The catalyst was filtered off, the solvent was removed in a vacuum, the reaction products were purified by HPLC.

From the least polar fraction we separated by crystallization from ethanol 0.055 g (11%) of **17β-acetoxy-2-methyl-3-methoxyestra-1,3,5,7,9-pentaene** (**XII**), mp 178–185°C (178–185°C [46]). The mixed probe with an authentic sample [46] melted without depression of the melting point. The ^{1}H and ^{13}C NMR spectra of steroid **XII** was identical to that of the authentic compound.

From the next fraction we separated by crystallization from ethanol 0.035 g (7%) of **17β-acetoxy-2-methyl-3-methoxyestra-1,3,5(10),8-tetraene (XIII)**, mp 148–150°C. ^{1}H NMR spectrum, δ, ppm: 0.81 s (3H, $C^{18}H_3$), 2.07 C (3H, $C\underline{H}_3CO$), 2.19 C (3H, C^2–CH_3), 3.82 C (3H, CH_3O), 4.77 d.d (1H, H^{17}, $J_1 = J_2 = 6.9$ Hz), 6.62 s (1H, H^4), 7.09 s (1H, H^1). Mass spectrum, *m/z* (I_{rel}, %): 340 (100) $[M]^+$, 325 (6), 309 (3), 297 (4), 278 (13.5), 265 (16), 249 (5), 240 (9), 239 (9), 225 (7), 186 (22), 165 (5). Found, %: C 77.51; H 8.35. $C_{22}H_{28}O_3$. Calculated, %: C 77.61; H 8.29.

From the most polar fraction we separated by crystallization from ethanol 0.26 g (51%) of **17β-acetoxy-2-methyl-3-methoxy-8α-estra-1,3,5(10)-triene (XIV)**, mp 132.5–133.5°C. ^{1}H NMR spectrum, δ, ppm: 0.91 s (3H, $C^{18}H_3$), 2.07 s (3H, $C\underline{H}_3CO$), 2.17 s (3H, C^2–CH_3), 3.79 s (3H, CH_3O), 4.62 d.d (1H, H^{17}, $J_1 = J_2 = 8.7$ Hz), 6.52 s (1H, H^4), 6.91 s (1H, H^1). Mass spectrum, *m/z* (I_{rel}, %): 342 (100) $[M]^+$, 282 (10), 267 (3.5), 253 (12), 241 (4.5), 225 (4.5), 213 (4.5), 200 (32.5), 187 (13), 185 (8), 174 (24.5), 161 (8), 159 (10). Found, %: C 76.91; H 8.90. $C_{22}H_{30}O_3$. Calculated, %: C 77.16; H 8.83.

REFERENCES

1. Chernyaev, G.A., Barkova, T.I., Ananchenko, S.N., Sorokina, I.B., Mataradze, G.D., and Rozen, V.B., *Bioorg. Khim.*, 1979, vol. 5, p. 869.
2. Gonzalez, F.B., Neef, G., Eder, U., Wiechert, R., Schillinger, E., and Nishino, Y., *Steroids*, 1982, vol. 40, p. 171.
3. Kaspar, P. and Witsel, H., *J. Steroid Biochem.*, 1985, vol. 25, p. 259.
4. Shavva, A.G., Vlasova, K.V., Tsogoeva, S.B., Egorov, M.S., and Yakutseni, P.P., Bioorg. Khim., 2002, vol. 28, p. 236.
5. Smith, H., Douglas, G.H., and Walk, C.R., *Experientia,* 1964, vol. 61, p. 418.
6. Smith, H. and Hughes, G., UK Patent 991593, 1965; *Chem. Abstr.*, 1965, vol. 63, 8449d-f.
7. Smith, H. and Hughes, G., UK Patent 1069845, 1967; *Chem. Abstr.*, 1967, vol. 68, 114833h.
8. Smith, H. and Hughes, G., UK Patent 1108664, 1968; *Chem. Abstr.*, 1968, vol. 69, 77599j.
9. Smith, H. and Hughes, G., US Patent 3407217, 1968; *Chem. Abstr.,* 1969, vol. 70, 88089q.
10. Stein, R.P., Buzby, G.C., Smith, R.C., and Smith, H., US Patent. 3465011, 1969; *Chem. Abstr.*, 1970, vol. 72, 21829d.
11. Prezewowsky, K., Laurent, H., Hofmeister, H., Wiechert, R., Neuman, F., and Nishino, Y., German Patent 2336431, 1975; *Chem. Abstr.*, 1975, vol. 83, 43607h.
12. Prezewowsky, K., Laurent, H., Hofmeister, H., Wiechert, R., Neuman, F., and Nishino, Y., German Patent 2336434, 1975; *Chem. Abstr.,* 1975, vol. 83, 43606h.
13. Korkhov, V.V., Nikitina, G.V., and Shavva, A.G., *Khim. Farm. Zh.*, 1983, p. 1315.
14. Korkhov, V.V., Makusheva, V.P., Lupanova, G.E., Eliseev, I.I., Zhukovskii, E.A., Boronoeva, T.R., Martynov, V.F., and Shavva, A.G., *Khim. Farm. Zh.*, 1986, vol. 20, p. 574.
15. Eder, U., Sauer, G., Haffer, G., Neef, G., and Wiechert, R., German Patent 2551214, 1977; *Chem. Abstr.*, 1977, vol. 87, 152463n.
16. Eder, U., Sauer, G., Haffer, G., Neef, G., and Wiechert, R., German Patent 4066674, 1978; *Chem. Abstr.*, 1977, 170384n.
17. Eder, U., Haffer, G., Neef, G., Prezewowsky, K., Sauer, G., and Wiechert, R., *Chem. Ber.,* 1978, vol. 111, p. 939.
18. Ryzhenkov, V.E., Prokop'ev, A.A., Kameneva, I.Yu., Nersisyan, G.G., and Shavva, A.G., *Vopr. Med. Khim.*, 1987, no. 2, p. 65.
19. Ryzhenkov, V.E., Kameneva, I.Yu., Lozovskii, V.T., and Shavva, A.G., *Byull. Eksp. Biol. Med.,* 1992, p. 148.

20. Gemmill, F.O., Orzech, C.E., and Adelman, S., US Patent 5395831, 1995; *Chem. Abstr.,* 1995, vol. 122, 291309w.
21. Kuenzer, H., Knaute, R., Lessl, M., Fritzmeier, K.-H., Hegele-Hartung, C., Boemer, U., Mueller, G., and Kosemund, D., German Patent, 19.509.729, 1996. *Chem. Abstr.,* 1996, vol. 125, 276295g.
22. Bohlman, R. and Rubanyi, G.M., German Patent, 19.906.159, 2000; *Chem. Abstr.*, 2000, vol. 133, 150782k.
23. Shavva, A.G., Selivanov, S.I., Starova, G.L., Boronoeva, T.R., Ishchenko, I. V., Gluzdikov, I.A., Sharetskii, A.N., Isaeva, V.G., and Surinov, B.P., *Bioorg. Khim*., 2002, vol. 28, p. 242.
24. Tsuda, K., Nozoe, S., and Okata, Y., *Chem. Pharm. Bull.,* 1963, vol. 11, p. 1271.
25. Rufer, C., Schrtsder, E., and Gibian, H., *Lieb. Ann.,* 1967, vol. 705, p. 211.
26. Al'-Safar, N., Zakharychev, A.V., Ananchenko, S.N., and Torgov, I.V., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1968, p. 2326.
27. Asako, T., Hiraga, K., and Miki, K., *Chem. Pharm. Bull.*, 1973, vol. 21, p. 697.
28. Blazejewski, J.-C., Dorme, R., and Wakselman, C., *J. Chem. Soc., Perkin Trans. I,* 1986, p. 337.
29. Dann, O., Hagedorn, K.W., and Hofmann, H., *Chem. Ber*., 1971, vol. 104, p. 3313.
30. Smith, H. and Hughes, G., French Patent 1397507, 1965;. *Chem. Abstr.*, 1965, vol. 63, 13358g.
31. Smith, H., US Patent 3365473, 1968; *Chem. Abstr*., 1968, vol. 69, 27608r.
32. Smith, H., UK Patent 1116810, 1968; *Chem. Abstr*., 1968, vol. 69, 96974u.
33. Akhrem, A.A., and Titov, Yu.A., *Polnyi sintez steroidov* (Total Synthesys of Steroids), Moscow: Nauka, 1967, 200 p.
34. Selivanov, S.I. and Shavva, A.G., *Bioorg. Khim.*, 2002, vol. 28, p. 220.
35. Eliseev, I.I., Boronoeva, T.R., Tsyrlina, E.V., Martynov, V.F., and Shavva, A.G., *Zh. Obshch. Khim.*, 1986, vol. 56, p. 1651.
36. Zlobina, I.V., Nersisyan, G.G., Prokop'ev, A.A., Ryzhenkov, V.E., Martynov, V.F., and Shavva, A.G., *Vestn. LGU.*, 1986, Ser. 4, no. 3, p. 91.
37. Eliseev, I.I., Nikitina, G.V., Martynov, V.F., and Shavva, A.G., *Zh. Obshch. Khim*., 1987, vol. 57, p. 964.
38. Eliseev, I.I., Andreeva, E.N., Kameneva, I.Yu., and Shavva, A.G., *Vestn. Leningrad. Gos. Univ.,* 1991, ser. 4, no. 4, p. 74.
39. Eliseev, I.I., Zhukovskii, E.A., and Shavva, A.G., *Vestn. SPb. Gos. Univ.*, 1992, ser. 4, no. 2, p. 67.
40. Shavva, A.G., Ishchenko, I.V., Eliseev, I.I., Abusalimov, Sh.N., and Gasparyan, E.G., RF Patent, 2057140, 1996; *Byull. Izobr*., 1996, no. 9.
41. Egorov, M.S., Grinenko, E.V., Zorina, A.D., Balykina, L.V., Selivanov, S.I., and Shavva, A.G., *Zh. Org. Khim.*, 2001, vol. 37, p. 849.
42. Egorov, M.S., Selivanov, S.I., and Shavva, A.G., *Zh. Org. Khim*., 2002, vol. 38, p. 219.
43. Kogan, L.M., Gulaya, V.E., Lakum, B., and Torgov, I.V., *Izv. Akad. Nauk SSSR, Ser. Khim*., 1970, p. 1356.
44. Rzheznikov, V.M., Ananchenko, S.N., and Torgov, I.V., *Khim. Polim. Soedin*., 1965, p. 90.
45. Bogoslovskii, B.M. and Kazakova, Z.S., *Skeletnye katalizatory ikh svoistva i primenenie v organicheskoi khimii* (Skeletal catalysts and Their Properties and Application in Organic Chemistry), Moscow: Gos. Nauchno-Tekhnich. Izd., 1957,144 p.
46. Urusova, E.A., Gluzdikov, I.A., Selivanov, S.I., Starova, G.L., Nikolaev, S.V., Shavva, A.G., *Zh. Org. Khim*., 2004, vol. 40, p. 537.