1240, 1260, 1620, 1680, 1740, 1760, 1770. PMR spectrum (δ, ppm): 1.04 s (18-Me), 1.18 s (19-Me), 2.15 s (17-OAc), 2.16 s (21-OAc), 4.78 d.d (H^{21}, AB system J = 17 Hz), 5.71 s (H^4).

b. A solution of 0.015 g 21-acetoxy-17β-hydroxy-17α-pregn-4-ene-3,20-dione [2] in 0.5 ml of a mixture prepared from 0.56 ml 85% phosphoric acid, 3 ml acetic anhydride, 1.6 g anhydrous potassium acetate, and 1 ml acetic acid was heated for 31 h at 70°C, cooled, and diluted with water. The precipitate was filtered off and purified by thin-layer chromatography on silica gel to give 0.003 g of a product consisting of 61% (IX) and 39% starting pregnene as shown by PMR spectral analysis.

17α,21-Dihydroxypregn-4-ene-3,20-dione 17,21-Diacetate (X). A mixture of 0.02 g (VIII), 0.018 g Bu_4NOAc, and 0.2 ml N-methylpyrrolidone maintained for 24 h at 20-25°C, was treated according to the above procedure to give 0.003 g (X), mp 215-220°C, which was identical to an authentic sample.

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ISOMERIZATION OF 14-HYDROXY-17-KETOSTEROIDS: NEW EXAMPLES OF TWO-CENTERED INVERSION OF THE C/D RING FUSION AND X-RAY DIFFRACTION STRUCTURAL ANALYSIS OF d,ℓ-3-METHOXY-14β-HYDROXY-8β,9α-ESTRA-1,3,5(10)-TRIEN-17-ONE

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d,ℓ-3-Methoxy-14β-hydroxy-8α,9β-estra-1,3,5(10)-trien-17-one (I) undergoes two-centered isomerization in alkaline medium to d,ℓ-3-methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II) in 70% yield. Under analogous conditions, natural isomer (II) is converted into synthetic isomer (I) in 20% yield. The crystalline and molecular structure of isomer (II) was established.

d,ℓ-3-Methoxy-18-methyl-8α,9β-estra-1,3,5(10)-trien-14β-ol-17-one undergoes isomerization in alkaline medium to d,ℓ-3-methoxy-18-methyl-8β,9α-estra-1,3,5(10)-trien-14β-ol-17-one [1] (conversion of trans-anti-cis to trans-syn-cis configuration) through retroaldol cleavage of the C^{13}–C^{14} bond [2]. Conformational calculations by the molecular mechanics

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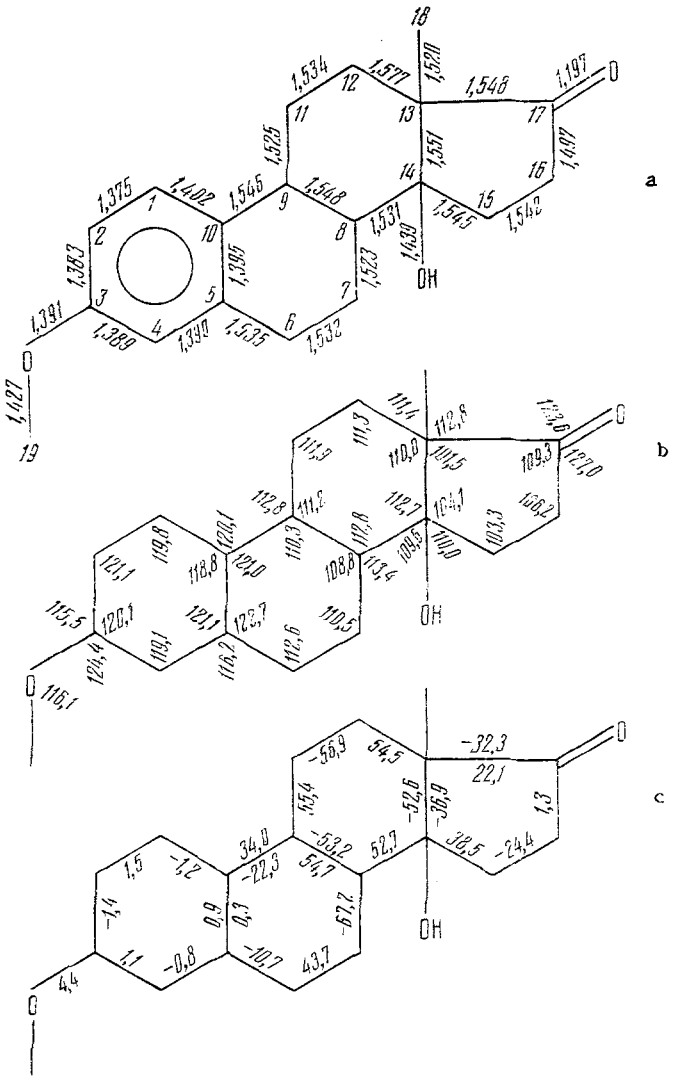


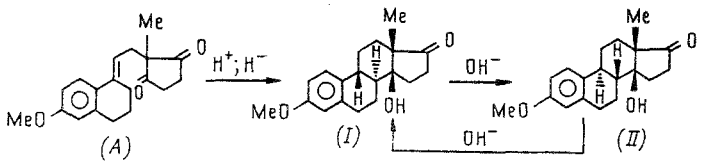
Fig. 1. Bond lengths in Å (a), bond angles (b), and torsion angles (c) in deg in d,ℓ-3-methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II). Mean standard deviations: a) 0.010 Å, b) 0.6, and c) 1.0°. Bond angles: C(12)–C(13)–C(17), 104.5; (C14)–C(13)–C(18), 115.8; C(8)–C(14)–C(15), 115.5; and C(13)–C(14)–O(14), 104.4°. Torsion angles: C(14)–C(8)–C(9)–C(10), -179.1; C(7)–C(8)–C(9)–C(11), -179.4; C(15)–C(14)–C(13)–C(12), 73.3; C(8)–C(14)–C(13)–C(17), -162.8; O(14)–C(14)–C(13)–C(18), -44.0; and C(7)–C(8)–C(14)–C(15), 57.3°.

method [2] showed that a decrease in the strain energy of the steroid molecule of about 1-2 kcal/mole is the driving force for this isomerization and this phenomenon is general for 14-hydroxy-17-ketoestratrienes [3].

In the present work, an additional example of two-centered inversion of the C/D ring fusion is described, namely, isomerization of d,ℓ-3-methoxy-14β-hydroxy-8α,9β-estra-1,3,5(10)-trien-17-one (I) to d,ℓ-3-methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II) and vice versa. The results of an x-ray diffraction structural analysis of (II) are also given.

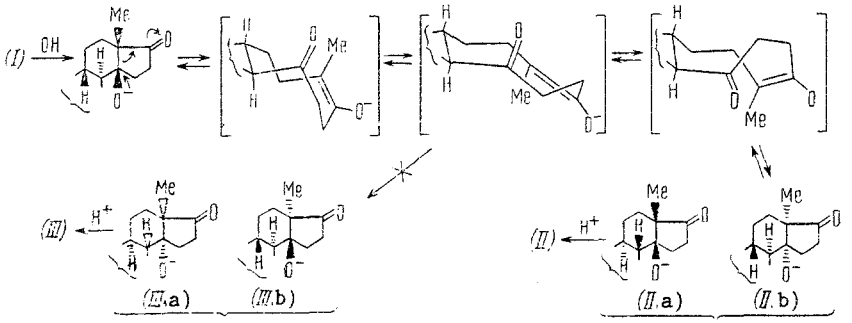
We have found that (I), which is the product of the reductive cyclization of 3-methoxy-8,14-seco-$\Delta^{1,3,5(10),9(11)}$-extratetraene-14,17-dione (A) [1], is isomerized under analogous conditions (including under Wittig reaction conditions) to (II) (Scheme 1).

Scheme 1



The yield of isomerization product (II) in alkaline media is 70%. Ketol (II) isomerizes under analogous conditions into ketol (I) in 20% yield. In our opinion, this isomerization proceeds through a retroaldol cleavage of the C^{13}–C^{14} bond and formation of an intermediate 13,14-secosteroid enol, whose conformational transformations and recyclization lead to two-centered inversion of the fusion of rings C and D to give natural isomer (II) (Scheme 2) [3].

Scheme 2



Since this study was carried out with racemic (I), anions (IIa) and (IIb) in Scheme 2 are the d and ℓ forms of the same compound, (II). Since all the steps in this reaction are reversible, a thermodynamic equilibrium is established between (I) and (II), which is shifted toward the energetically more favorable natural isomer (II).

We propose that the decrease in strain energy in going from synthetic isomer (I) to natural isomer (II) of about 1 kcal/mole is the driving force for the observed rearrangement. Evidence for this hypothesis is that the conversion of natural isomer (II) to synthetic (I) is only 20%.

We note that the isomerization according to the mechanism indicated in Scheme 2 also permits the formation of isomer (III). However, since the strain energy of this isomer is greater than for isomers (I) and (II) [2], its formation is unlikely [4]. This is also true for other possible isomers.

The two-centered isomerization under the Wittig reaction conditions may be attributed to the possibility of steric hindrance in the reaction of the ylid and 17-keto group in the case of isomer (I) due to the repulsion of the angular C^{13} methyl group and Wittig reagent methyl group such that the two-centered isomerization is favored in alkaline media.

The reversible isomerization of (I) to give (II) was indicated by an x-ray diffraction structural analysis of (II) in addition to spectral methods (see Experimental).

The atomic coordinates are given in Table 1. The bond lengths, bond angles, and selected torsion angles are given in Fig. 1. The molecular conformation is shown in Fig. 2. Ring A is planar, ring B is in a conformation intermediate between a 7α,8β-half-chair and 8β-sofa, $\Delta C_2^{7,8} = 11.3°$ and $\Delta C_s^{8} = 15.5°$, and the conformation of ring C is a slightly distorted chair: $\Delta C_2^{8,14} = 1.1°$ and $\Delta C_s^{8} = 2.2°$. The conformation of five-membered ring D is intermediate between a 14β,15α-half-chair ($\Delta = -72.0°$, $\Phi_m = 46.7°$ and 14β-envelope ($\Delta = -36.0°$, $\Phi_m = 46.7°$); $\Delta = -40.7°$ and $\Phi_m = 41.0°$, where ΔC_2 and ΔC_S are asymmetry parameters (see [5] in our previous work [4]), while Δ and Φ_m are pseudorotation parameters (see [6] in our previous work [4]).

Isomer (II) has a fragment with 8,9-trans-8,14-syn-13,14-cis configuration characteristic for natural cardioactive steroids.

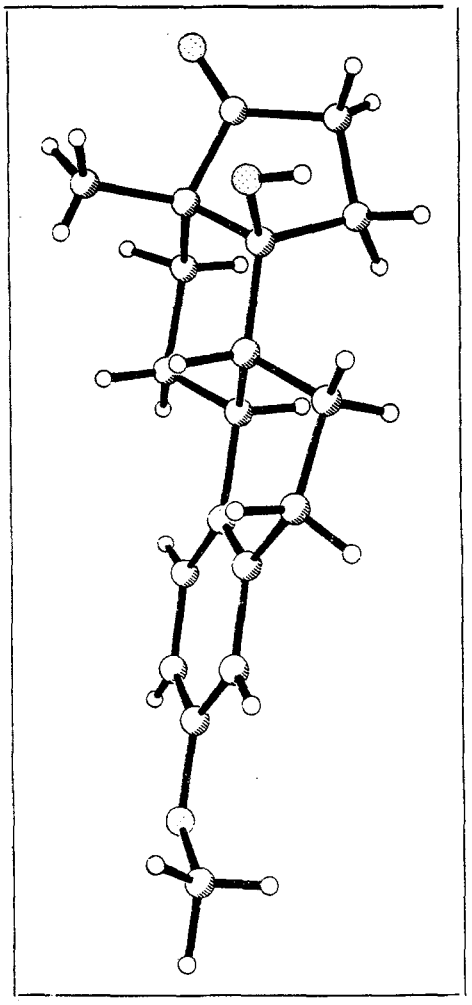


Fig. 2. Molecular conformation of isomer (II).

The packing of (II) in the crystal involves O(14)–H···O(17) intermolecular hydrogen bonds (x, y, z; -1 - x, -½ + y, -½ - z; H···O, 1.99(20) Å; O–H···O, 169.0(2.0°) giving rise to molecular chains along the b axis and van der Waals forces.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer. The PMR spectra were taken on a Varian SC-300 spectrometer for solutions in deuterochloroform with TMS as the internal standard. The mass spectra were obtained on an LKB mass spectrometer at 70 eV.

Isomerization of d,ℓ-3-Methoxy-14β-hydroxy-8α,9β-estra-1,3,5(10)-trien-17-one under Alkaline Conditions. A solution of 500 mg (1.6 mmoles) steroid (I) in 350 mg (3.2 mmoles) potassium tert-butylate in 50 ml abs. tetrahydrofuran with a catalytic amount of 18-crown-6 ether was left overnight and then heated at reflux for 1 h. The cooled solution was poured into water and extracted thrice with ether. The ethereal extracts were dried over sodium sulfate. The solvent was evaporated to give 500 mg oil, which was subjected to chromatography with gradient elution from hexane to 3:2 hexane–ether. Elution gave 100 mg (20%) (I) [5] and 350 mg (70%) (II), mp 175-176°C (ethanol). IR spectrum (ν, cm^{-1}): 3370 (OH), 1720 (C=O). Mass spectrum, m/z (I, %): 300 (M^+, 100%), 282 ($M^+ - H_2O$, 20%). PMR spectrum (δ, ppm): 1.29 t (3H, 13-CH_3), 3.78 s (3H, CH_3O), 6.73 d (1H, H^4); 7.19 d (1H, H^1).

Isomerization of d,ℓ-3-Methoxy-14β-hydroxy-8α,9β-estra-1,3,5(10)-trien-17-one (I) under Wittig Reaction Conditions. A sample of 240 mg (2.1 mmoles) potassium tert-butylate was dissolved in 17 ml dimethylsulfoxide and stirred for 1 h at 65°C in an argon atmosphere. Then, a sample of 1.63 g triphenylethylphosphonium iodide was added at ~20°C and stirred for 30 min. A sample of 360 mg (1.2 mmole) ketol (I) was added to the reaction mixture and stirred for 2 h at ~20°C. The solvent was evaporated and the oil obtained

TABLE 1. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors for the Carbon and Oxygen Atoms ($Å^2 \times 10^3$)

Atom	X	Y	Z	U_{eq}	Atom	X	Y	Z
C(1)	−8253(12)	−3813(7)	−242(2)	40(2)	H(4A)	−3304	−6439	−163
C(2)	−7847(14)	−4539(8)	152(2)	48(3)	H(6A)	−2040	−4938	−853
C(3)	−6072(13)	−5503(8)	192(2)	42(2)	H(6B)	−3204	−6502	−953
C(4)	−4692(12)	−5778(8)	−173(2)	42(2)	H(7A)	−3163	−4952	−1623
C(5)	−5101(11)	−5053(7)	−573(2)	36(2)	H(7B)	−5657	−5505	−1499
C(6)	−3534(13)	−5429(9)	−962(2)	50(3)	H(8A)	−4066	−2724	−1176
C(7)	−4399(14)	−4850(8)	−1411(2)	47(3)	H(9A)	−8520	−3940	−1232
C(8)	−5260(11)	−3292(8)	−1360(2)	33(2)	H(11A)	−9888	−1756	−792
C(9)	−7385(12)	−3311(8)	−1064(2)	36(2)	H(11B)	−7220	−1184	−830
C(10)	−6883(11)	−4074(8)	−614(2)	37(2)	H(12A)	−9938	−1593	−1604
C(11)	−8339(12)	−1777(8)	−1005(2)	40(2)	H(12B)	−9268	56	−1369
C(12)	−8818(12)	−1039(9)	−1455(2)	44(2)	H(14)	−3220	−3005	−2177
C(13)	−6645(11)	−973(8)	−1775(2)	40(2)	H(15A)	−6582	−4249	−2301
C(14)	−5638(11)	−2527(8)	−1809(2)	37(2)	H(15B)	−8553	−3821	−1988
C(15)	−7272(13)	−3505(8)	−2132(2)	41(2)	H(16A)	−6733	−2108	−2704
C(16)	−7895(14)	−2096(10)	−2469(3)	60(3)	H(16B)	−9328	−2177	−2622
C(17)	−7537(13)	−674(10)	−2232(3)	48(3)	H(18A)	−3721	336	−1766
C(18)	−5033(14)	200(9)	−1593(3)	54(3)	H(18B)	−4644	33	−1353
C(19)	−3979(15)	−7131(8)	657(3)	52(3)	H(18C)	−5929	1242	−1631
O(3)	−5855(10)	−6176(5)	606(2)	51(2)	H(19A)	−3899	−7647	984
O(14)	−3516(8)	−2289(5)	−2026(2)	46(2)	H(19B)	−2494	−6617	617
O(17)	−7838(11)	527(7)	−2379(2)	69(2)	H(19C)	−4148	−7981	485
H(1A)	−9513	−3074	−251					
H(2A)	−8883	−4395	380					

was subjected to chromatography on a silica gel column with hexane–ether as the eluent to give 290 mg (I), mp 138-140°C [5], and 20 mg (5%) (II), mp 174-176°C (ethanol).

Isomerization of d,ℓ-3-Methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II). A solution of 50 mg (0.17 mmole) ketol (II) and 35 mg (0.32 mmole) potassium tert-butylate in 50 ml absolute tetrahydrofuran and 5 mg 18-crown-6 ether was left overnight at −20°C. Ordinary work-up and chromatography gave 38 mg starting (II) and 9 mg (19%) (I), which was identical to an authentic sample [5], mp 138-140°C (ethanol).

X-Ray Diffraction Structural Analysis of d,ℓ-3-Methoxy-14β-hydroxy-8β,9α-estra-1,3,5(10)-trien-17-one (II). The unit cell parameters and reflection intensities from a monocrystal of (II) were measured on a Siemens P3/PC four-circle automatic diffractometer using MoK_α radiation ℓ(λ = 0.71069 Å) and graphite monochromator. Colorless needles of (II) grown from ethanol have the following unit cell parameters: $C_{19}H_{24}O_3$, molecular mass 300.4, space group $P2_12_12_1$, a = 5.961(1), b = 9.150(2), c = 29.938(6) Å, V = 1632.9(6) $Å^3$, Z 4, d_{calc} = 1.222 g/cm^3, $\mu(MoK_\alpha)$ 0.76 cm^{-1}, R 6.46%, and R_w 7.12%.

The reflection intensities were measured by $\theta/2\theta$ scanning at $2 < 2\theta < 56°$. A total of 1294 independent reflections with $F > 6\sigma(F)$ were considered observed and used in the subsequent calculations.

The structure was solved by the direct method and refined by the full-matrix method of least squares anisotropically for the nonhydrogen atoms. The positions of the hydrogen atoms with fixed U_{iso} = 0.08 $Å^2$ (U_{iso} = 0.05 $Å^2$ for the hydroxy group hydrogen atom) were given geometrically after each refinement cycle and included in the calculation for $|F_{calc}|$. The standard weighting scheme of the PC version of the Siemens SHELXTL PLUS program was used in the calculations. In the final Fourier difference maps, the height of the greatest positive electron density background peaks was less than 0.27 $eÅ^{-3}$.

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