SYNTHESIS OF METHYL ETHER OF (±)-14β-D-HOMOESTRONE

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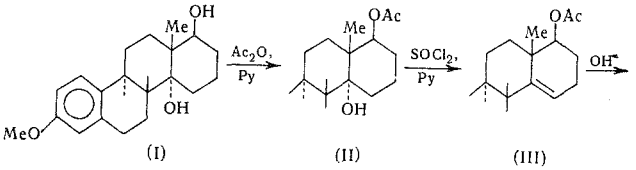
Steroids with a nonnatural configuration are attracting attention in recent years in connection with the problem of the relation between the structure and the biological activity. The synthesis of the methyl ether of 14-β-D-homoestrone is described in the present paper.

The acetylation of the 3-methyl ether of 14α-hydroxy-D-homoestra-17aβ-diol (I) [1] gave the 17a-monoacetate (II), as is evidenced by the absorption band at 1720 cm^{-1}, which corresponds to the acetoxy group, and the band at 3500 cm^{-1}, which indicates the presence of a hydroxyl. In the mass spectrum of acetate (II), besides the peak of the molecular ion with m/e 358, is present a dehydration peak and the peak of the fragment with m/e 298, which corresponds to the elimination of the elements of CH_3CO_2H from the molecular ion.

The dehydration of acetate (II) with $SOCl_2$ in pyridine leads in 72% yield to the 17a-acetate of the 3-methyl ether of 14(15)-dehydro-D-homoestradiol (III). In the NMR spectrum of (III) is present the triplet of an olefinic proton at 5.48 ppm, which proves the 14(15)-position of the double bond. The presence of the acetoxy group is in agreement with the absorption maximum at 1732 cm^{-1} in the IR spectrum, and the presence of a fragment with m/e 280 in the mass spectrum, which corresponds to the cleavage of the elements of CH_3COOH from the molecular ion. The saponification of acetate (III) with alcoholic alkali gave the 3-methyl ether of 14(15)-dehydro-D-homoestra-17aβ-diol (IV), the structure of which was proved by the IR, NMR, and mass spectra, and also by its oxidation to the known 3-methyl ether of 14(15)-dehydro-D-homoestrone (V) [1]. As was shown in [1], the 14(15)-double bond in ketone (V) undergoes catalytic hydrogenation with difficulty, in which connection the hydrogen adds from the sterically less hindered α-region and the methyl ether of D-homoestrone is formed. We found that the 14(15)-double bond in acetate (III) fails to undergo catalytic hydrogenation on 30% $Pd/SrCO_3$, whereas in carbinol (IV) the hydrogen adds from the sterically less hindered β-region, in which connection the 3-methyl ether of 14β-D-homoestra-17aβ-diol (VI) was obtained in 65% yield. The structure of the latter (besides the spectral data) was proved by chemical transformations. Oxidation with CrO_3 in pyridine gave the methyl ether of 14β-D-homoestrone (VII) in 74% yield, which in its constants is sharply different from the known 14α-epimer [2]. The condensation of ketone (VII) with benzaldehyde in alkaline medium gave the benzylidene derivative (VIII), the oxidation of which with alkaline hydrogen peroxide gave the known 3-methyl ether of 14β-homomarrianolic acid (IX) with mp 232-234° [3]. The 14α-epimer of the acid has mp 225-227.5° [3]. As a result, the nature of the substituent at C-17a exerts a controlling effect on the rate and stereospecificity of the catalytic hydrogenation of the 14(15)-double bond



(I) (II) (III)

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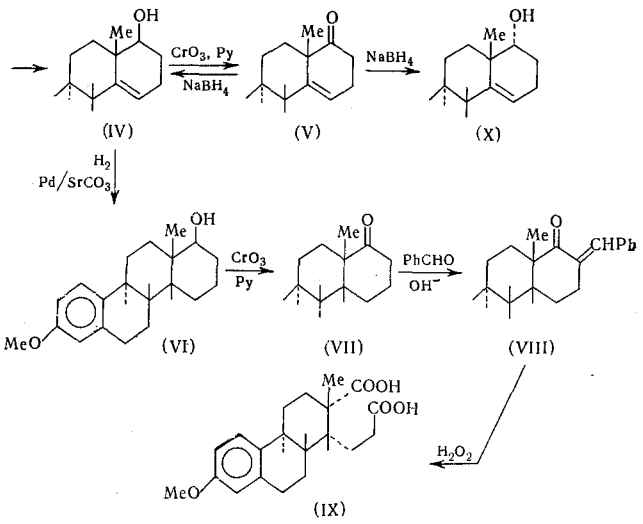

EXPERIMENTAL METHOD

The IR spectra were taken on a UR-10 instrument as Nujol mulls, unless it is indicated otherwise. The UV spectra (in alcohol) were taken on an SF-4 instrument, the NMR spectra were taken on a JNM-4H100 instrument in $CDCl_3$, while the mass spectra were taken on an MX-1303 instrument.

17aβ-Acetate of the 3-Methyl Ether of 14α-Hydroxy-D-homoestra-17aβ-diol (II). To a solution of 1 g of diol (I) in 20 ml of absolute pyridine was added 5 ml of Ac_2O and the mixture was kept at 20° for 24 h. The crystalline precipitate was filtered and washed with methanol. We obtained 900 mg of acetate (II) with mp 248-250°.(MeCOOEt : $CHCl_3$, 2 : 1). Infrared spectrum (ν, cm^{-1}): 3500 (OH), 1720 ($COCH_3$), 1610, 1510, 1470 ($>C=C<$, aromatic). Mass spectrum (m/e): 358 (M^+), 340 (M^+-H_2O), 298 ($M^+-CH_3CO_2H$). The mother liquor was decomposed with dilute HCl solution and extracted with $CHCl_3$. After washing with 2% HCl solution and aqueous $NaHCO_3$ solution the extract was dried and the solvent was evaporated to give an additional 230 mg of acetate (II) with mp 245-249°.

17a-Acetate of 3-Methyl Ether of 14(15)-Dehydro-D-homoestra-17aβ-diol (III). To a solution of 900 mg of acetate (II) in 12 ml of absolute pyridine at −18 and −20° was added 0.9 ml of $SOCl_2$ in 6 ml of absolute pyridine. The reaction mixture was stirred at −18 and −20° for 4 h, decomposed with water, and extracted with ether. The extract was washed in succession with 2% HCl solution, aqueous $NaHCO_3$ solution and water, dried, and the solvent was evaporated. Recrystallization of the residue from a 5 : 1 MeOH −AcOH mixture gave 615 mg (72%) of (III), mp 147-149°. Infrared spectrum (ν, cm^{-1}): 1732 ($COCH_3$), 1611, 1503, 1470 ($>C=C<$, aromatic). NMR spectrum (δ, ppm): (1.15 singlet, CH_3); 2.05 (singlet, $OCOCH_3$); 3.76 (singlet, OCH_3); 4.92 (triplet, $\Delta W_{1/2} \sim 12$ Hz, 17aα-H); 5.48 (triplet, $>C=C(-H)-$ ~). Mass spectrum (m/e): 340 (M^+), 280 ($M^+-CH_3CO_2H$).

3-Methyl Ether of 14(15)-Dehydro-D-homoestra-17aβ-diol (IV). A solution of 350 mg of acetate (III) in 10 ml of 5% alcoholic KOH solution was stirred at 20° for 2 h, and at 50° for 2.5 h. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried, and the solvent was evaporated. Recrystallization of the residue in sequence from MeOH and n-hexane gave 275 mg (90%) of (IV), mp 109-111°. Infrared spectrum (CCl_4, ν, cm^{-1}): 3635 (OH), 1612, 1507, 1470 ($>C=C<$ aromatic). NMR spectrum (δ, ppm): 1.17 (singlet, CH_3); 3.66 (triplet, $\Delta W_{1/2} \sim 12$ Hz, 17aα-H); 3.82 (singlet, OCH_3); 5.42 (triplet, $>C=C(-H)-$). Mass spectrum (m/e): 298 (M^+), 280 (M^+-18).

Oxidation of 3-Methyl Ether of 14(15)-Dehydro-D-homoestra-17aβ-diol (IV). A solution of 150 mg of carbinol (IV) in 3 ml of absolute pyridine was added to the Sarett reagent that was obtained from 200 mg of CrO_3 in 3 ml of absolute pyridine, and the mixture was allowed to stand at 20° for 24 h. Then the reaction mixture was poured into 600 ml of ice water and extracted in sequence with benzene and ether. The combined extract was washed in succession with 2% HCl solution, $NaHCO_3$ solution and water, dried, and the solvent was evaporated. Recrystallization of the residue from MeOH gave 80 mg of (V), mp 104-106°. The mixed melting point with an authentic sample [1] was not depressed.

3-Methyl Ether of 14β-D-Homoestra-17aβ-diol (VI). A solution of 1.58 g of carbinol (IV) in 100 ml of ethyl acetate was hydrogenated over 1.5 g of 30% Pd/$SrCO_3$ until the hydrogen absorption was complete. After filtration, evaporation, and recrystallization of the residue from alcohol we obtained 520 mg of (VI), mp 147-148° (from alcohol). Infrared spectrum (CCl_4, ν, cm^{-1}): 3632 (OH), 1611, 1507, 1470 (>C=C<, aromatic). Mass spectrum (m/e): 300 (M^+), 282 (M^+-H_2O).

Methyl Ether of 14β-D-Homoestrone (VII). The oxidation of 900 mg of carbinol (VI) was run the same as described above (1.2 g of CrO_3, 18 ml of absolute pyridine, 20°, 24 h). After extraction of the reaction mixture with benzene and ether, evaporation of the extract, and recrystallization from MeOH we obtained 660 mg (74%) of (VII), mp 99-102°. Infrared spectrum (ν, cm^{-1}): 1705 (C=O), 1610, 1507, 1472 (>C=C< aromatic). The molecular weight of (VII) was 298 (by mass spectrometry).

Benzylidene Derivative of Methyl Ether of 14β-D-Homoestrone (VIII). To a solution of 300 mg of ketone (VII) in 33 ml of MeOH were added 106 mg of freshly-distilled benzaldehyde and 13 ml of methanolic NaOH solution in an argon stream, and the mixture was allowed to stand at 20° for 12 h. The obtained crystals were filtered and washed with aqueous MeOH. We obtained 270 mg of the benzylidene derivative (VIII) with mp 141-142°. λ_{max} 287, 242 nm, log ε 4.25, 3.94. Infrared spectrum (ν, cm^{-1}): 1669 (>C=C–C=O), 1612, 1570, 1500, 1460 (>C=C<, aromatic). Molecular weight 386 (by mass spectrometry).

3-Methyl Ether of 14β-Homomarrianolic Acid (IX). To a methanol solution of MeONa (from 4.8 g of Na and 68 ml of MeOH) were added a solution of 250 mg of the benzylidene derivative (VIII) in 43 ml of MeOH, and then 48 ml of 30% H_2O_2 solution. The mixture was stirred at 30-55° for 9 h, decomposed with water, acidified with 10% H_2SO_4 solution, and extracted with ether. The extract was washed with saturated NaCl solution until neutral, dried, and the solvent was evaporated. The residual oil partially crystallized in benzene. We obtained 24 mg of (IX), mp 232-234° (benzene) [3]. Infrared spectrum (ν, cm^{-1}): 2660 ($-CO_2H\ldots HCO_2^-$), 1711 (>C=O), 1609, 1507, 1475 (>C=C<, aromatic). Molecular weight 346 (by mass spectrometry).

CONCLUSIONS

1. By starting with the 3-methyl ether of 14α-hydroxy-D-homoestra-17aβ-diol we obtained the methyl ether of 14β-D-homoestrone in five steps.

2. When the 17aβ-OH group is present the catalytic hydrogenation of the 14(15)-double bond in D-homosteroids leads to the 14β-isomers, and to the 14α-isomers when the 17a-CO group is present.

LITERATURE CITED

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