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SHORT COMMUNICATIONS

Synthesis of 17α-Acetoxyestra-1,3,5(10)-triene-3,11α-diol

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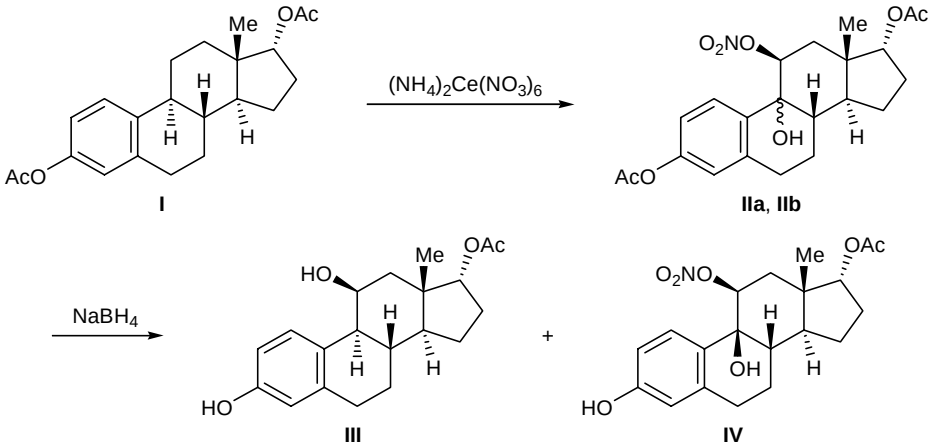
Introduction of a hydroxy group into position *11* of natural estrogens and its subsequent modification often enhance biological activity of the initial steroid and endows it with new properties [1–3]. 11α-Hydroxyestra-1,3,5(10)-trienes can also be used as synthons for the preparation of various 19-norsteroids [4]; for example, compounds exhibiting antitumor activity were obtained on the basis of such 17α-ethynylestradiol analogs [5].

The goal of the present work was to synthesize 17α-acetoxyestra-1,3,5(10)-triene-3,11α-diol. 17α-Estradiol is superior to natural estrogens in antioxidant activity [6]; therefore, synthesis of its derivatives analogous to those possessing antitumor activity, attracts undoubted interest.

We used the procedure for 11α-hydroxylation of estratrienes via oxidative nitration with cerium ammonium nitrate, which was proposed previously [7]. Stereochemical aspects of this reaction also attract some interest, for it is known to afford both 9α,11β-disubstituted steroids like **IIa** and the corresponding 9β-epimers. Taking into account published data on the effect of the substituent on C^{17} on the reaction stereochemistry [8], we also planned to determine the isomeric composition of products formed by oxidative nitration of 17α-estradiol diacetate **I**.

Treatment of compound **I** with 5.5 equiv of cerium ammonium nitrate gave a mixture of nitrates **II**, in which the fraction of 9β-epimer **IIa** was larger than the fractions of the corresponding isomers formed by analogous transformations of 17-oxo- and 17β-acyloxyestratrienes [9, 10]. According to the HPLC data, the ratio of the 9α- and 9β-epimers was 62:38 (against 20–25% of the 9β-epimer in [9, 10]). Thus 9β-hydroxylation is more favorable in the oxidative nitration of estrogen with unnatural configuration of the 17-hydroxy group.

In order to avoid losses during separation of epimers with similar chromatographic mobilities, the obtained mixture of nitrates **II** was subjected to reduction with $NaBH_4$. In the reduction process, only 9α-epimer **IIa** underwent strong structural variation: it



II, 9α (**a**), 9β (**b**).

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was converted into the target product **III**. The reaction of 9β-epimer **IIb** with $NaBH_4$ resulted only in hydrolysis of the 3-acetoxy group. Compounds **III** and **IV** thus obtained were readily separated by chromatography on silica gel, and both steroids were isolated as individual substances. The overall yield of 17α-acetoxyestra-1,3,5(10)-triene-3,11α-diol (**III**) was 45.4%.

17α-Acetoxyestra-1,3,5(10)-triene-3,11α-diol (III). To a solution of 0.63 g (1.77 mmol) of diacetate **I** in 37 ml of acetic acid we added a solution of 5.4 g (9.85 mmol) of cerium ammonium nitrate in 4.1 ml of water. The orange solution was stirred for 1.5 h at 20°C and was poured into 100 ml of a 1:1 chloroform–water mixture. The organic phase was separated, the aqueous phase was additionally extracted with chloroform, and the extracts were combined with the organic phase, washed with a 10% solution of $NaHCO_3$ and a saturated solution of NaCl, dried over $MgSO_4$, and evaporated. The residue was dissolved in benzene, the solution was filtered through a layer of silica gel, and the solvent was removed to leave 0.71 g of a mixture of nitrates **IIa** and **IIb** as a colorless foam-like material (**IIa**:**IIb** ratio 62:38, according to the HPLC data; retention times 5.8 and 4.6 min, respectively). By preparative thin-layer chromatography (system A) from 50 mg of the mixture we isolated 28 mg of compound **IIa** as an oily substance. ^{1}H NMR spectrum, δ, ppm: 0.89 s (3H, 18-Me), 2.05 s (3H, 17-OAc), 2.27 s (3H, 3-OAc), 4.78 d.d (1H, 17-H, J = 6.5, 0.8 Hz), 5.81 t (1H, 11-H, J = 2.8 Hz), 6.88 d (1H, 4-H, J = 2.4 Hz), 6.90 d.d (1H, 2-H, J = 8.5, 2.4 Hz), 7.27 d (1H, 1-H, J = 8.5 Hz).

Sodium tetrahydridoborate, 0.5 g (13.1 mmol), was added to a solution of 0.55 g (1.27 mmol) of nitrate mixture **IIa**/**IIb** in 15 ml of ethanol, and the mixture was stirred for 3 h at 20°C. The suspension was diluted with 50 ml of ethyl acetate, 10% hydrochloric acid was carefully added on cooling to pH 5–5.5, and 20 ml of water was added. After appropriate treatment, the extract was evaporated, and the residue was subjected to chromatography on 40 g of silica gel using ethyl acetate–hexane (3:7) as eluent to isolate (in the order of elution) 142 mg (28.6%) of nitrate **IV** and 202 mg (48.2%) of compound **III**.

17α-Acetoxy-11β-nitroxyestra-1,3,5(10)-triene-3,9β-diol (IV). mp 140–143°C, R_f 0.51 (B), $[\alpha]_D$ = +16.5° (c = 0.61). UV spectrum: λ_{max} 278 nm (log ε 3.65). IR spectrum, ν, cm^{-1}: 3430 (OH); 1750, 1290–1320 (OAc); 1650, 870 (ONO_2); 1630, 1525 (C=C_{arom}). ^{1}H NMR spectrum,* δ, ppm: 0.99 s, 1.8 s, 2.28 s, 4.68 d (17-H, J = 6.5 Hz), 6.13 t (11-H, J = 3.3 Hz), 6.93 m (2-H, 4-H), 7.56 d. Found, %: C 68.38; H 5.02; N 2.76. $C_{20}H_{25}NO_7$. Calculated, %: C 68.60; H 5.23; N 2.91.

Compound **III**. mp 143–145°C, R_f 0.31 (B), $[\alpha]_D$ = –65.5° (c = 0.97). UV spectrum: λ_{max} 279.5 nm (log ε 3.32). IR spectrum, ν, cm^{-1}: 3470, 3400, 1710, 1500, 1275. ^{1}H NMR spectrum,* δ, ppm: 0.75 s, 2.05 s, 4.22 t.d (11-H, J = 10, 5 Hz), 4.81 d, 4.86 s (OH), 6.58 d, 6.62 d.d, 7.77 d. Found, %: C 72.43; H 8.12. $C_{20}H_{26}O_4$. Calculated, %: C 72.70; H 7.93.

The melting points were determined on a Boetius melting point apparatus. The optical rotations were measured on a Polamat polarimeter from solutions in $CHCl_3$. The UV spectra were recorded in ethanol on a Specord UV-Vis instrument. The IR spectra were obtained in KBr on a Specord 75IR spectrometer. The ^{1}H NMR spectra were measured on a Bruker DPX-400 spectrometer from solutions in $CDCl_3$ using TMS as internal reference. HPLC was performed on a Millikhrom-1 chromatograph (λ 280 nm; 80×2-mm column packed with Silasorb C_{18}; eluent acetonitrile–water, 3:2). Silufol UV-254 plates were used for thin-layer chromatography with chloroform (A) and ethyl acetate–hexane (3:7) (B) as eluents. Preparative thin-layer chromatography was performed using 20×20-cm silica gel plates (Aldrich).

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