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SHORT COMMUNICATIONS

Selective Deacetylation of 11α-Hydroxyestrone 17-Oxime Triacetate in the Synthesis of 11α-Acetoxyestrone

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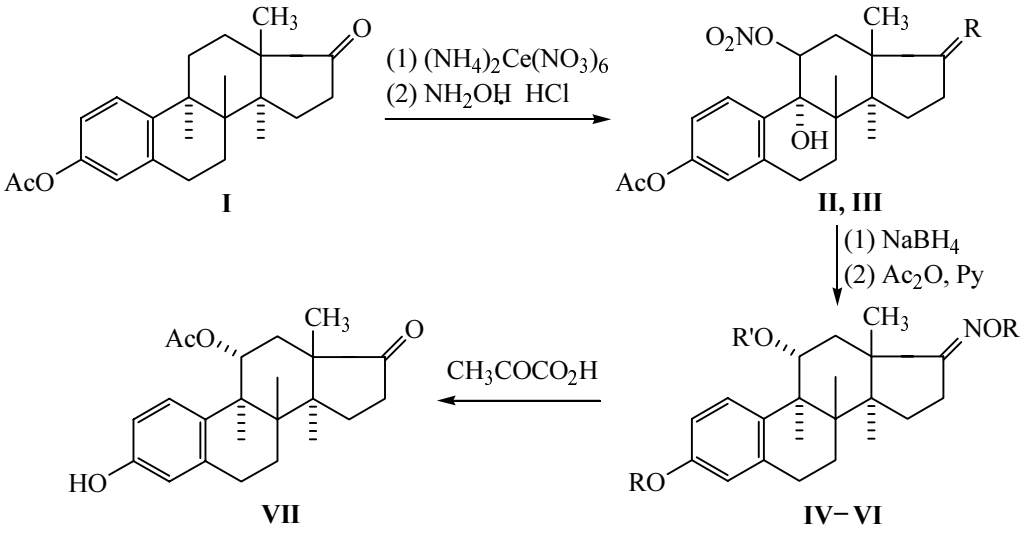
We formerly reported on the synthesis of antitumor steroids in the series of 17α-ethynylestradiol [1, 2]. The presence in their structure of a fragment containing a bis(β-chloroethyl)amino group in the position *3* and an *11*α-acyloxy-substituent provides a valuable combination of antiestrogen and cytotoxic properties in these compounds.

Aiming at the search of new analogs and planning to study the dependence of the activity on the structure of this type steroids we undertook the synthesis of similar compounds in the estrone series.

11α-Acetoxyestrone (**VII**) is an acceptable synthons for their preparation, and this study is dedicated to its synthesis. The main synthetic goal, the introduction of a hydroxy group into position *11*α of steroid with an aromatic A ring, might be solved by the previously used procedure [3, 4] involving two principal stages: oxidative nitration with the cerium ammonium nitrate, and reduction with $NaBH_4$. Before the reduction with the sodium borohydride it was necessary to protect the keto group of estrone (**I**) acetate. The best protection proved to be the oxymation [5]. The reduction of compound **III** occurred stereoselectively, and the yield of oxime **IV** was 79%. The ^1H NMR spectrum did not reveal the presence of its 9β-epimer, whereas at the similar reduction of 17-ethyleneketal formed up to 15% of 9β-steroid.

We failed to perform regioselective acetylation of oxime **IV** either with $Cu(OAc)_2$ [6] or by transesterific-



I **II, III** **VII** **IV–VI**

R = O (**II**), NOH (**III**); R = R' = H (**IV**), Ac (**V**); R = H, R' = Ac (**VI**).

ation with ethyl acetate in the presence of *p*-TsOH [7]. But its triacetate **V** turned out to be capable of regioselective transformations. At treatment with pyruvic acid occurred both the removal of protection and deacetylation in position C^3 resulting in 80% yield of the target 11α-acetoxyestrone (**VII**). The hydrolysis of triacetate **V** occurred also regioselectively with retention of only 11α-acetoxy group. The yield of monoacetate **VI** was 95%.

17-Hydroxyiminoestra-1,3,5(10)-triene-3,11α-diol triacetate (V). To a solution of 2.0 g (4.95 mmol) of oxime **III** [5] in 50 ml of ethanol was added by portions at stirring 0.9 g (23.7 mmol) of $NaBH_4$. The dispersion was stirred for 3.5 h at 20°C, diluted with water, acidified with 10% HCl till pH 3–4, filtered from the precipitate of salts, the filtrate was evaporated by 1/3. The separated precipitate of oxime **IV** was dissolved in ethyl acetate, dried with $MgSO_4$, and evaporated to obtain 1.18 g (90%) of crystalline 17-oximinoestra-1,3,5(10)-triene-3,11α-diol (**IV**), mp 217–220°C, $[\alpha]_D$ –(36 ± 4°). IR spectrum, ν, cm^{-1}: 3375–3400 (OH), 1707 (C=N), 1610, 1580, 1500 ($C=C_{arom}$), 920 (N–O). ^1H NMR spectrum (C_5D_5N), δ, ppm: 1.0 s (3H, 18-CH_3), 4.56 t.d (1H, $C^{11}H$, *J* 10 and 5 Hz), 7.06 m (2H, C^2H and C^4H), 8.66 d (1H, C^1H, *J* 8.5 Hz).

A solution of 0.88 g of oxime **IV** in 8 ml of a mixture acetic anhydride–pyridine, 1:1, was maintained for 16 h at 20°C, and then diluted with water. The precipitate of triacetate **V** was dissolved in chloroform, dried over $MgSO_4$, and the solvent was evaporated to furnish 1.2 g of compound **V**, mp 165–167°C (from a mixture of acetone with ether), $[\alpha]_D$ –(110 ± 10°). UV spectrum: λ_{max} 274 nm (log ε 2.93). IR spectrum, ν, cm^{-1}: 1765, 1730, 1225 (OAC), 1490 ($C=C_{arom}$), 925 (N–O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.05 s (3H, 18-CH_3), 2.06 s (3H, 11-OAC), 2.16 s (3H, N–OAc), 2.28 s (3H, 3-OAc), 5.49 t.d (1H, $C^{11}H$, *J* 9.8 and 5 Hz), 6.9 m (2H, C^2H and C^4H), 7.09 d (1H, C^1H, *J* 9 Hz). Found, %: C 67.11; H 6.63, N 3.50. $C_{24}H_{29}NO_6$. Calculated, %: C 67.43; H 6.84; N 3.28.

11α-Acetoxy 17-hydroxyiminoestra -1,3,5(10)-trien-3-ol (VI). A solution of 330 mg of triacetate **V** in 7 ml of methanol was stirred with 1 ml of triethylamine for 5 h at 20°C, then the mixture was evaporated, and the dark-yellow oily residue was dissolved in a mixture benzene–chloroform, 2:1. The solution was passed through 10 g of silica gel, and on evaporating the filtrate the residue was ground with ether to obtain 252 mg (95%) of compound **VI**, mp 210–213°C (from a mixture ethyl acetate–hexane), $[\alpha]_D$ –(139 ± 10°). UV spectrum: λ_{max} 280 nm (log ε 3.39). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 s, 2.06 s, 5.44 t.d, 6.58 m, 6.88 d. Found, %: C 69.67; H 7.08; N 4.26. $C_{20}H_{25}NO_4$. Calculated, %: C 69.95; H 7.34; N 4.08.

11α-Acetoxy-3-hydroxyestra-1,3,5(10)-trien-17-one (VII). A solution of 260 mg (0.61 mmol) of triacetate **V** and 180 mg (2.04 mmol) of pyruvic acid in 3.8 ml of 70% acetic acid was heated under argon at 70°C for 20 h. The solution turned yellow; it was diluted with 25 ml of water, the separated precipitate was dissolved in chloroform, and the solution was passed through 10 g of silica gel. The column was additionally washed with 20 ml of chloroform, and on evaporating the solvent we obtained 160 mg (80%) of compound **VII**, mp 261–263°C, $[\alpha]_D$ –(66 ± 4°), R_f 0.42. UV spectrum: λ_{max} 280 nm (log ε 3.32). IR spectrum, cm^{-1}: 3400, 1735, 1697 (CO), 1605, 1500, 1265. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.94 s, 2.07 s, 5.38 t.d, 6.59 m, 6.89 d. Found, %: C 69.92; H 7.12. $C_{20}H_{24}O_4$. Calculated, %: C 73.15; H 7.36.

Melting points were determined on the Boëtius heating block. The optical rotation was measured on a polarimeter Polamat from solutions in $CHCl_3$. UV spectra were recorded on a spectrophotometer Specord UV-Vis in ethanol solutions, IR spectra, on Specord 75 IR instrument from KBr pellets. ^1H NMR spectra were registered on a spectrometer Bruker DPX-400, internal reference TMS. TLC analysis was carried out on Silufol-254 plates in a system hexane–ethyl acetate, 3:2.

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