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SHORT COMMUNICATIONS

Oxidation of 3-Acetoxy-17β-nitroxyestra-1,3,5(10)-triene with Ceric Ammonium Nitrate in the Synthesis of Steroid Dinitrates*

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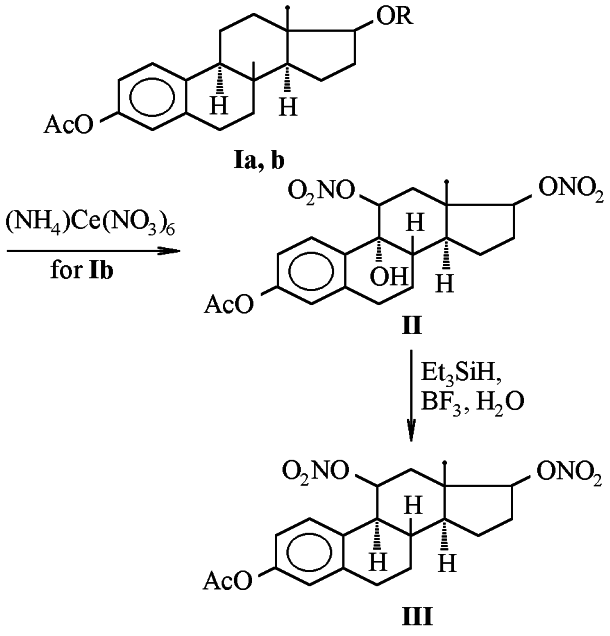
Among the few steroid nitrates attention of researchers is attracted by O-nitroestrogens, and first of all 11-β-nitroxyestra-1,3,5(10)-trienes that possess both the predictable estrogen activity [1] and unexpected cardioprotective qualities [2]. In the light of the latest data and by analogy with the known cardioactive organic dinitrates [3] it was presumable that O-dinitroestrogens **II, III** would show anti-ischemia activity, and therefore the present study was devoted to their preparation. In the synthesis of steroid nitrates the nitration is usually performed with acetyl nitrate [4], and only with estrogens is reported a direct introduction of ONO_2 group into a steroid with ceric ammonium nitrate [5].

We applied both the procedures in succession including previously not described oxidation of compound **Ib** with ceric ammonium nitrate. The special interest in this process regards the reaction stereochemistry where alongside the products with the natural 9α-configuration of the hydroxy group as in compound **II** may arise the 9β-epimers [5, 6]. The existing data on effect of the substituent in C^{17} position on the stereodirection of oxidation are ambiguous [5, 7]. Therefore apart the synthesis of steroid dinitrates among which only compound **III** was shortly described in a patent [8] the target of this work consisted in evaluation of isomer composition of the oxidation products arising from **Ib**. The latter compound was obtained from estradiol **Ia** acetate by the known procedure [9].

The treatment of mononitrate **Ib** with 5.5 equiv of ceric ammonium nitrate in acetic acid resulted mainly in dinitrate (**II**). Its 9β-epimer was revealed in the mixture with dinitrate **II** by means of ^1H NMR spectroscopy by appearance of additional signals of the angular CH_3 group and of the proton at C^{11} atom that were shifted downfield with respect to the principal signals of the mentioned protons in agreement with the published data [5, 10]. The 9α- to 9β-epimer ratio was 7 : 3 according to HPLC analysis, close to our data for the best known estrogens [7]. This fact apparently evidences that the direction of oxidation of steroids with aromatic A ring is independent of the substituent in C^{17} position.



R = H (**a**), NO_2 (**b**).

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To eliminate the 9α-hydroxy group in steroid **II** and to convert it into compound **III** we carried out ionic hydrogenation with triethylsilane in the presence of boron trifluoride etherate that resulted as already had been described [6] in hydrogenolysis of benzyl hydroxy group. We obtained dinitrate **III** in 41% yield.

3-Acetoxy-9α-hydroxy-11β,17β-dinitroxyestra-1,3,5(10)-triene (II). To a solution of 1 g (2.79 mmol) of nitrate **Ib**, mp 106–108°C (publ. 107–109°C [9]), in 50 ml of glacial acetic acid was added a solution of 8.4 g (15.35 mmol) of ceric ammonium nitrate in 6.5 ml of water. The orange solution was stirred for 2 h at 20°C, then diluted by equal amount of water, the reaction products were extracted into chloroform. The extract was washed with 10% solution of $NaHCO_3$ and dried on $MgSO_4$. The solvent was evaporated, the residue was dissolved in benzene, filtered rapidly through 10 g of neutral Al_2O_3 (**II** activity grade), and additionally eluted with 50 ml of benzene. We separated 1.03 g of oily substance containing mainly a mixture of dinitrate **II** with its 9β-epimer in 7:3 ratio (data of HPLC, retention times 8.4 and 7.6 min respectively).

^{1}H NMR spectrum (δ, ppm): 1.01 s and 1.10 s (CH_3), 2.29 s (OAc), 4.68 t and 4.97 t ($C^{17}H$), 5.77 br.s and 6.12 br.s ($C^{11}H$), 6.9–7.6 m (H arom). By grinding the mixture under ether we separated 317 mg of colorless crystals of dinitrate **II**, mp 181–183°C (from ethyl acetate–hexane mixture), $[\alpha]_D$ +43 ±2°. IR spectrum, cm^{-1}: 3450 (OH), 1740, 1280 (OAc), 1630 (ONO_2), 1490 (C=C arom). ^{1}H NMR spectrum (δ, ppm): 1.01 s (3H, CH_3), 2.29 s (3H, OAc), 4.97 t (1H, $C^{17}H$, *J* 7.7 Hz), 5.77 br.s (1H, $C^{11}H$), 6.92 m (2H, C^2H + C^4H), 7.28 d (1H, C^1H, *J* 8.5 Hz). Found, %: N 6.34. $C_{20}H_{24}N_2O_9$. Calculated, %: N 6.42.

3-Acetoxy-11β,17β-dinitroxyestra-1,3,5(10)-triene (III). To a solution of 100 mg (0.23 mmol) of dinitrate **II** in 2 ml of anhydrous CH_2Cl_2 under argon atmosphere at 20°C was added 0.2 ml (1.26 mmol) of Et_3SiH and at −10°C was added 0.3 ml (2.43 mmol) of freshly distilled boron trifluoride etherate. The yellow solution was stirred for 30 min, was added 10% $NaHCO_3$ till the solution became colorless, and the reaction mixture was diluted with chloroform–water mixture. The extract was dried on $MgSO_4$, the residue after evaporation of the solvent was crystallized by grinding under ether. We isolated 40 mg (41%) of dinitrate **III**, mp 157–159°C (from ethyl acetate–hexane mixture), $[\alpha]_D$ +40 ±4° (publ.: mp 160–161°C, $[\alpha]_D$ +35.6° [8]). IR spectrum, cm^{-1}: 1760, 1620, 1490. ^{1}H NMR spectrum (δ, ppm): 1.05 s and 2.30 s (each 3H), 4.74 t (1H, *J* 7.5 Hz), 5.94 m (1H), 6.91 m (2H), 7.41 d (1H, *J* 8.5 Hz).

Melting points were measured on the Boëtius heating block. The optical rotation was measured on Polamat A polarimeter from chloroform solutions (*c* 1.0–1.05). IR spectra were recorded of Specord 75 IR spectrophotometer from KBr pellets. ^{1}H NMR spectra were registered on spectrometer Tesla BS-587 A (80 MHz) in $CDCl_3$, internal reference TMS. The HPLC analysis was carried out on Millichrom11 instrument equipped with UV detector at wavelength 230 nm, column 80 × 2mm packed with Silasorb C_{18}, eluent acetonitrile–water, 3:2.

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