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SHORT COMMUNICATIONS

C,O-Nitration of 17β-Acetoxy-17α-ethynylestra-1,3,5(10)-triene-3,11α-diol

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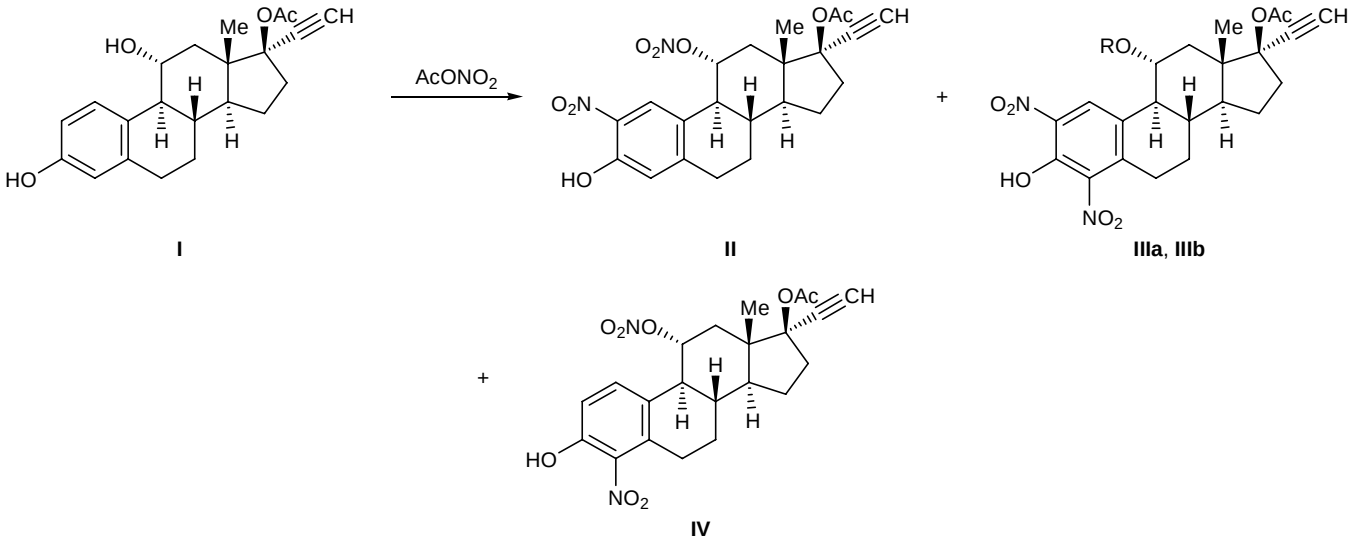
A combination of antiestrogenic and cytostatic properties in a single molecule could give rise to antitumor compounds which are especially effective in the treatment of breast cancer [1]. We previously described [2, 3] the synthesis of 11α-nitroxy-17α-ethynylestradiol 3,17-diacetate; the corresponding phenol exhibits antiestrogenic activity [4]. The present work was aimed at synthesizing 2- and 4-nitro derivatives of that phenol, i.e., compounds **II** and **IV**, respectively. It is known that introduction of a nitro group into aromatic ring makes estrogen cytotoxic [5]. Taking into account our previous results, we tried to obtain the target products in a single step, by nitration of 17β-acetoxy-17α-ethynylestra-1,3,5(10)-triene-3,11α-diol (**I**) with acetyl nitrate. The presence of a hydroxy group in the aromatic ring of compound **I** should favor electrophilic substitution. Among two *ortho*-carbon atoms with respect to the 3-hydroxy group, the C^4 atom is more sterically hindered than C^2, and we expected predominant formation of 2-nitro steroid **II**.

Acetyl nitrate was prepared from copper nitrate and acetic anhydride [3]. Analysis of the nitration products by HPLC revealed formation of two major and two minor products at a ratio of 46:20:2:1. 17β-Acetoxy-17α-ethynyl-2-nitro-11α-nitroxyestra-1,3,5(10)-trien-3-ol (**II**) was isolated with the maximal yield (45%); compound **II** displayed signals from two aromatic protons in the ^{1}H NMR spectrum. The IR spectrum of **II** contained a strong absorption band at 1630 cm^{-1} due to stretching vibrations of the nitroxy group. The other major product (yield 19%) was 2,4-dinitro steroid **IIIb**; its ^{1}H NMR spectrum contained a signal from one aromatic proton. 11-Hydroxy analog of **IIIb**, compound **IIIa** was isolated in less than 2% yield. The other minor product was 4-nitro derivative **IV**.



I **II** **IIIa**, **IIIb** **IV**

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

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The nitration of 3-*O*-acetyl derivative of **I** under analogous conditions occurs chemoselectively at the oxygen atom [2, 3]. Only under severe conditions (a large excess of acetyl nitrate in the presence of concentrated nitric acid), a mixture of 3-*O*-acetyl derivatives of compounds **II** and **IV** is obtained. These data indicate that replacement of the 3-acetoxy group by hydroxy strongly affects the reaction direction; the process follows exclusively the C,O-nitration pattern with formation of the exhaustive substitution product, 2,4-dinitro-11-nitroxy steroid **IIIb**.

17β-Acetoxy-17α-ethynyl-2-nitro-11α-nitroxyestra-1,3,5(10)-trien-3-ol (II). A 10% suspension of 3.4 g (14.1 mmol) of $Cu(NO_3)_2 \cdot 3H_2O$ in acetic anhydride was stirred for 1 h at room temperature under argon. It was then cooled to –10°C, and a solution of 1.0 g (2.8 mmol) of compound **I** in 10 ml of acetic anhydride was added. The mixture was stirred for 1 h at –10°C and diluted with water until complete precipitation of the products. The dark yellow precipitate was filtered off and dissolved in chloroform. The solution was dried over magnesium sulfate and evaporated, and the residue was subjected to chromatography on Al_2O_3 (activity grade II, neutral). Elution with diethyl ether afforded 0.77 g of a mixture of nitro steroids **II** and **IV** as a yellow oily substance which crystallized on grinding under a layer of diethyl ether containing a few drops of hexane. By recrystallization from ethyl acetate–hexane we isolated compound **II**. Yield 45%, R_f 0.53 (A), mp 178–180°C, $[\alpha]_D$ = –189±10°. UV spectrum, λ_{max}, nm (log ε): 288.5 (3.79), 346 (3.49). IR spectrum, ν, cm^{-1}: 3310 (OH); 1750 (CO); 1630, 840 (ONO_2); 1527 ($PhNO_2$). ^1H NMR spectrum, δ, ppm: 0.98 s (3H, CH_3), 2.07 s (3H, OAc), 2.68 s (1H, C≡CH), 5.62 t.d (1H, 11-H, *J* = 10.0, 5.0 Hz), 6.92 s (1H, 4-H), 7.96 s (1H, 1-H). From the mother liquor we isolated 34 mg (2.7%) of compound **IV** as a foam-like substance, R_f 0.38 (B), $[\alpha]_D$ = –106±10°. UV spectrum: λ_{max} 276 nm (log ε 3.36). IR spectrum, ν, cm^{-1}: 3350, 3250 (C≡CH), 1740, 1630, 1525, 840. ^1H NMR spectrum, δ, ppm: 0.99, 2.06, 2.67, 5.51, 7.1 d (1H, 2-H, *J* = 9.5 Hz), 7.35 d (1H, 1-H, *J* = 9.5 Hz). Elution with a 0.1% solution of acetic acid in chloroform gave (in succession) 260 mg (20.7%) of compound **IIIb** and 18 mg (1.4%) of its 11-hydroxy analog **IIIa**. Analytical samples of **IIIa** and **IIIb** were obtained by preparative thin-layer chromatography (Silufol plates, 20×20 cm; ethyl acetate–hexane, 3:7).

17β-Acetoxy-17α-ethynyl-2,4-dinitroestra-1,3,5(10)-triene-3,11α-diol (IIIa). R_f 0.4 (B), mp 132–134°C. UV spectrum, λ_{max}, nm (log ε): 277 (3.77), 347 (3.46). IR spectrum, ν, cm^{-1}: 3390, 3250, 1730, 1525, 845. ^1H NMR spectrum, δ, ppm: 0.98, 2.07, 2.64, 4.62 t.d (1H, 11-H, *J* = 9.7, 5.0 Hz), 8.16.

17β-Acetoxy-17α-ethynyl-2,4-dinitro-11α-nitroxyestra-1,3,5(10)-trien-3-ol (IIIb). R_f 0.54 (B), mp 125–126°C, $[\alpha]_D$ = –147±10°. UV spectrum, λ_{max}, nm (log ε): 274.5 (3.79), 346 (3.49). IR spectrum, ν, cm^{-1}: 3290, 3250, 1740, 1630, 1530, 840. ^1H NMR spectrum, δ, ppm: 0.97, 2.05, 2.67, 5.48, 8.18 s (1H, 1-H).

The melting points were determined on a Boetius melting point apparatus. The optical rotations were measured on a Polamat polarimeter in chloroform (*c* = 1.0–1.2 M). The UV spectra were recorded on a Specord UV-Vis spectrophotometer in ethanol. The IR spectra were obtained on a Specord 75IR instrument from samples prepared as KBr pellets. The ^1H NMR spectra were run on a Tesla BS-587A spectrometer (80 MHz) from solutions in chloroform-*d* using tetramethylsilane as internal reference. HPLC analysis was performed on a Millikhrom-1 instrument (λ 280 nm); 80 × 2-mm column packed with Silasorb C_{18}; eluent acetonitrile–water (3 : 2). Thin-layer chromatography was performed on Silufol-254 plates using chloroform (A) or ethyl acetate–hexane (3 : 7) (B) as eluent. Satisfactory elemental analyses were obtained for the newly synthesized compounds.

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