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Note

NOTE

A novel route to 3-hydroxy-16,17-seco-estrone derivatives

SUZANA S. JOVANOVIĆ-ŠANTA,[1] VJERA M. PEJANOVIĆ[2] and JULIJANA A. PETROVIĆ[1*]

[1]*Faculty of Science, University of Novi Sad, Trg Dositeja Obradovića 3, YU-21000 Novi Sad, and* [2]*ICN Yugoslavia, Institute, 29. Novembra 111, YU-11000 Belgrade, Yugoslavia*

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Starting from 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**), 17-tosylate **2b** and also 17-chloro-, 17-bromo- and 17-iodo-derivatives **4b, 5**b, and **6b,** were obtained. The fluoro-derivative **3b** was obtained from **2b** in the reaction with tetrabutyl ammonium fluoride. The deprotection of the 3-hydroxyl group was achieved by action of hydrogen in presence of Pd/C as a catalyst, yielding six new 3-hydroxy-16,17-seco-estrone derivatives.

Key words: 3-hydroxy-16,17-seco-estrone derivatives, halogeno steroids, hydrogenolysis.

We previously synthesized a series of 3-methoxy-16,17-seco-estrone derivatives, which in biological tests performed on experimental animals showed a complete loss of estrogenic activity, with most of them demonstrating a pronounced antiestrogenic action.[1,2] However, the presence of the 3-methoxy funciton prevented us from investigating the mechanism of their biological action. Namely, it is known that antiestrogens (steroidal or nonsteroidal) act at the level of estrogen or progesterone receptors, whereby the presence of a free hydroxyl group at the aromatic moiety in the tested molecule is necessary.[3]

All attempts to deprotect the phenolic function in the synthesized derivatives led to the formation of various by-products, resulting, therefore, in low yields of derivatives bearing a free hydroxyl function at C-3.[4]

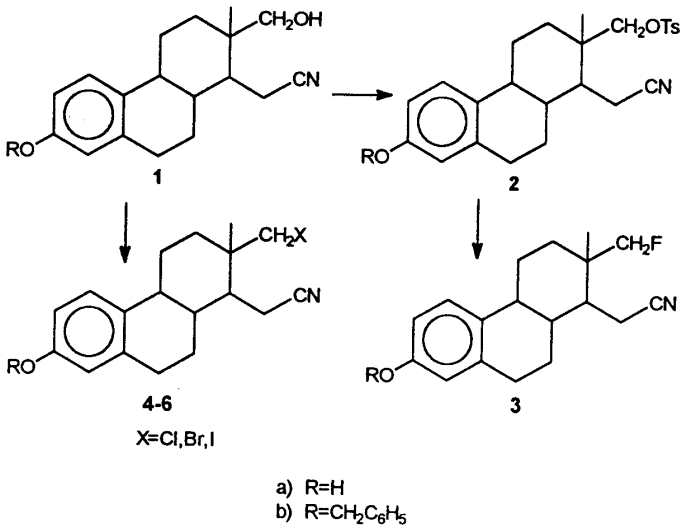
We presumed that this obstacle could be overcome by synthesizing 3-benzyloxy-16,17-seco-estrone derivatives, followed by hydrogenolysis of the benzyl ether function.

RESULTS AND DISCUSSION

As the starting compound we selected 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**, Scheme 1), which was obtained from estrone

* Author for correspondence

in four steps, applying a known synthetic route.[5] Treating the secocyanoalcohol **1b** with *p*-toluenesulfonyl chloride afforded tosylate **2b**, which upon action of tetrabutyl ammonium fluoride in refluxing methyl ethyl ketone gave the 17-fluoro derivative **3b** in 70.4% yield. The chloro **4b** and bromo **5b** derivatives were obtained from **1b**, under the action of thiphenylphosphine in the presence of carbon tetrachloride, *i.e.*, tetrabromide.[6] On the other hand, the iodo derivative **6b** was formed in the reaction of **1b** with iodine, triphenylphosphine and imidazole in toluene at reflux temperature.[7]



Scheme 1.

Deprotection of the 3-hydroxyl function was performed by hydrogenolysis at room temperature and low hydrogen pressure, using Pd/C as catalyst. High yields of 3-hydroxy-16,17-seco-estrone derivatives were obtained, except in the case of the iodo derivative **6b**. Therefore, 3-hydroxy-17-iodo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**6a**) was prepared from 3-hydroxy-17-*p*-toluenesulfonyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**2a**), by the action of tetrabutyl ammonium iodide.

EXPERIMENTAL

Compound **1a**. Yield 40.8%, m.p. 198–199 °C. IR-spectrum: 3600–3100, 2920, 2250, 1620, 1505, 1230, 1020. ^{1}H-NMR-spectrum (acetone-d_6): 0.92 (*s*,3H,CH_3); 3.28 (*dd*, 1H, H_a–C-17, J_{gem}=11.06Hz, $J_{Ha,OH}$ = 5.09Hz); 3.55 (*dd*, 1H, H_b–C-17, $J_{Hb,OH}$ = 5.12Hz); 6.62–7.12 (group of signals, 3H, arom.protons); 8.04 (*s*,1H, **H**O–C-3). ^{13}C-NMR-spectrum (acetone-d_6): 15.79 (C-15); 16.44 (C-18); 71.08 (C-17); 120.87 (C≡N); 156.06 (C-3). Mass spectrum: 343 (68; $(M+i\text{-Bu})^+$); 342 (100; $(M+i\text{-Bu}-1)^+$); 303 (17); 286 (87; $(M+1)^+$); 285 (38; M^+); 268 (17; $(M+1-H_2O)^+$).

Compound **2a**. Yield 93.94%, m.p.138–140 °C. IR-spectrum: 3500, 2920, 1600, 1500, 1450, 1375, 1310, 1180, 940, 670, 550. ^{1}H-NMR-spectrum (acetone-d_6): 0.95 (*s*, 3H, CH_3); 2.50 (*s*,3H,CH_3

from Ts); 2.65 (*dd*, 2H, C-15); 3.80 (*d*,1H, H_a–C-17); 4.07 (*d*,1H, H_b–C-17, J_{gem}=10.01Hz); 6.60–7.81(group of signals, 7H, arom. protons); 8.05 (*s*,1H, **H**O–C-3). ^{13}C-NMR-spectrum (acetone-d_6): 15.77 (C-15); 15.92 (C-18); 26.66 (CH_3 from Ts); 38.78 (C-17); 77.48 (**C**H_2–OTs); 120.13 (C≡N); 156.16(C-3). Mass spectrum: 497 (28; $(M+i\text{-Bu})^+$); 496 (88; $(M+i\text{-Bu}-1)^+$); 440 (7; $(M+1)^+$); 323 (100). Anal. Calcd. for $C_{25}H_{29}NO_4S$: C, 68.32; H, 6.65; N, 3.19, S, 7.28. Found: C, 67.87; H, 7.02; N, 3.10; S, 7.67.

Compound **3a**. Yield 47.22%, m.p. 182 ºC. IR-spectrum: 3600–3100, 2920–2880, 2250, 1620, 1505, 1450, 1215, 1000, 940, 620. ^{1}H-NMR-spectrum (acetone-d_6): 0.97 (*d*, 3H, CH_3, $J_{H,F}$=2.34Hz); 2.47(*dd*,1H, H_a–C-15); 2.68 (H_b–C-15); 4.19 (*dd*, 1H, H_a–C-17, J_{gem} = 9.53Hz, $J_{17a,F}$=47.37Hz); 4.41 (*dd*, 1H, H_b–C-17, $J_{17b,F}$=48.51Hz); 6.60–7.13 (group of signals, 3H, aromatic protons); 7.99 (*s*,1H, **H**O–C-3). ^{13}C-NMR-spectrum (acetone-d_6): 14.85 (*d*, C-18, $J_{C,F}$=6.29Hz); 17.76 (C-15); 91.18 (*d*,CH_2–F, $J_{C,F}$=173.60Hz); 120.41 (C≡N); 156.14 (C-3). Mass spectrum: 288 (100; $(M+1)^+$); 199 (72); 133 (52); 107 (48).

Compound **4a**. Yield 78.9%, m.p. 196–198 ºC. IR-spectrum: 3600–3100, 2930–2860, 2250, 1605, 1500, 1450, 1290, 1225, 740. ^{1}H-NMR-spectrum (acetone-d_6): 1.08 (*s*,3H, CH_3); 2.38 (*dd*,1H, H_a–C-15); 2.62 (*dd*, 1H, H_b–C-15); 3.42 (*d*,1H, H_a–C-17); 3.59 (*d*,1H, H_b–C-17, J_{gem}=10.95Hz); 6.60–7.18 (group of signals, 3H, arom. protons). ^{13}C-NMR-spectrum (acetone-d_6): 15.28 (C-15); 18.13 (C-18); 54.51 (**C**H_2–Cl); 118.97 (C≡N); 153.66 (C-3). Mass spectrum: 362 (64; $(M+i\text{-Bu})^+$); 361 (98; $(M+i\text{-Bu}-1)^+$); 360 (100; $(M+i\text{-Bu}-2)^+$); 346 (16); 304 (27; M^+). Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61. Found: C, 71.06; H, 7.20; N, 5.39.

Compound **5a**. Yield 88.3%, m.p. 212 ºC. IR-spectrum: 3400, 2920, 2250, 1605, 1500, 1240. ^{1}H-NMR-spectrum (acetone-d_6): 1.08 (*s*,3H, CH_3); 2.52 (*dd*, 1H H_a–C-15); 2.75 (*dd*, 1H, H_b–C-15, $J_{15a,15b}$=18Hz, $J_{15a,14}$=4.1Hz, $J_{15b,14}$=5.1Hz); 3.63 (*dd*, 2H, C**H**$_2$–Br, J_{gem}=10.7Hz); 6.55–7.13 (group of signals, 3H, arom. protons); 8.12 (*s*,1H,**H**O–C-3). ^{13}C-NMR-spectrum (acetone-d_6): 15.47 (C-15); 17.99 (C-18); 47.05 (**C**H_2–Br); 120.31 (C≡N); 156.07(C-3). Mass spectrum: 349 (97; $(M+1)^+$); 348 (27;M^+); 347 (100; $(M-1)^+$); 198 (70). Anal. Calcd. for $C_{18}H_{22}BrNO$: C, 62.08; H, 6.31; N, 4.02. Found: C, 61.97; H, 6.26; N, 3.93.

Compound **6a**. Yield 85.5%, m.p. 188 ºC. IR-spectrum: 3500, 2920, 1610, 1550, 1440, 1290, 930, 870, 610. ^{1}H-NMR-spectrum (acetone-d_6). 1.13 (*s*,3H, CH_3); 2.50 (*dd*, 2H, C-15); 3.50 (C**H**$_2$–I); 6.56–7.10 (group of signals, 3H, aromatic protons); 8.07 (*s*, 1H, **H**O–C-3). ^{13}C-NMR-spectrum (acetone-d_6): 15.51 (C-15); 17.99 (C-18); 25.48 (C-17); 120.21 (C≡N); 156.06 (C-3). Mass spectrum: 396 (62; M^++1); 395 (100; M^+); 268 (42; M^+–1I); 133 (49).

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ИЗВОД

НОВИ ПОСТУПАК ЗА ДОБИЈАЊЕ 3-ХИДРОКСИ-16,17-СЕКО-ЕСТРОНСКИХ ДЕРИВАТА

СУЗАНА С. ЈОВАНОВИЋ-ШАНТА,[1] ВЈЕРА М. ПЕЈАНОВИЋ[2] и ЈУЛИЈАНА А. ПЕТРОВИЋ[1]

[1]*Природно-математички факултет, Универзитет у Новом Саду, Трг Доситеја Обрадоавића 3, 21000 Нови Сад и* [2] *ICN Југославија, Институт, 29. Новембра 111, 11000 Београд*

Полазећи од 3-бензилокси-17-хидрокси-1,3,5(10)-триен-16-нитрила (**1b**), добијени су 17-тозилокси дериват **2b**, односно 17-хлоро, 17-бромо и 17-јодо деривати **4b, 5b** и **6b**, док је 17-флуоро дериват **3b** добијен у реакцији **2b** са тетрабутил амонијум флуоридом. Уклањање заштитне групе са C-3 изведено је дејством водоника у присуству Pd/C, при чему је добијено шест нових 3-хидрокси-16,17-секо-естронских деривата.

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8. IR spectra (wave nombers in cm^{-1}) were recorded using a Perkin-Elmer 457 spectrometer in KBr pellets. The ^{1}H and ^{13}C-NMR spectra were recorded with a Brucker AC 250E instrument with tetramethylsilane as internal standard. The chemical shifts are given in ppm (δ-scale). The mass spectra were measured using a Finnigan-MAT 8230 (the first number denotes the m/z value, and the ion abundances are given in parentheses). The melting points were determined with a Büchi SMP-20 apparatus and are uncorrected.

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