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

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Starting from 3-benzzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitriile (1b), 17-acetate 2b and also 17-chloro-, 17-bromo- and 17-iodo-derivatives 4b, 5b, and 6b, were obtained. The fluoro-derivative 3b was obtained from 2b in the reaction with tetraethyl ammonium fluoride. The deprotection of the 3-hydroxy 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 function 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.2

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-benzzyloxy-16,17-seco-estrone derivatives, followed by hydrogenolysis of the benzyl ether function.

RESULTS AND DISCUSSION

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

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in four steps, applying a known synthetic route.\textsuperscript{5} Treating the secocyanooalkalcohol 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 tetra-chloride, \textit{i.e.}, tetrabromide.\textsuperscript{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.\textsuperscript{7}

![Scheme 1](image)

The 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-secoestrone-1,3,5(10)-triene-16-nitrile (6a) was prepared from 3-hydroxy-17-\( p \)-toluenesulfonyl oxy-16,17-secoestrone-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\(_\alpha\)-C-17, \( J_{\text{gem}}=11.06\text{Hz}, J_{\text{H\(_\alpha\)-OH} \text{-H\(_\beta\)-OH}}= 5.09\text{Hz}\)); 3.55 (dd, 1H, H\(_\beta\)-C-17, \( J_{\text{H\(_\alpha\)-OH} \text{-H\(_\beta\)-OH}}= 5.12\text{Hz}\)); 6.62–7.12 (group of signals, 3H, arom.protons); 8.04 (s,1H, 1O-C-3). \(^{13}\)C-NMR-spectrum (acetone-d\(_6\)): 15.79 (C-15); 16.44 (C-18); 71.08 (C-17); 120.87 (C=\text{N}); 156.06 (C-3). Mass spectrum: 343 (68; (M+\( i \)-Bu\(^+\)); 342 (100; (M+\( i \)-Bu\(^-\)))\(^+\)); 303 (17); 286 (87; (M+1\(^+\))\(^+\)); 285 (58; M\(^+\))\(^+\)); 268 (17; (M+1--H\(_2\)O\(^-\))\(^+\)).

*Compound 2a.* Yield 93.9\%, 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, Hα-C-17); 4.07 (d, 1H, Hβ-C-17, $J_{gem}=10.01$ Hz); 6.60–7.81 (group of signals, 7H, arom. protons); 8.05 (s, 1H, HO-C-3). $^{13}$C-NMR-spectrum (acetone-d6): 15.77 (C-15); 15.92 (C-18); 26.66 (CH$_3$ from Ts); 38.78 (C-17); 77.48 (CH$_2$–O–Ts); 120.13 (C=N); 156.16(C-3). Mass spectrum: 497 (28; (M+–Bu)–); 496 (88; (M+–Bu–1)–); 440 (7; (M+1)–); 323 (100). Anal. Calcd. for C$_{25}$H$_{34}$NO$_5$: 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 °C. IR-spectrum: 3600–3100, 2920–2880, 2250, 1620, 1505, 1450, 1215, 1000, 940, 620. $^1$H-NMR-spectrum (acetone-d6): 0.97 (d, 3H, CH$_3$), $J_{HH}=2.34$ Hz; 2.47 (dd, 1H, Hα-C-15); 2.68 (Hβ-C-15); 4.19 (dd, 1H, Hα-C-17, $J_{gem}=9.53$ Hz, $J_{HH}=47.37$ Hz); 4.41 (dd, 1H, Hβ-C-17, $J_{HH}=48.51$ Hz); 6.60–7.13 (group of signals, 3H, aromatic protons); 7.99 (s, 1H, HO-C-3). $^{13}$C-NMR-spectrum (acetone-d6): 14.85 (d, C-18, $J_{HH}=6.29$ Hz); 17.76 (C-15); 91.18 (d,CH$_2$–F, $J_{HH}=173.60$ Hz); 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 °C. IR-spectrum: 3600–3100, 2930–2860, 2260, 1605, 1500, 1450, 1200, 1225, 740. $^1$H-NMR-spectrum (acetone-d6): 0.80 (s, 3H, CH$_3$); 2.38 (dd, 1H, Hα-C-15); 2.62 (dd, 1H, Hβ-C-15); 3.42 (d, 1H, Hα-C-17); 3.59 (d, 1H, Hβ-C-17, $J_{gem}=10.95$ Hz); 6.60–7.18 (group of signals, 3H, arom. protons). $^{13}$C-NMR-spectrum (acetone-d6): 15.28 (C-15); 18.13 (C-18); 54.51 (CH$_2$–Cl); 118.97 (C=N); 153.66 (C-3). Mass spectrum: 362 (64; (M+–Bu)–); 361 (98; (M+–Bu–1)–); 360 (100; (M+–Bu–2)–); 346 (16); 304 (27; M+). Anal. Calcd. for C$_{18}$H$_{22}$CINO: 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 °C. IR-spectrum: 3400, 2920, 2250, 1605, 1500, 1240. $^1$H-NMR-spectrum (acetone-d6): 1.08 (s, 3H, CH$_3$); 2.52 (dd, 1H, Hα-C-15); 2.75 (dd, 1H, Hβ-C-15, $J_{HH}=18$ Hz); 4.41 Hz, $J_{HH}=4.51$ Hz, 3.63 (dd, 2H, CH$_2$–Br, $J_{gem}=10.71$ Hz); 6.55–7.13 (group of signals, 3H, arom. protons); 8.12 (s, 1H, HO-C-3). $^{13}$C-NMR-spectrum (acetone-d6): 15.47 (C-15); 17.99 (C-18); 47.05 (CH$_2$–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 °C. IR-spectrum: 3500, 2920, 1610, 1550, 1440, 1290, 930, 870, 610. $^1$H-NMR-spectrum (acetone-d6): 1.13 (s, 3H, CH$_3$); 2.50 (dd, 2H, C-15); 3.50 (CH$_2$–Br); 6.56–7.10 (group of signals, 3H, aromatic protons); 8.07 (s, 1H, HO-C-3). $^{13}$C-NMR-spectrum (acetone-d6): 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+–1); 133 (49).

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ИЗВОД

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

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Полагају се 3-бензилокси-17-хидрокси-1,3,5(10)-триен-16-интрил (1b), добијени су 17-гидрокси дериават 2b, односно 17-хино, 17-брому и 17-јодо дериават 4b, 5b и 6b, док је 17-флуор дериават 3b добијен у реакцији 2b са тетрабутил аммонијумфталоидом. Укупане запитане групе са C-3 изведено је иглекристалних у присутству Pd/C, при чему је добијено пет нових 3-хидрокси-16,17-секо-естронских дериавата.

REFERENCES AND NOTES

8. IR spectra (wave numbers in cm⁻¹) were recorded using a Perkin-Elmer 457 spectrometer in KBr pellets. The ¹H and ¹³C-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.