SYNTHESIS OF 3-BENZYLOXY-17-MALEYLOXY-16,17-SECOESTRA-1,3,5(10)-TRIENE-16-NITRILE

ABSTRACT: Under the conditions of Beckmann fragmentation reaction, 3-benzylhydroxyestra-1,3,5(10)-triene-16-one oxime (2) gave the D-seco derivative 3. Sodium borohydride reduction of this compound afforded 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (4). The esterification of seco-cyanoalcohol 4 was achieved by action of maleic acid anhydride in dry pyridine, yielding 3-benzyloxy-17-maleyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5).

KEY WORDS: Steroids, 16,17-seco-estrone derivatives, synthesis, Beckmann fragmentation reaction, esterification, hemiesters

INTRODUCTION

In the frame of a broader project directed towards obtaining potential antiestrogens, a series of new 16,17-seco-estrone derivatives has been prepared [Petrović et al., 1990; Pejanović, 1991; Sakač, 1997; Petrović et al., 1998; Jovanović-Šanta, 2000; Jovanović-Šanta et al., 2000]. One of them, 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-trien-16-nitrile (4, Scheme 1), exhibited high antihormone action. We assumed that this activity could be increased by functionalizing this compound with a moiety possessing a free carboxyl group. Namely, it is known that steroid hormone derivatives having a side chain with a carboxyl function react with the ε-amino group of testosterone-binding globulin (TEBG), forming amide bonds [Erlanger et al., 1957]. Therefore, it can be expected that dicarboxylic acid monoesters of seco-cyanoalcohol 4 will behave in the same way with estrogen receptors, thus enhancing the desired antihormone activity.
EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi SMP apparatus and are uncorrected. NMR-spectra were taken on a Bruker AC 250E spectrometer and are reported in parts per million downfield from a tetramethylsilane internal standard; symbols s, bs, d, dd, q and m denote singlet, broad singlet, doublet, double doublet, quartet and multiplet, respectively.

3-Benzylxy-17 -hydroxyestra-1,3,5(10)-triene-16-one oxime (2)
Compound 1 (1 g, 2.57 mmol) was dissolved under heating in a mixture of methanol (20 cm³), methylene chloride (8 cm³) and 1% aqueous solution of KOH (30 cm³). To the cooled solution, NaBH₄ (0.95 g, 25.11 mmol) was added portionwise. The reaction mixture was stirred for 20 min at room temperature and then refluxed for 40 min. After cooling, acetic acid was added to pH 5 and the white precipitate collected and washed thoroughly with water (0.98 g, 98.00% yield, mp 193—195°C). Recrystallization from methanol afforded analytically pure 2: 0.83 g (83.00%), mp 195—196°C.

1H-NMR (CDCl₃): 0.80 (s, 3H, CH₃,C₁₈); 3.68 (bs, 1H, C₁₇); 4.20 (s, 1H, C₁₇-OH); 5.13 (s, 2H, O-C₆H₂-C₆H₅); 6.72—7.34 (group of signals, 8H, aromatic protons); 8.87 (bs, 1H, C=O).

13C-NMR (CDCl₃): 11.22 (CH₃,C₁₈); 69.93 (O-C₆H₂-C₆H₅); 156.81 (C₃); 165.59 (C=O).

3-Benzylxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (3)
-Hydroxy oxime 2 (1 g, 2.56 mmol, finely ground and dried for 3 hrs at 90°C) and p-toluenesulfonyl chloride (1.53 g, 8 mmol) were dissolved in absolute pyridine (15 cm³). The reaction mixture was kept at room temperature for 3 hrs and than poured into an excess of cold diluted HCl. The separated precipitate of the crude 3-benzylxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (3) was collected, washed with water and dried (0.954 g, 95.40%). Column chromatography on silica gel (70 g, toluene-ethyl acetate, /95:5/) afforded 0.72 g (71.66%) of pure compound 3, mp 137—138°C.

1H-NMR (CDCl₃): 1.18 (s, 3H, CH₃,C₁₈); 2.95 (d, 2H, C₁₅); 5.08 (s, 2H, O-C₆H₂-C₆H₅); 6.78—7.35 (group of signals, 8H, aromatic protons); 9.40 (s, 1H, CHO).

13C-NMR (CDCl₃): 13.11 (CH₃,C₁₈); 69.97 (O-C₆H₂-C₆H₅); 118.63 (C₃); 156.94 (C₃); 204.76 (C=O).

3-Benzylxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16- nitrile (4)
3-Benzylxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (3, 1g, 2.68 mmol) was dissolved under heating in methanol (35 cm³). To the cooled solution NaBH₄ (0.81 g, 22.2 mmol) was added portionwise. After stirring for 30 min at room temperature and refluxing for 20 min, the reaction mixture was diluted with water (100 cm³). The white precipitate was filtered off, washed with water and dried, yielding 0.98 g (98.00%) of crude secoxyanoalcohol 4. The product was purified on a silica gel column (100 g, toluene-ethyl acetate
3-Benzyl-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (4), mp 135—136°C, was obtained.

$^1$H-NMR(CDCl$_3$): 0.95 (s, 3H, CH$_3$C$_{18}$); 2.16 (d, 1H, OH); 2.54 (dd, 1H, H$_a$-C$_{15}$, J$_{gem}$ = 16.08 Hz, J$_{15a, 14}$ = 6.80 Hz); 2.68 (dd, 1H, H$_b$-C$_{15}$, J$_{15b, 14}$ = 7.15); 3.44 (q, 2H, C$_{17}$); 5.03 (s, 2H, O-CH$_2$-C$_6$H$_5$); 6.78—7.35 (group of signals, 8H, aromatic protons).

$^{13}$C-NMR (CDCl$_3$): 15.47 (CH$_3$, C$_{18}$); 69.87 (O-CH$_2$-C$_6$H$_5$); 72.32 (C$_{17}$); 119.15 (C N); 156.81 (C$_3$).

3-Benzyloxy-17-maleyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5)

Seco-cyanoalcohol 4 (1.16 g, 3.10 mmol) and maleic acid anhydride (0.91 g, 9.3 mmol) were dissolved in absolute pyridine (10 cm$^3$). The reaction mixture was intensively stirred at room temperature for 6 hrs, than poured into a mixture of ice and water and acidified with diluted HCl (1:1) to pH 5. From the formed suspension compound 5 was extracted with diethyl ether (3 x 30 cm$^3$), the extract was dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was purified by column chromatography on silica gel (70 g, methylene chloride-methanol /1:1/) giving 0.58 g (39.73%) of analytically pure 3-benzyloxy-17-maleyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5), in the form of a pale yellow oil.

$^1$H-NMR (CDCl$_3$): 1.05 (s, 3H, CH$_3$, C$_{18}$); 2.95 (d, 2H, C$_{15}$); 3.98 (d, 1H, H$_{17a}$); 4.24 (d, 1H, H$_{17b}$, J$_{gem}$=11.61 Hz); 5.07 (s, 2H, O-CH$_2$-C$_6$H$_5$); 6.40 (d, 2H, HC=CH); 6.79—7.50 (group of signals, 8H, aromatic protons); 9.38 (s, 1H, COOH).

$^{13}$C-NMR (CDCl$_3$): 15.29 (C$_{15}$); 15.73 (CH$_3$, C$_{18}$); 69.54 (O-CH$_2$-C$_6$H$_5$); 72.32 (C$_{17}$); 119.15 (C N); 156.56 (C$_3$); 165.83 (COOH); 166.96 (COOR).

RESULTS AND DISCUSSION

As already mentioned, the aim of this paper was the synthesis of a new D-seco-estrone derivative possessing a free carboxyl function in the side chain at C-17, namely 3-benzyloxy-17-maleyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5, Scheme 1).

Starting from oximinoketone 1, oximinoalcohol 2 was obtained in a high yield by reducing of 1 with sodium borohydride in a mixture of methylene chloride, methanol and water.

The Beckmann cleavage of oximinoalcohol 2 was carried out under the action of p-toluenesulfonyl chloride in dry pyridine, yielding seco-cyanoaldehyde 3 in 95.4% yield. Further, by sodium borohydride reduction this compound was converted, in a high yield, into the corresponding derivative 4. The esterification of seco-cyanoalcohol 4 was achieved by action of maleic acid anhydride in dry pyridine, yielding its maleic hemiester, 3-benzyloxy-17-maleyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5) in the form of a pale yellow oil.
According to the described procedure, syntheses of other hemiesters of compound 4 are in progress, in order to study the influence of the side chain length at C-17 on the biological activity.

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REFERENCES


СИНТЕЗА 3-БЕНЗИЛОКСИ-17-МАЛЕИЛОКСИ-16,17-СЕКОЭСТРА-1,3,5(10)-ТРИЕН-16-НИТРИЛА

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Резиме

У раду је описана вишефазна синтеза једног новог D-секо-естронског деривата са карбоксилном функцијом у бочном нizu, 3-бензилоксi-17-малеилоксi-16,17-секоестра-1,3,5(10)-триен-16-нитрила (5). Ово једињење је добијено естерификацијом секо-цијаноалкохола 4 са анхидридом малеинске киселине у апсолутном пиридину, док је једињење 4 добијено по познатом поступку из оксими-нокетона 1.