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SCIENTIFIC WORK

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SYNTHESIS OF SOME 16,17-SECO-ANDROST-5-ENE DERIVATIVES

*Starting from 3β-acetoxy-17-oxo-16,17-secoandrost-5-ene-16-nitrile (**1**), 3β-acetoxy-16,17-secoandrost-5-ene-16-nitrile (**4**) was synthesized by a three-stage procedure. First, the formyl group of compound **1** was reduced, to yield the alcohol **2**. Compound **2** was further transformed to the mesyloxy derivative **3**, whose reduction with $NaBH_3CN$ gave compound **4**. Apart from compound **4** as the main reaction product, two additional products were obtained, for which the GC/MS analysis suggested that they are $\Delta^{8(14)}$ and Δ^{14} derivatives of compound **4**. Compound **4** was transformed into 3β-hydroxy-16,17-secoandrost-5-ene-16-nitrile (7), the Oppenauer oxidation of which afforded 3-oxo-16,17-secoandrost-4-ene-16-nitrile (**8**).*

There are various ways of reducing the C=O group of aldehydes and ketones to a CH_2 [1]. The two oldest methods are the Wolff–Kishner reduction and the Clemensen reduction. In the Wolff–Kishner reduction, the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). There are also a number of modifications of the Wolff–Kishner reaction, one of them being the Huang–Minlon reaction [2]. Another modification of the Wolff–Kishner reduction treats a ketone with hydrazine in toluene with microwave irradiation [3]. Also, a microwave-assisted Huang-Minlon procedure has been reported [4]. An indirect method of accomplishing the reaction is to use tosylhydrazones with $NaBH_4$, $NaBH_3CN$ or BH_3 [5]. We have recently reported the reaction of reduction of tosylhydrazones, obtained from the corresponding steroidal 17-oxo-16,17--seco-16-nitriles with the aid of $NaBH_4$, which yielded the steroidal 16,17-triazoles [6]. Namely, the presence of the nitrile group close to the tosylhydrazone function facilitated the intramolecular 1,3-dipolar cycloaddition of the C≡N group onto the *in situ* generated diazo compound, which resulted in the formation of a triazole ring. Sulfonate esters, such as tosylates or mesylates, can also be reduced with $NaBH_4$ in polar aprotic solvents [7]. In this paper we used this indirect method for preparing a C-13 methyl derivative from the starting 3β-hydroxy--17-oxo-16,17-secoandrost-5-ene-16-nitrile by three synthetic steps.

EXPERIMENTAL

General procedure

Melting points were determined using a Büchi SMP 20 apparatus and are uncorrected. IR spectra (wave numbers in cm^{-1}) were recorded on a Nexus 670 FT-IR spectrometer. NMR spectra were taken on a Bruker AC 250E spectrometer operating at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) and are reported in ppm (δ-scale), using standard Bruker software; the tetramethylsilane peak (δ 0.00 ppm) was used as reference for ^{1}H-NMR, whereas the central carbon line of chloroform-d was set at 77.0 ppm for ^{13}C-NMR. GC/MS analyses were performed on an Agilent Technologies GC 6890N instrument with Mass Selective Detector 5973. High resolution mass spectra was recorded on a 6210 Time-of-Flight (TOF) LC/MS Agilent Technologies (ESI+) instrument. All solutions were dried over anhydrous Na_2SO_4.

3β-Acetoxy-17-metanesulfonyloxy-16,17-secoandrost-5-ene-16-nitrile (3)

Compound **2** (0.50 g, 1.45 mmol) in dry pyridine (16 ml) was stirred in an ice bath at 0 °C, while methanesulfonyl chloride (0.90 ml, 1.32 g, 11.5 mmol) was added. The reaction mixture was kept at 4 °C for 22 h and then poured into ice water (100 ml). After adding HCl (6 M) to pH 1.0, the precipitated crude product was purified by flash chromatography (toluene–ethyl acetate 3:1), affording a pure compound (0.53 g, 86%; m.p. 178–179 °C) after recrystallization from *n*-hexane–acetone in the form of white crystals.

IR (KBr): 3025, 2938, 2907, 2870, 2243, 1715, 1354, 1260, 1176, 965, 857. ^{1}H-NMR ($CDCl_3$): 1.05 (*s*, 6H, H-18 and H-19); 2.05 (*s*, 3H, CH_3 from Ac); 3.06 (*s*, 3H, CH_3 from Ms); 3.85 (*d*, 1H, J_{gem} = 10.7 Hz, H--17a); 4.14 (*d*, 1H, J_{gem} = 10.7 Hz, H-17b); 4.61 (*m*, 1H, H-3); 5.39 (*m*, 1H, H-6). ^{13}C-NMR ($CDCl_3$): 15.39 (C--15); 16.02 and 19.14 (C-18 and C-19); 19.77 (C-11); 21.38 (CH_3 from Ac); 27.54 (CH_2); 31.73 (CH_2); 31.77 (C-10); 35.40 (CH_2); 36.57 (CH_2); 36.85 (C-13); 37.38 (CH_3 from Ms); 37.67 (CH_2); 37.73 (Cq); 42.69 (CH); 48.78 (C-9); 73.52 (C-3); 75.75 (C-17); 118.81 (C≡N); 121.14 (C-6); 139.42 (C-5); 170.51 (C=O). M (*m*/*z*): 364 (M^+ + 1 – AcOH). Anal. calcd. for $C_{22}H_{33}NO_5S$ (423.57): C, 62.38; H, 7.85; N, 3.31; S, 7.57; found: C, 62.17; H, 7.98; N, 3.31; S, 7.34.

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3*β*-Acetoxy-16,17-secoandrost-5-ene-16-nitrile (4), 3*β*-acetoxy-16,17-secoandrosta-5,8(14)-diene-16-nitrile (5) and 3*β*-acetoxy-16,17-secoandrosta-5,14-diene-16-nitrile (6)

Sodium cyanoborohydride (0.13 g, 3.7 mmol) was added to the solution of compound **3** (0.17 g, 0.40 mmol) in DMSO (2 ml), and the reaction mixture was stirred at 160 °C for 15 h. After that, the reaction mixture was poured into water (40 ml) and acidified (6 M HCl) to pH 1.0. The solid product was purified by column chromatography (15 g, *n*-hexane–acetone 6:1), giving a mixture of compounds **4**–**6**. Pure compound **4** was obtained after the recrystallization from *n*-hexane–acetone (45 mg, 34%, m.p. 153 °C). The mixture of compounds **5** and **6** was straggled behind in the water liquor and could not be separated.

Compound **4**: IR (KBr): 2966, 2942, 2895, 2852, 2237, 1731, 1244, 1041, 1030. ^{1}H-NMR ($CDCl_3$): 0.95 (*s*, 3H); 0.97 (*s*, 3H); 1.04 (*s*, 3H); 2.05 (*s*, 3H, CH_3 from Ac); 4.61 (*m*, 1H, H-3); 5.38 (*m*, 1H, H-6). ^{13}C-NMR ($CDCl_3$): 15.80 (C-15); 19.18, 20.11 and 20.59 (CH_3); 21.38 (CH_3 from Ac); 27.63; 30.75; 32.00; 32.60 (C-10); 33.77; 36.66; 36.90; 37.76; 41.21; 49.47; 49.63; 73.68 (C-3); 119.70 (C≡N); 121.44 (C-6); 139.48 (C-5); 170.50 (C=O). HRMS (TOF) (*m*/*z*): $C_{21}H_{31}NNaO_2$ $[M+Na]^+$; 352.22470; found 352.22427. GC/MS: 56.43%, 269 $[M\text{-}AcOH]^+$, ret. time: 18.022 min.

Compound **5:** GC/MS: 27.63%, 267 $[M\text{-}AcOH]^+$, ret. time: 18.262 min.

Compound **6**: GC/MS: 15.94%, 267 $[M\text{-}AcOH]^+$, ret. time: 18.393 min.

3*β*-Hydroxy-16,17-secoandrost-5-ene-16-nitrile (7)

Compound **4** (57 mg, 0.17 mmol) was added to the solution of sodium ethoxide in ethanol (0.10 M, 1.7 ml), and the reaction mixture was heated to 55 °C with intensive stirring for 75 min. After that the mixture was poured into water (2 ml), acidified (6 M HCl) to pH 1.0, and extracted with dichlormethane (3×1 ml). The joined extracts were dried and the solvent removed. The crude product in the form of oil was chromatographed on silica gel (5 g, *n*-hexane–acetone 12:1), giving compound **7** in the form of a colorless oil. Yield: 71% (34.7 mg).

IR (film): 3404, 2964, 2931, 2901, 2862, 2240, 1424, 1368, 1075, 1053, 1030. ^{1}H-NMR ($CDCl_3$): 0.94 (*s*, 3H); 0.97 (*s*, 3H); 1.02 (*s*, 3H); 3.54 (*m*, 1H, H-3); 5.37 (*m*, 1H, H-6). ^{13}C-NMR ($CDCl_3$): 15.81 (C-15); 19.24 (C-18); 20.06 (C-17); 20.59 (C-11); 30.73; 31.39; 31.95; 32.61 (C-10); 33.72; 36.73; 36.82; 41.14; 41.83; 49.42; 49.63; 71.55 (C-3); 119.84 (C≡N); 120.54 (C-6); 140.41 (C-5). MCI (*m/z*): 287 (M^+).

3-Oxo-16,17-secoandrost-4-ene-16-nitrile (8)

Compound **7** (46.8 mg, 0.16 mmol) was dissolved in cyclohexanone (2.7 ml), and then aluminum isopropyloxide (104 mg, 0.50 mmol) was added. The reaction mixture was heated at the boiling temperature for 3 h. After that it was acidified (6 M HCl) to pH 3.0 and subjected to steam distillation. Upon the distillation and cooling the product was extracted with dichloromethane (3×10 ml). The joined extracts were dried and the solvent was removed. The crude product was purified by column chromatography on silica gel (3 g, *n*-hexane–acetone 8:1), giving compound **8** in the form of a colorless oil. Yield: 28% (7.1 mg).

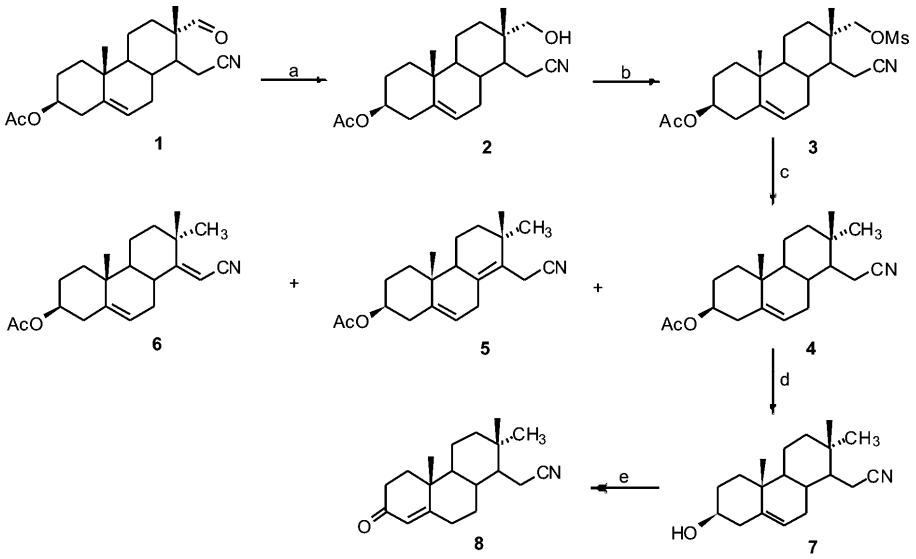
IR (film): 2940, 2242, 1673, 1618, 1433, 1392, 1270, 1232, 1186, 865. ^{1}H-NMR ($CDCl_3$): 0.98 (*s*, 6H); 1.21 (*s*, 3H); 5.76 (*s*, 1H, H-4). ^{13}C-NMR ($CDCl_3$): 15.96 (C-15); 17.56 (CH_3); 20.10 (CH_3); 20.67; 30.75; 31.56; 32.51; 33.81; 33.86; 35.47; 36.25; 38.66; 41.28; 48.55; 53.15; 119.54 (C≡N); 123.79 (C-4); 169.99 (C-5); 199.43 (C-3).

RESULTS AND DISCUSSION

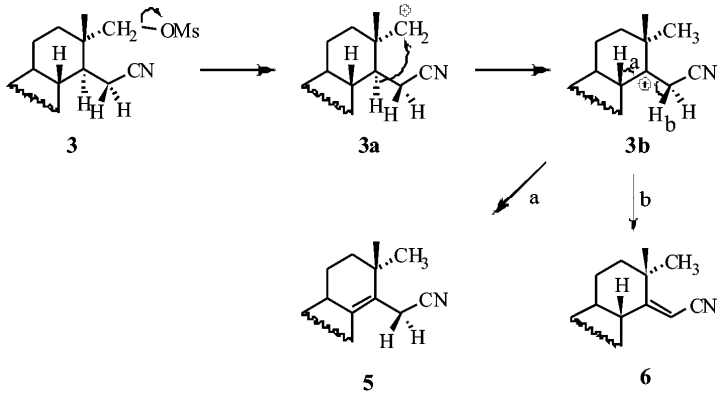
The starting compound in this synthesis was 3*β*-acetoxy-17-oxo-16,17-secoandrost-5-ene-16-nitrile (**1**), the synthesis of which has been described previously [8]. Compound **1** was reduced first with sodium borohydride ($NaBH_4$) and thus transformed to compound **2** [8].

The hydroxyl group in the molecule of compound **2** was further transformed to the mesyloxy function using methylsulfonyl chloride in absolute pyridine, which resulted in compound **3** (Scheme 1). With the aim of obtaining a methyl group at the C-13 position, compound **3** was subjected to reduction with sodium borohydride in dimethylsulfoxide. This reducing agent was chosen because of the presence of the cyano group in compound **3**, since it is known that in a polar aprotic solvent it reduces selectively sulfonate esters in the presence of a number of functional groups, such as the ester, carboxylic, amide, nitrile, nitro, olefine, aldehyde, keto, and epoxide [7]. The reaction was performed at 160 °C during 15 h, and it yielded 3*β*-acetoxy-16,17-secoandrost-5-ene-16-nitrile (**4**) in the mixture with another two compounds, **5** and **6**, which could not be separated by colum chromatography. Pure compound **4** was obtained after recrystallization, but the compounds **5** and **6** remained in the mother liquor, and could not be separated. The GC/MS analysis showed that these two compounds differ from compound **4** only by two mass units. We suppose that compounds **5** and **6** contain a double bond, that is that they are $\Delta^{8(14)}$ and Δ^{14} derivatives of compound **4**.

Scheme 2 shows the postulated mechanism of formation of compounds **5** and **6**. According to this mechanism, in the first phase the disruption of the C_{17}–O bond takes place, followed by the elimination of the mesyloxy group and formation of the primary carbocation **3a**. The rearrangement of the hydride anion from the C-14 atom yields the more stable, tertiary carbocation **3b**. The



*Scheme 1. Synthesis of compounds **3**–**8**. Reagents and reaction conditions: a) $NaBH_4$, EtOH, rt, 30 min; b) MsCl, Py, 4 °C, 22 h; c) $NaBH_3CN$, DMSO, 160 °C, 15 h; d) EtONa, EtOH, 55 °C, 75 min; e) cyclohexanone, $Al(iPro)_3$, reflux, 3 h.*



*Scheme 2. Proposed mechanism for the formation of compounds **5** and **6**.*

elimination of the proton from the C-8 atom (direction a) yields the formation of the $\Delta^{8(14)}$ double bond, whereas the elimination of the proton from the C-15 atom yields the Δ^{14} double bond (direction b).

The deprotonation of compound **4** was carried out under basic reaction conditions with sodium ethoxide in ethanol, and the resulting 3β-hydroxy derivative **7** was subjected to the Oppenauer oxidation with cyclohexanone and aluminum isopropoxide, rendering 3-oxo-16,17--secoandrost-4-ene-16-nitrile (**8**).

CONCLUSION

This paper describes a multistage synthesis of D--seco compounds **2**–**8**, starting from compound **1**. By reducing the OH group of compound **2** with sodium borohydride and of mesyloxy group in compound **3** with sodium cyanoborohydride in dimethylsulfoxide, a methyl group was introduced at the C-13 position (compound **4**). Apart from the expected 16,17-seco derivative **4**, two additional products were obtained, for which it was supposed that they contain $\Delta^{8(14)}$ (**5**) and Δ^{14} (**6**) double bonds. The proposed mecahnism of formation of compounds **5** and **6** is based on the assumption of the rearrangement of the hydride anion from the C-14 atom to the intermedate primary carbocation **3a**, with further elimination of the proton from the C-8, *i.e.* C-15, atom.

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IZVOD

SINTEZA DERIVATA 16,17-SEKOANDROST-5-ENA

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Polazeći od 3β-acetoksi-17-okso-16,17-sekoandrost-5-en-16-nitrila (**1**) sinetizovan je 3β-acetoksi-16,17-sekoandrost-5-en-16-nitril (**4**) iz tri sintetske faze. Najpre je kod jedinjenja **1** redukovana formil grupa, pri čemu je dobijen alkohol **2**. Jedinjenje **2** je dalje prevedeno u meziloksi derivat **3**, a ovaj je redukcijom sa $NaBH_3CN$ dao jedinjenje **4**. Pored jedinjenja **4** koje je dobijeno kao glavni proizvod reakcije, dobijena su i dva proizvoda za koja se na osnovu GC/MS analize pretpostavlja da su $\Delta^{8(14)}$ (jedinjenje **5**) i Δ^{14} (jedinjenje **6**) derivati jedinjenja **4**. Jedinjenje **4** je prevedeno u 3β--hidroksi-16,17-sekoandrost-5-en-16-nitril (**7**), koji je *Oppenauer*-ovom oksidacijom dao 3-okso-16,17-sekoandrost-4-en-16-nitril (**8**). U radu je dat i pretpostavljeni mehanizam građenja jedinjenja **5** i **6**.

Ključne reči: Derivati androst-5-ena • 16,17-Seko steroidi • Redukcija aldehida

Key words: Androst-5-ene derivatives • 16,17-Seco steroids • Reduction of aldehydes