ANDREA R. GAKOVIĆ
MAJA DJ. DJURENDIĆ BRENESEL
EVGENIJA A. DJURENDIĆ
KATARINA M. PENOV GAŠI
MARIJA N. SAKAČ

Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Serbia

SCIENTIFIC WORK

UDC 547.92.057:615.2

DOI: 10.2298/HEMIND100212009G

# 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 $\Delta^{14}$ 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 ($\delta$-scale), using standard Bruker software; the tetramethylsilane peak ($\delta$ 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.

Corresponding author: A.R. Gaković, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad.
E-mail: andrea.gakovic@dh.uns.ac.rs
Paper received: 12 February, 2010
Paper accepted: 11 March, 2010

**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).

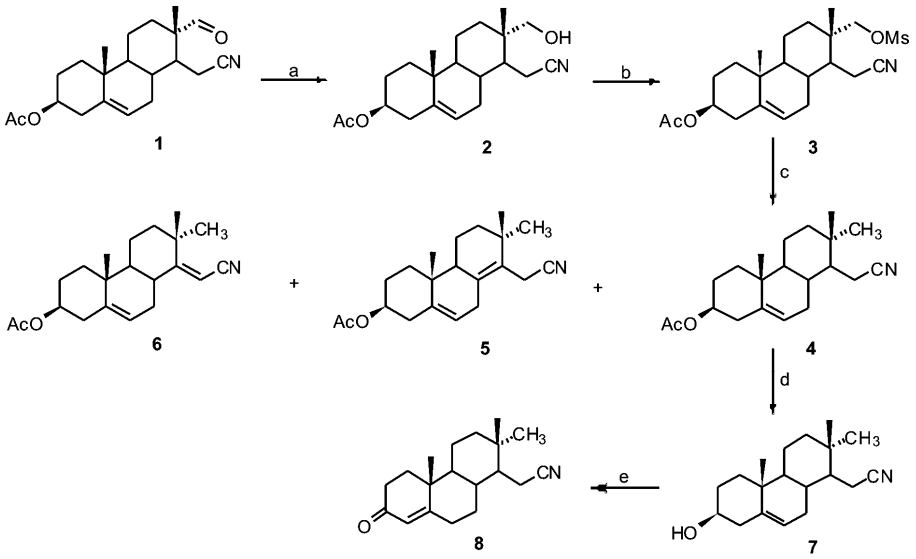
IR (film): 2940, 2242, 1673, 1618, 1433, 1392, 1270, 1232, 1186, 865. $^1$H-NMR ($CDCl_3$): 0.98 (*s*, 6H); 1.21 (*s*, 3H); 5.76 (*s*, 1H, H-4). $^{13}$C-NMR ($CDCl_3$): 15.96 (C-15); 17.56 ($CH_3$); 20.10 ($CH_3$); 20.67; 30.75; 31.56; 32.51; 33.81; 33.86; 35.47; 36.25; 38.66; 41.28; 48.55; 53.15; 119.54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

## RESULTS AND DISCUSSION

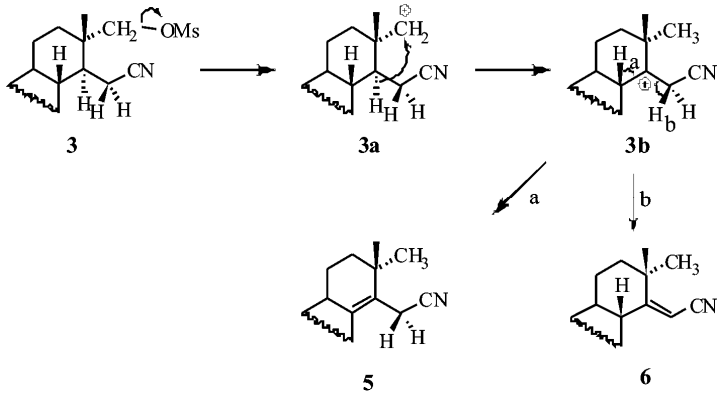
The starting compound in this synthesis was 3*β*-acetoxy-17-oxo-16,17-secoandrost-5-ene-16-nitrile (**1**), the synthesis of which has been described previously [8]. Compound **1** was reduced first with sodium borohydride ($NaBH_4$) and thus transformed to compound **2** [8].

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 $\Delta^{14}$ 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 $\Delta^{14}$ double bond (direction b).

The deprotonation of compound **4** was carried out under basic reaction conditions with sodium ethoxide in ethanol, and the resulting 3$\beta$-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 $\Delta^{14}$ (**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.

**Acknowledgement**

The authors thank the Ministry of Science and Technological Development of the Republic of Serbia for financial support (Grant No. 142052).

## REFERENCES

[1] M.B. Smith, J. March, March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 6th ed., John Wiley & Sons, Inc., Hoboken, NJ, 2007, 1835––1839.

[2] a) Huang-Minlon, A simple modification of the Wolff––Kishner reduction, J. Am. Chem. Soc. **68** (1946) 2487–2488; b) Huang-Minlon, Reduction of steroid ketones

and other carbonyl compounds by modified Wolff–Kishner method, J. Am. Chem. Soc. **71** (1949) 3301–3303.

[3] S. Gadhwal, M. Baruah, J.S. Sandhu, Microwave induced synthesis of hydrazones and Wolff–Kishner reduction of carbonyl compounds, Synlett **10** (1999) 1573––1574.

[4] P. Jaisankar, B. Pal, V.S. Giri, Microwave assisted McFadyen–Stevens and Huang-Minlon reactions, Synth. Commun. **32** (2002) 2569–2573.

[5] a) G.W. Kabalka, D.T.C. Yang, J.D. Baker Jr., Deoxygenation of $\alpha,\beta$-unsaturated aldehydes and ketones *via* the catecholborane reduction of the corresponding tosylhydrazones, J. Org. Chem. **41** (1976) 574–575; b) E.J. Taylor, C. Djerassi, Mechanism of the sodium cyanoborohydride reduction of $\alpha,\beta$-unsaturated tosylhydrazones, J. Am. Chem. Soc. **98** (1976) 2275–2281; c) R.O. Hutchins, N.R. Natale, Sodium borohydride in acetic acid. A convenient system for the reductive deoxygenation of carbonyl tosylhydrazones, J. Org. Chem. **43** (1978) 2299––2301; d) A.E. Greene, An unusual reduction of a cross conjugated dienone. Stereoselective synthesis of (–)-Dictyolene, Tetrahedron Lett. **20** (1979) 63–66.

[6] M.N. Sakač, A.R. Gaković, J.J. Csanádi, E.A. Djurendić, O. Klisurić, V. Kojić, G. Bogdanović, K.M. Penov Gaši, An intramolecular one-pot synthesis of steroidal triazoles via 1,3-dipolar cycloadditions of in situ generated diazo compounds, Tetrahedron Lett. **50** (2009) 4107–4109.

[7] R.O. Hutchins, D. Kandasamy, F. Dux III, C.A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, J. Puglis, Nucleophilic borohydride: selective reductive displacement of halides, sulfonate esters, tertiary amines, and *N*,*N*-disulfonimides with borohydride reagents in polar aprotic solvents, J. Org. Chem. **43** (1978) 2259–2267.

[8] K. Penov Gaši, S. Stojanović, M. Sakač, E. Djurendić, S. Jovanović-Šanta, S. Stanković, N. Andrić, M. Popsavin, Synthesis, crystal structure and antiaromatase activity of 17-halo-16,17-seco-5-androstene derivatives, J. Serb. Chem. Soc. **68** (2003) 707–714.

## IZVOD

SINTEZA DERIVATA 16,17-SEKOANDROST-5-ENA

Andrea R. Gaković, Maja Dj. Djurendić Brenesel, Evgenija A. Djurendić, Katarina M. Penov Gaši, Marija N. Sakač

Departman za hemiju, biohemiju i zaštitu životne sredine, Prirodno-matematički fakultet, Univerzitet u Novom Sadu

(Naučni rad)

Polazeći od 3$\beta$-acetoksi-17-okso-16,17-sekoandrost-5-en-16-nitrila (**1**) sinetizovan je 3$\beta$-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 $\Delta^{14}$ (jedinjenje **6**) derivati jedinjenja **4**. Jedinjenje **4** je prevedeno u 3$\beta$--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