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INVESTIGATION OF REACTION CONDITIONS ON SYNTHESIS OF STEROIDAL BROMOHYDRIN AND STRUCTURAL ANALYSIS OF NOVEL 6α-BROM-5β-HYDROXY DERIVATIVE†

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Abstract. *Reaction conditions variation and its influence on the reaction of 3β-acetoxy-17-oxa-17a-homoandrost-5-en-16-one with in situ generated hypobromous acid was investigated. Hypobromous acid was generated from N-bromoacetamide or N-bromosuccinimide and perchloric acid, and as solvent dioxane, dimethoxyethane or tetrahydrofuran were used. After a series of experiments, it was determined that the number of the reaction products depends on the reagent used, solvents, perchloric acid concentration and the presence/absence of daylight. It has also been found that the yields of certain compounds depend also on the reaction time and temperature. 6α-Bromo-5β-hydroxy derivate is obtained by usage of NBA and 0.28 M perchloric acid in dioxane on daylight. Its structure was confirmed by NMR and X-ray crystal structure analysis.*

Keywords: *NBA, NBS, epoxide, halogen derivatives, D-homoandrostane lactone*

1. INTRODUCTION

Chemically modified steroidal compounds have shown a broad range of biological activities. Due to those activities, they found a significant number of medical applications. Synthetic steroids do not have only antihormonal, anesthetic, anti-inflammatory, antiasthmatic, antibiotic, contraceptive activities, but they are also good cardiovascular agents and osteoporosis drugs. Moreover, these compounds have found significant

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application in the treatment of a number of different types of hormone-dependent cancers (Salvador et al., 2013). Among these cancers, the most widely spread is breast cancer that occurs primarily in women (Gupta et al., 2013). Breast cancer is one of the leading causes of death among women. Having that in mind, researchers have focused on modifications of steroid structure in order to provide more effective and selective antihormonal drug for this invasive disease. This is possible due to the fact that two-thirds of breast cancers are hormone-dependent (Jemal et al. 2011).

Chemically modified androgens and estrogens are usually used as hormonal therapeutics in the treatment of breast cancer. Modifications can be found in different parts of steroid structure; this gives a large number of possibilities for synthesis of new compounds (Yadav et al., 2015). By analyzing the structure-activity relationships of anticancer steroids, it can be observed due to which modification certain compound has its activity. Guided by this fact, in our previous work (Kuzminac et al., 2017), we have conducted the reaction of 3β-acetoxy-17-oxa-17a-homoandrost-5-en-16-one with *N*-bromoacetamide (NBA) in order to obtain steroidal 5α,6β-bromohydrin. In this reaction, besides the desired product, we have obtained two more compounds, 5β,6β-epoxide and 5α,6β-dibromide. We have tested all three synthesized compounds against a panel of human cancer cell lines. These new compounds have shown significant activity and selectivity towards breast and cervical carcinoma. Also, we have observed that by variation of reaction conditions we can obtain different products, as well as vary their yields. Having in mind this results and potential of synthesized steroids for further chemical transformations (Iglesias-Arteaga et al., 2005; Numazawa and Yamada, 1998; Numazawa and Yamada, 1999), we have conducted an investigation of the influence of different reaction conditions on the number of products and their yields.

2. EXPERIMENTAL

2.1. Syntheses

IR spectra were recorded on a PerkinElmer Spectrum Two FTIR spectrometer (wave numbers in cm^{-1}). NMR spectra were taken on a Bruker AVANCE III 400 spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C); residual solvent signals were used for the chemical shift (ppm; δ-scale) calibration. Melting points were determined using an electrothermal 9100 apparatus and are reported uncorrected. Chromatographic separations were performed on silica gel columns (Kieselgel 60, 0.04–0.063 mm, Merck). All the reagents used were of analytical grade.

General procedure for bromohydrin preparation: A mixture of compound **1** (500 mg, 1.44 mmol), *N*-bromoacetamide (NBA) (460 mg, 3.33 mmol) or N-bromosuccinimide (NBS) (593 mg, 3.33 mmol), $HClO_4$ (0.03-0.28 M, 0.36 mL) and dioxane, dimethoxyethane (DME) or tetrahydrofuran (THF) (10 mL) was stirred at room temperature for 30 to 40 min in the dark or at daylight. Subsequently, the reaction mixture was diluted with EtOAc (40 mL); sequentially washed with saturated $Na_2S_2O_3$, $NaHCO_3$, NaCl (40 mL) solutions and water; and dried (Na_2SO_4). The organic solvent was evaporated to give an oil. Flash chromatography (petrol ether/acetone = 4:1, v/v) of the residue afforded two to five products: 3β-acetoxy-5α-bromo-6β-hydroxy-17-oxa-17a-homoandrostan-16-one (**2**), 3β-acetoxy-5β,6β-epoxy-17-oxa-17a-homoandrostan-16-one (**3**), 3β-acetoxy-5α,6β-dibromo-17-oxa-17a-homoandrostan-16-one (**4**),

3β-acetoxy-6α-bromo-5β-hydroxy-17-oxa-17a-homoandrostan-16-one (**5**) and 3β,6β-diacetoxy- 5α-hydroxy-17-oxa-17a-homoandrostan-16-one (**6**).

Compound **5**: colorless crystals, m.p. 169 °C (from petrol ether/acetone). IR (CH_2Cl_2 film, ν_{max}, cm^{-1}): 3580, 2948, 1733, 1380, 1240, 1039, 1029, 735. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 0.87 (s, 3H, H-18), 0.89 (s, 3H, H-19), 1.10 (m, 1H, H-12a), 1.24 (overlapping signals, 2H, H-4a i H-11a), 1.41-1.65 (overlapping signals, 8H, H-2, H-7a, H-8, H-9, H-11b, H-12b, H-14), 1.84 (td, J_1 = 14.1, J_2 = 3.2 Hz, 1H, H-4b), 1.94-2.17 (overlapping signals, 7H, H-1, H-7b, H-15a, Ac), 2.56 (m, 1H, H-15b), 3.86 (d, 1H, J = 10.5 Hz, H-17aa), 3.89 (d, 1H, J = 10.5 Hz, H-17ab), 4.12 (s, 1H, OH), 4.51 (dd, J_1 = 12.1 Hz, J_2 = 4.9 Hz, 1H, H-6), 4.99 (s, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 14.86 (C-18), 16.78 (C-19), 19.71 (C-11), 22.01 (CH_3 from Ac), 24.38 (C-2), 26.54 (C-4), 31.48 (C-1), 31.79 (C-15), 32.30 (C-13), 33.71 (C-12), 36.87 (C-8), 38.75 (C-7), 40.79 (C-9), 43.08 (C-14), 43.18 (C-10), 66.17 (C-6), 69.31 (C-3), 73.78 (C-5), 80.36 (C-17a), 170.34 (C=O from Ac), 170.39 (C-16).

Compound **6**: white powder, m.p. 243-245 °C (from petrol ether/acetone). IR (CH_2Cl_2 film, ν_{max}, cm^{-1}): 3440, 2926, 1732, 1381, 1242, 1031, 735. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 0.91 (s, 3H, H-18), 1.15 (m, 1H, H-12a), 1.26 (s, 3H, H-19), 1.30 (m, 1H, H-4a), 1.45 (d, J = 12.6 Hz, 1H, H-12b), 1.53-1.72 (overlapping signals, 6H, H-1a, H-4b, H-8, H-9, H-11), 1.86 (d, J = 7.2 Hz, 1H, H-1b), 2.00-2.13 (overlapping signals, 8H, Ac on C-3 and C-6, H-2a, H-15a), 2.22 (dd, J_1 = 13,7 Hz, J_2 = 10,6 Hz, 1H, H-2b), 2.57 (m, 1H, H-15b), 3.88 (d, 1H, J = 10.5 Hz, H-17aa), 3.95 (d, 1H, J = 10.5 Hz, H-17ab), 5.19 (s, 1H, H-6), 5.28-5.31 (m, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 15.19 (C-18), 17.55 (C-19), 19.62 (C-4), 21.44 (CH_3, Ac on C-3), 21.47 (CH_3, Ac on C-6), 26.26 (C-1), 29.90 (C-9), 31.50 (C-15), 31.74 (C-8), 32.38 (C-14), 33.69 (C-12), 34.59 (C-11), 38.07 (C-2), 40.70 (C-7), 43.37 (C-13), 46.51 (C-10), 71.33 (C-3), 74.40(C-6), 80.28 (C-17a), 85.67 (C-5), 169.90 (C=O, from Ac on C-6), 170.30(C-16), 170.36 (C=O from Ac on C-3).

2.2. X-Ray crystallographic analysis of compound 5

The diffraction data for compound **5** were collected at room temperature on an Oxford Diffraction Gemini S diffractometer. Graphite-monochromated CuKα radiation (λ = 1.54184 Å) was used for diffraction on a suitable single crystal. CrysAlisPro and CrysAlis RED software packages (Oxford Diffraction, 2009) were used for data collection and data integration. The space group determinations were based on an analysis of the Laue class and the systematically absent reflections. Collected data were corrected for absorption effects by using analytical numeric absorption correction applying a multifaceted crystal model (Clark and Reid, 1995). Structure solution and refinement were carried out with the programs SHELXT and SHELXL-2014/6 respectively (Sheldrick, 2015). ORTEP-3 for Windows (Farrugia, 1997) and MERCURY (Bruno, 2002) was employed for molecular graphics and WinGx software (Farrugia, 1999) was used to prepare material for publication. For all three compounds non-hydrogen atoms were refined anisotropically, the C—H hydrogen atoms were included in calculated positions riding on their attached atoms with fixed distances C–H = 0.96–0.98 Å with U_{iso}(H) = 1.2U_{eq}(C) for methylene and methine groups, and U_{iso} (H) = 1.5 U_{eq}(C) for methyl groups. Hydrogen atom from hydroxyl (OH) group and methine (CH) hydrogen atom on C6 in compound **5** were identified on difference electron density maps and isotropically refined. The crystal data and refinement parameters are summarized in Table 1.

Table 1 Experimental details: crystalographic data and refinement parameters

Compound 5	
Chemical formula	$C_{21}H_{31}BrO_5$
M_r	443.37
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	300
a, b, c (Å)	8.5809 (2), 13.8675 (6), 17.2854 (3)
V (Å^3)	2056.89 (11)
Z	4
Radiation type	Cu $K\alpha$
No. of reflections for cell measurement	2358
θ range (°) for cell measurement	6.0–72.2
μ (mm^{-1})	2.96
Crystal shape	Prism
Crystal size (mm)	0.37 × 0.15 × 0.12
Data collection	
Diffractometer	Xcalibur, Sapphire3, Gemini
Detector resolution (pixels mm^{-1})	16.3280
Absorption correction	Analytical *CrysAlis PRO* 1.171.38.41 (Rigaku Oxford Diffraction, 2015) Analytical numeric absorption correction using a multifaceted crystal model (Clark and Reid, 1995)
T_{min}, T_{max}	0.534, 0.762
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7301, 3973, 3390
R_{int}	0.025
θ values (°)	θ_{max} = 72.5, θ_{min} = 4.1
Range of h, k, l	h = -10→7, k = -14→17, l = -21→18
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.111, 1.05
No. of reflections	3973
No. of parameters	255
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.46, -0.89
Absolute structure	Flack x determined using 1283 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, 2013)
Absolute structure parameter	-0.035 (12)

3. RESULTS AND DISCUSSION

3.1. Synthesis

Steroidal bromohydrins are usually synthesized from olefins by addition of hypobromous acid generated *in situ*. For this purpose most often are used NBA, sometimes NBS, and perchloric acid in various solvents (Numazawa and Yamada, 1998; Numazawa and Yamada, 1999; Grenville et al., 1957; Bowers et al., 1962; Šoškić et al., 1993; Zhang et al., 2010). In our previous work (Kuzminac et al., 2017), we have reported the synthesis of 5α-bromo-6β-hydroxy **2**, 5β,6β-epoxy **3** and 5α,6β-dibromo **4** compounds starting from 3β-acetoxy-17-oxa-17a-homoandrost-5-en-16-one (**1**, Fig. 1). By applying the most common procedure for this synthesis, the starting compound was treated with NBA and perchloric acid in dioxane, it was observed that the number of reaction products depends on the acid concentration and reaction time. Having in mind this fact, in this paper were varied not just these two parameters but also temperature, the presence of light, type of reagent and solvent. Reaction conditions and yields of obtained compounds are summarized in Table 2.

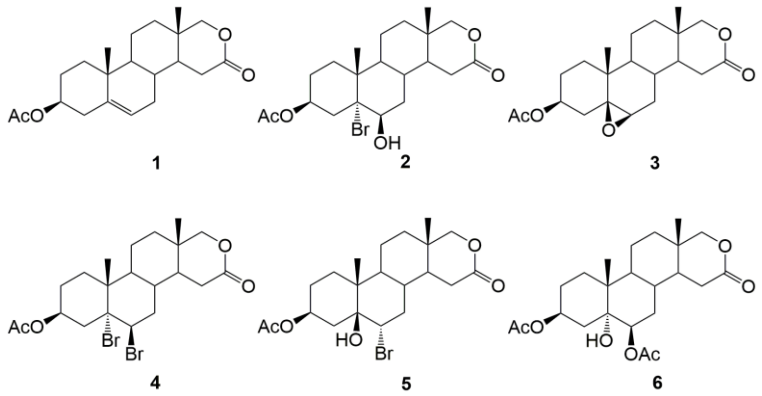

Fig. 1 Structure of the starting (**1**) and synthesized (**2**-**6**) compounds

Table 2 Reaction conditions and yields of obtained compounds

Exp No	Reag	Solvent	Acid conc. (M)	Temp.	Light	React. time (min.)	Compound yield (%)				
							2	**3**	**4**	**5**	**6**
1[1]	NBA	Dioxane	0.28	rt	Dark	40	49	27	3	0	0
2	NBA	Dioxane	0.28	rt	Dark	35	52	16	7	0	0
3	NBA	Dioxane	0.28	0 °C	Dark	40	44	22	2	0	0
4	NBA	Dioxane	0.28	rt	Day	40	67	23	1.4	1.9	0.8
5	NBA	Dioxane	0.28	rt	Day	30	36	22	9	0	0
6	NBA	DME	0.28	rt	Day	40	55	36	2.7	0	0
7	NBS	Dioxane	0.28	rt	Day	40	21	43	3.1	0	0
8	NBA	Dioxane	0.14	rt	Day	40	67	19	2.7	0	0
9	NBA	Dioxane	0.03	rt	Day	40	61	31	0	0	0
10[1,2]	NBA	Dioxane	0.03	rt	Dark	35	51	42	0	0	0

[1] Kuzminac et al., 2017; [2] In this experiment, 23% of starting compound **1** was also isolated. When calculated based on the entire amount of compound **1** yields are 32% for bromohydrin **2** and 40% for epoxide **3**.

Firstly, this reaction was conducted in the dark. It can be observed that shorter reaction time (35 min.) gives higher dibromide **4** yield and lower yield of compound **3**, in comparison to yields obtained when the reaction time was 5 minutes longer (experiments 1 and 2 in Table 2). Further experiments lasted 40 minutes since it can be observed that the yields of two main products of the reaction are increased or virtually unchanged when the reaction time is longer. In order to investigate temperature influence on compound yields, synthesis was carried out at 0 °C (experiment No. 3). This change did not significantly impact compound yields.

Furthermore, the reaction was conducted at room temperature but in daylight (experiment No. 4). Longer reaction time and the presence of daylight gave not just a higher yield of the main product, but also two new compounds, 6α-bromo-5β-hydroxy **5** and 6β-acetoxy-5α-hydroxy compound **6**. Shorter reaction time (30 min., experiment No. 5) does not give these two products and decreases yields of bromohydrin **2** and epoxide **3** even on daylight. From results obtained in these five experiments, it can be concluded that the highest yield of bromohydrin **2** is obtained when the reaction was conducted at room temperature, daylight and with longer reaction time. Having in mind this result, further reactions were conducted in these conditions. Usage DME instead dioxane leads to a decrease in the number of products and only compounds **2**, **3** and **4** were synthesized (experiment No. 6). Yield of bromohydrin **2** was reduced, while yields of epoxide **3** and dibromide **4** were almost doubled. When THF was used as a solvent, a very complex mixture of products was obtained. It was not possible to separate components of this mixture using flash chromatography. Furthermore, in the next experiment, NBS was used instead of NBA and dioxane as the solvent (experiment No. 7). Like in the previous runs, in this reaction, only three products were obtained. Yields of compounds **3** and **4** were increased, but the yield of bromohydrin **2** was reduced three times. Change of the solvent, i.e. the usage of THF also led to a complex mixture of products.

Finally, the influence of different perchloric acid concentrations on a number of products and their yields was investigated (experiments No. 8 and 9). In previous experiments acid concentration was 0.28 M. By reducing this concentration of perchloric acid, the number of products obtained is reduced. When the concentration was 0.14 M, compounds **2**, **3** and **4** were obtained. The yields of compounds **2** and **3** were virtually unchanged, but the yield of dibromide **4** was twice as high. With even lower concentration, 0.03 M, only bromohydrin **2** and epoxide **3** were produced. The yield of bromohydrin **2** was lower and epoxide **3** was higher than in previous reactions with higher acid concentrations. This reaction was conducted in our previous work[5] but in the dark and with shorter reaction time. Under those conditions, there was a significant amount of unreacted compound **1** isolated. Also, the yield of bromohydrin **2** was lower, but epoxide **3** yield was higher compared to previous experiment No. 9.

The structures of compounds **5** and **6** were confirmed by IR, ^{1}H and ^{13}C NMR, while compound **5** structure was also assessed by X-ray diffraction analyses. In the ^{1}H NMR spectrum of compound **5** there is only one singlet from acetate methyl group on C-3, but in compound **6** spectrum there are two such signals. The signal of H6 proton in compound **5** spectrum was observed as a doublet of doublets at δ_H=4.51 ppm with high coupling constants (12.1 and 4.9 Hz). This indicates axial (β-orientation) orientation of H6, thus, it is clear that the bromine atom at C6 is equatorial. In compound **6** ^{1}H NMR spectrum, the signal of H6 proton gives singlet at δ_H=5.19 ppm, this indicates the equatorial orientation of H6, thus, it is clear that acetoxy group at C6 is axial (β-orientation).

3.2. Crystal Structure Discussion

ORTEP (Farrugia, 1997) drawing of the molecular structure of **5** is depicted in Fig. 2, while selected bond distances, bond angles and torsion angles within the compound are given in Table 3. Compound 5 crystallizes in the orthorhombic, non-centrosymmetric $P2_12_12_1$ space group. The X-ray diffraction analyses confirmed that orientation of H6 is β-orientation while bromine atom at C6 is equatorial. The torsion angles C10—C5—C6—Br1 and C8—C7—C6—Br1 with the values of 178.6(3)° and -179.7(4)° respectively (Table 3) indicate the equatorial orientation of Br1 in compound **5**.

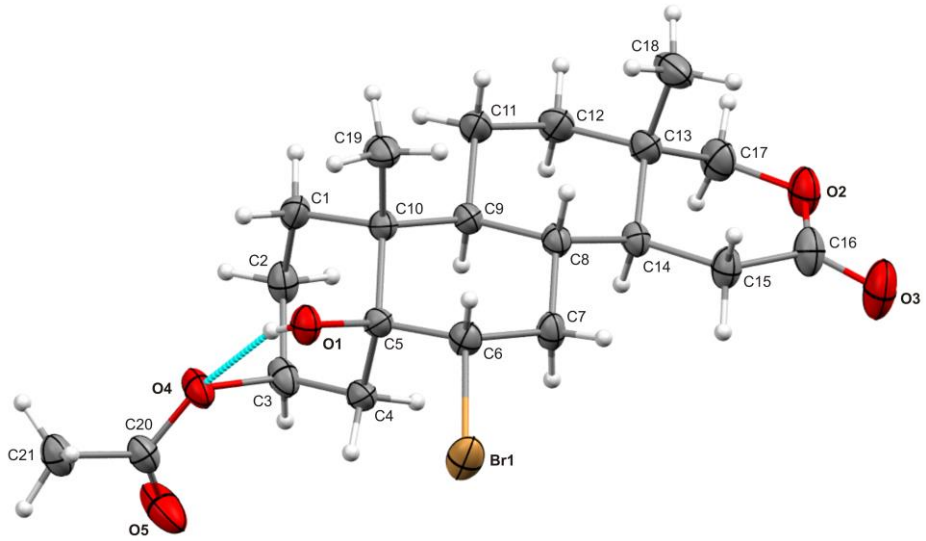

Fig. 2 ORTEP (Bruno, 2002) drawing of the molecular structure of compounds **5** with labeled non-H atoms. Displacement ellipsoids are shown at 30% probability, and H atoms are drawn as spheres of arbitrary radii. An intramolecular hydrogen bond is shown as a dashed line.

Information concerning intra- and inter-molecular hydrogen bonding can often be very useful for understanding various molecular properties (i.e., molecular geometries, the stability of certain predominant conformations and, consequently, biological activity). As can be seen in Fig. 2 molecular conformation of compound **5** is stabilized by O-H...O hydrogen bond with H…O distance of 2.27(7) Å, donor-acceptor distance of 2.892(6) Å and hydrogen bond angle of 157(8)°. The crystal packing of **5** is dominantly arranged by Van der Waals forces and corresponds to a discrete arrangement of molecules (Fig. 3). We have not found classic hydrogen bonding in the intermolecular space of compound **5**.

Table 3 Selected bond lengths and angles for compound **5**

Bond lengths [Å]	
Br1—C6	1.976 (5)
O1—C5	1.435 (6)
O4—C20	1.313 (6)
O4—C3	1.473 (5)
O2—C16	1.348 (8)
O2—C17	1.445 (8)
Bond angles [°]	
C5—C6—Br1	111.4 (4)
C7—C6—Br1	108.3 (4)
O1—C5—C6	107.1 (4)
O1—C5—C4	109.3 (4)
O3—C16—O2	119.0 (6)
O3—C16—C15	121.9 (7)
O2—C16—C15	119.1 (6)
C16—O2—C17	121.5 (4)
C20—O4—C3	118.2 (4)
O4—C3—C2	106.6 (4)
O4—C3—C4	108.7 (4)
Torsion angles [°]	
O1—C5—C6—Br1	61.1 (5)
C4—C5—C6—Br1	-58.7 (5)
C10—C5—C6—Br1	178.6 (3)
C8—C7—C6—C5	55.2 (6)
C8—C7—C6—Br1	-179.7 (4)
O1—C5—C10—C1	-66.3 (5)
O1—C5—C6—C7	-175.4 (4)
C20—O4—C3—C2	122.4 (5)

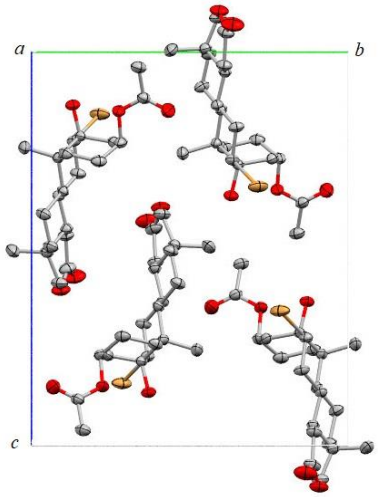

Fig 3 MERCURY (Bruno, 2002) drawing showing the crystal packing of compound **5** (along *a* axis)

4. CONCLUSIONS

In previous work, the reaction of a steroidal alkene with *in situ* generated hypobromous acid was conducted. Since there were three products obtained, and their number and yields were dependent on the reaction conditions, herein reaction conditions variation in the synthesis of steroidal bromohydrin was investigated. First, it was determined that the extension of the reaction time reduces the yield of dibromide **4** and increases the yield of epoxide **3**. Furthermore, the reduction of temperature did not significantly impact compound yields. Additional two products are obtained in the presence of daylight, 6α-bromo-5β-hydroxy derivative **5** and 3β,6β-diacetate **6**, but lowering the concentration of perchloric acid reduces the number of products. The number of products also varies depending on the solvent and reagent used. The X-ray crystal structure analysis of compound **5** reviled the equatorial orientation of Br1 atom and indicated that the molecular conformation of compound **5** is stabilized by O-H...O intramolecular hydrogen bond.

SUPPLEMENTARY DATA

Crystallographic data are deposited in the Cambridge Crystallographic Data Centre as supplementary material number CCDC 1826224. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB21FZ, UK (email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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ISPITIVANJE REAKCIONIH USLOVA U SINTEZI STEROIDNOG BROMHIDRINA I STRUKTURNA ANALIZA NOVOG 6α-BROM-5β-HIDROKSI DERIVATA

Ispitana je varijacija reakcionih uslova i njihov uticaj na reakciju 3β-acetoksi-17-oksa-17a-homoandrost-5-en-16-ona sa in situ generisanom hipobromastom kiselinom. Hipobromasta kiselina je dobijena iz N-bromacetamida (NBA) ili N-bromsukcinimida (NBS) i perhlorne kiseline, a kao rastvarači su korišćeni dioksan, dimetoksietan ili tetrahidrofuran. Nakon serije eksperimenata utvrđeno je da broj reakcionih proizvoda zavisi od upotrebljenog reagensa, rastvarača, koncentracije perhlorne kiseline i prisustva/odsustva dnevne svetlosti. Takođe je utvrđeno da prinosi pojedinih jedinjenja zavise od reakcionog vremena i temperature. 6α-Brom-5β-hidroksi derivat je dobijen upotrebom NBA i 0,28 M perhlorne kiseline u dioksanu na dnevnom svetlu. Njegova struktura je potvrđena NMR i rendgenskom strukturnom analizom.

Ključne reči: *NBA, NBS, epoksid, halogeni derivati, D-homo lakton androstana*