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NOTE

Synthesis and chemical behaviour of 17α-butyl-3β,17β-dihydroxy-16-oximino-5-androstene

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Starting from 3 -hydroxy-16-oximino-5-androsten-17-one (**1**), the recently synthesized 16-oximino-17 -hydroxy-17 -butyl derivative **2** gave by the Beckmann fragmentation reaction with titanium(III) chloride or *p*-toluenesulphonyl chloride the corresponding D-seco derivative **3**. However, using acetic anhydride, in addition to the 3 -acetoxy D-seco derivative **4**, the 17-aza D-homo derivative **5** was obtained. The structure of compound **5** was proposed on the basis of NMR-spectroscopy.

Keywords: 17-aza-D-homo derivatives of androstene, Beckmann fragmentation.

In our previous paper[1] the synthesis of the 16-oximino-17 -hydroxy-17 -picolyl- and 17 -benzyl derivatives of 5-androstene by the regio-selective addition of -picolyllithium and benzyllithium to the 17-keto group of 3 -hydroxy-16-oximino-5-androsten-17-one (**1**) was reported. In this work, the -hydroxy oxime **2** was prepared by the selective addition of butyllithium to the 17-keto group of **1** (mole ratio 90:1) (Scheme 1). The reaction was carried out in a mixture of absolute diethyl ether-THF, at –10ºC for 3 h. The oximino-alcohol **2** was obtained in a yield of 54 %, m.p. 82 ºC (from acetone-hexane, 1:1). [IR (KBr): 3250–3600, 2950, 1640, 1060 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 0.71 (*s*, 3H, H-18), 0.85 (*t*, 3H, *J* = 7.3 Hz, H-21), 0.96 (*s*, 3H, H-19), 3.25 (*m*, 1H, H-3), 4.31 (*s*, 1H, C_{17}–OH), 4.62 (*d*, 1H, *J* = 4.6 Hz, C_3–OH), 5.27 (*m*, 1H, H-6), 10.43 (*s*, 1H, =N–OH). ^{13}C-NMR (DMSO-d_6): 164.0 (C-16, C=NOH), 141.3 (C-5), 120.2 (C-6), 82.1 (C-17, Cq-OH), 70.0 (C-3, CH-OH), 49.6, 46.0, 45.2, 42.2, 36.9, 36.2, 31.6, 31.4, 30.7, 30.2, 27.2, 26.7, 25.2, 24.8, 22.8, 19.6, 19.1, 14.3. Calculated for: C, 73.56, H, 9.93, N, 3.73. Found: C, 73.21, H, 9.43, N. 3.43 .[2]

A side product in the synthesis of compound **2** was the corresponding D-seco derivative **3**. Compound **2** was subjected to the Beckmann fragmentation reaction using titanium(III) chloride or *p*-toluenesulphonyl chloride with the aim of preparing the new

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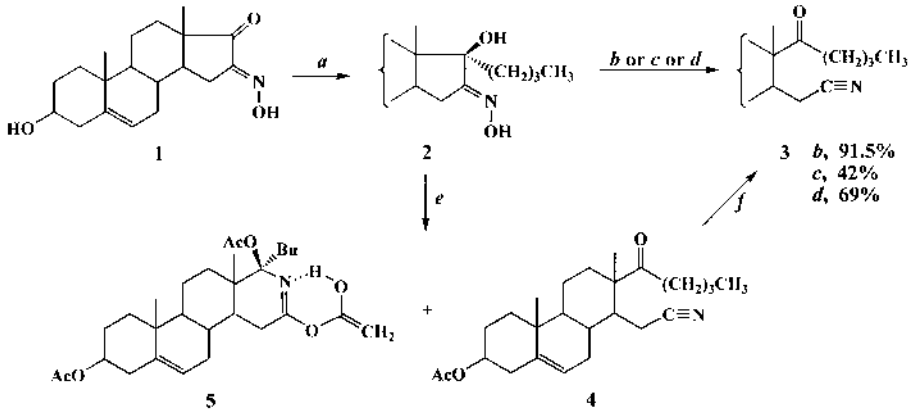


Scheme 1. a) BuLi, Et_2O, THF, –10ºC, 3 h; b) $TiCl_3$, HCl, H_2O, EtOH, reflux, 20 min; c) $TiCl_3$, HCl, H_2O, EtOH, RT, 12 h; d) TsCl, Py, RT, 17 h; e) Ac_2O, Py, reflux, 1 h; f) KOH, MeOH, reflux, 1 h.

D-seco derivative **3**. The use of titanium(III) chloride in acidic medium (hydrochloric acid) in ethanol as solvent, at the boiling temperature for 20 minutes, resulted in the 17-butyl-derivative of 3 -hydroxy-16-cyano-16,17-seco-5-androsten-17-one (**3**, 91.5 %, colourless oil). [IR (film): 3300–3500, 2240, 1690, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.93 (*t*, 3H, *J* = 7.1 Hz, H-23), 0.93 (*s*, 3H, H-19), 1.05 (*s*, 3H, H-18), 3.55 (*m*, 1H, H-3), 5.35 (*m*, 1H, H-6). ^{13}C-NMR ($CDCl_3$): 214.7 (C-17, C=O), 140.8 (C-5), 120.1 (C-16, CN), 119.7 (C-6), 69.9 (C-3), 51.1, 48.1, 41.9, 41.6, 36.5, 36.3, 35.9, 35.3, 32.1, 31.3, 31.0, 25.5, 21.7, 19.1, 19.0, 17.6, 14.4, 13.9 .

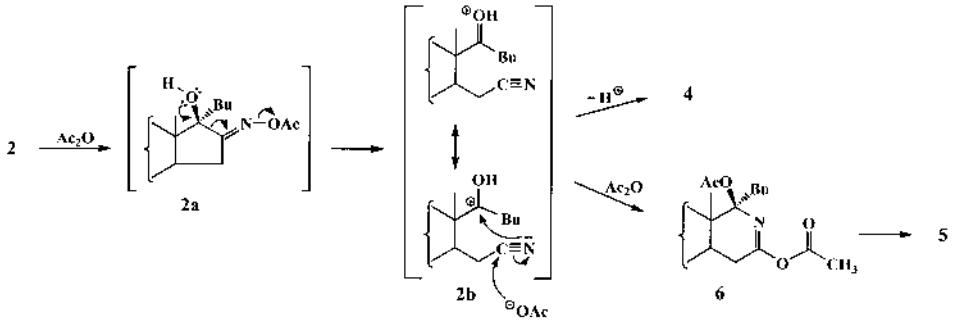
Repetition of the experiment at room temperature during 12 h yielded again the corresponding D-seco derivative **3**, but in a lower yield (42 %), whereby this reaction was essentially different from the analogous reaction of the 17 -benzyl derivative.[1] In the latter case, under these reaction conditions, the C-16 oximino group was transformed predominantly into the C-16 keto group, accompanied by the inversion of the configuration at the C-17 atom. However, compound **2** afforded only the fragmentation product **3**.

The fragmentation of the D-ring of compound **2** was carried out with the aid of *p*-toluenesulphonyl chloride (mole ratio 1:1) in absolute pyridine as solvent, at room temperature for 17 h. It was found that compound **2** gives directly the corresponding 3 -hydroxy D-seco derivative **3** (69 %) without the 3 -*p*-toluenesulphonyloxy derivative.

Compound **2** showed the most significant differences in the nature of reaction products when acetic anhydride was used as the fragmentation reagent. Namely, the reaction of compound **2** and acetic anhydride in absolute pyridine as solvent, at the boiling temperature for one hour, in addition to the 3 -acetoxy D-seco derivative **4** (60 %, m.p. 123 ºC from methanol) as the main reaction product, gave unexpectedly compound **5** (32 %, colourless oil). [IR (KBr) for **4**: 2950, 2240, 1720, 1680, 1220, 1020 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 0.85 (*t*, 3H, *J* = 7.3 Hz, H-23), 0.98 (*s*, 3H, H-19), 1.15 (*s*, 3H, H-18), 1.98 (*s*, 3H, Ac), 4.47 (*m*, 1H, H-3), 5.39 (*m*, 1H, H-6). ^{13}C-NMR (DMSO-d_6): 214.3 (C-17, C=O), 169.7 (C=O,Ac), 139.0 (C-5), 121.4 (C-6), 120.1 (C-16, CN), 73.0 (C-3, CH-OAc), 51.0, 48.8, 41.5, 37.3, 36.3, 36.1, 35.9, 35.3, 32.0,

31.0, 27.2, 25.5, 21.7, 21.0, 19.0, 18.8, 17.6, 14.3, 13.9. Calculated for: C, 75.15, H, 9.33, N, 3.51. Found: C, 74.92, H, 8.92, N, 3.14. IR (film) for **5**: 3350–3600, 2950, 1710, 1220, 980, 720 cm^{-1}. ^{1}H-NMR (DMSO-d_6): 0.72 (*s*, 3H, H-18), 0.86 (*t*, 3H, *J* = 7.2 Hz, H-23), 0.99 (*s*, 3H, H-19), 1.98 (*s*, 3H, Ac), 2.02 (*s*, 3H, Ac), 4.50 (*m*, 1H, H-3), 4.53 (*s*, 1H, OH), 5.33 (*m*, 1H, H-6), 5.61 (ABq, 2H, *J* = 6.8 Hz, =CH_2). ^{13}C-NMR (DMSO-d_6): 169.7 (2 Cq), 169.1 (2 Cq), 121.9 (C-6), 89.2 (C-17), 82.9 (=CH_2), 73.1 (C-3, CH-OAc), 49.3, 46.2, 44.9, 37.6, 36.4, 36.2, 32.9, 31.4, 30.8, 30.0, 27.6, 27.3, 25.1, 22.8, 21.0, 20.8, 20.0, 18.9, 14.3, 14.2 .

A possible mechanism for the formation of compounds **4** and **5** involves the same intermediate **2a**, which either undergoes Beckmann fragmentation to compound **4**, or by fragmentation and recyclisation to product **5** (Scheme 2).



Scheme 2.

It can be assumed that 17-aza D-homo derivative **5** is stabilized by the intramolecular hydrogen bond formed between the N-17 atom and the hydroxyl group of the enolic form of the C-16 acetoxy function, whereby a stable pseudo-six-membered ring is formed. The enolic form of the OAc group is indicated by an AB quartet at 5.61 ppm [–C(OH) = CH_2] in the ^{1}H-NMR spectrum and the signals at 82.9 ppm and 169.1 ppm in the ^{13}C-NMR spectrum, as well as by the characteristic vinylic streching vibration =CH_2 at 3023 cm^{-1} in the IR spectrum. The presence of an OH group in compound **5** [–C(OH) = CH_2] is confirmed by the signal at 4.53 ppm, singlet, exchangeable with D_2O, and the broad absorption band at 3300–3600 cm^{-1} in the IR spectrum. In the ^{1}H-NMR spectrum, singlets at 1.98 ppm and 2.02 ppm are characteristic for methyl protons of OAc groups, the multiplet at 4.50 ppm (H-3) which indicates an OAc group in the C-3 position, and H-18 (0.72 ppm, *s*), H-19 (0.99 ppm, *s*), and H-23 (0.86 ppm, *t*, *J* = 7.2 Hz) signals for methyl groups. In the ^{13}C-NMR spectrum, the signals at 89.2 ppm (C-17), 73.1 ppm (C-3) and 169.7 ppm prove the presence of two OAc groups (at C-3 and C-17).

It is known[3] that steroidal -keto oximes react with acetic anhydride to give D-homo derivatives of the type **6**. In view of the fact that compound **2** represents a 17-substituted -hydroxy oxime (and not an -keto oxime), the reaction of **2** with acetic anhydride represents a special case of the simultaneous formation of both D-seco and D-homo derivatives (**4** and **5**).

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И З В О Д

СИНТЕЗА И ХЕМИЈСКО ПОНАШАЊЕ 17 -БУТИЛ-3 ,17 -ДИХИДРОКСИ-16-ОКСИМИНО-5-АНДРОСТЕНА

СРЂАН СТОЈАНОВИЋ, ДОРА МОЛНАР ГАБОР, ЉУБИЦА МЕДИЋ-МИЈАЧЕВИЋ, МАРИЈА САКАЧ и КАТАРИНА ПЕНОВ ГАШИ

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Полазећи од оксимино-кетона **1** синтетизован је 17 -бутил дериват **2** који је Бекман-овом фрагментацијом помоћу титан(III)-хлорида и *p*-толуенсулфонил-хлорида дао одговарајући D-секо дериват **3**. Међутим, са анхидридом сирћетне киселине поред 3 -ацетокси D-секо деривата **4**, настао је и 17-аза D-хомо дериват **5**, чија је структура претпостављена на основу NMR спектроскопије.

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REFERENCES AND NOTE

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