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A Novel Rearrangement Of Steroidal α-Hydroxy Oximes

Dušan Miljković, Katarina Penov-Gaši*, Evgenija Djurendić, and Marija Sakač

Institute of Chemistry, Faculty of Sciences, University of Novi Sad, 21000 Novi Sad, Trg Dositeja Obradovića 3, Yugoslavia

Ljubica Medić-Mijačević, and Vjera Pejanović

ICN Galenika Institute, 29. Novembar 111, 11000 Beograd, Yugoslavia

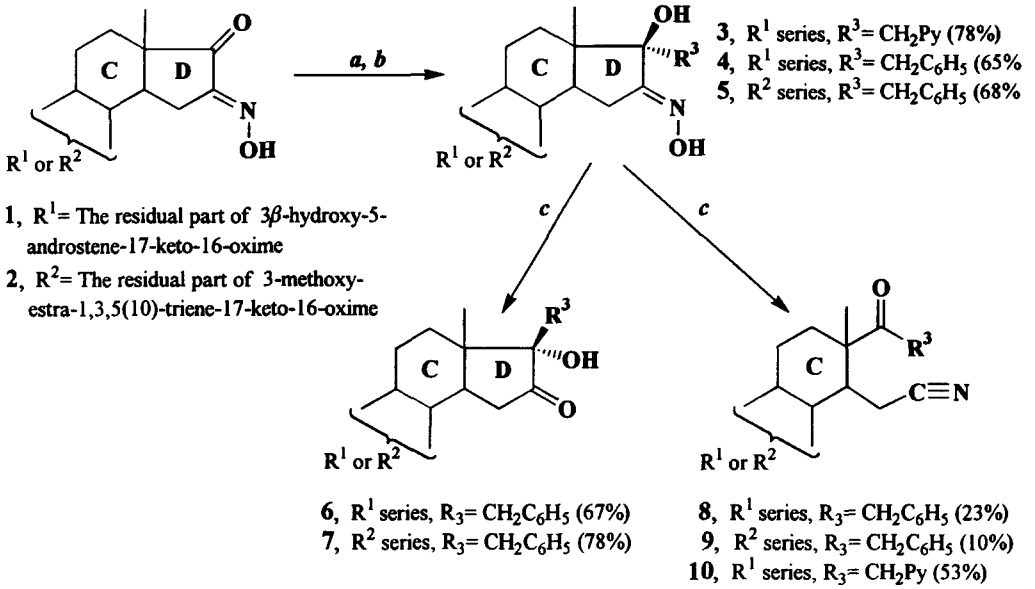
Slobodanka Stanković, and Dušan Lazar

Institute of Physics, Faculty of Sciences, University of Novi Sad, 21000 Novi Sad, Trg Dositeja Obradovića 4, Yugoslavia

Abstract: By the action of acidic titanium trichloride upon 16-oximino-17α-benzyl-17β-hydroxy derivatives in the androstane and estrane series the 16-oxo-17β-benzyl-17α-hydroxy derivatives **6** and **7** with inversed configuration at C_{17} were obtained. A mechanism for this novel rearrangement is proposed. © 1997 Published by Elsevier Science Ltd.

In our previous work[1] we synthesized the compound **3** (Scheme 1) by selective addition of α-picolyl-lithium to the 17-keto group of **1**. By using standard acidic reagents including $TiCl_3$ for conversion of the 16-oximino group into the corresponding 16-oxo function, only the fragmentation product **10** could be isolated.

In the present work, by replacing the 17α-picolyl substituent (compound **3**) with the benzyl group (compound **4**), we unexpectedly discovered a novel rearrangement reaction. Namely, instead of the fragmentation reaction (observed with **3**), acidic aqueous $TiCl_3$ mainly caused the hydrolysis of the 16-oximino group to the corresponding 16-keto group with simultaneous rearrangement of the benzyl substituent from the 17α to the 17β position (compound **6**, Scheme 1). The same rearrangement reaction was observed in the case of compound **5** (in estrane series), which under analogous reaction conditions afforded compound **7**, as the main reaction product (Scheme 1). The X-ray structural analysis unambiguously proved that the absolute stereochemistry at C_{17} corresponds to the benzyl group of **5** being 17α while that of **7** being 17β. The same stereochemical features have been observed in androstane series (compounds **4** and **6**). Detailed X-ray structural analysis of **4-7** will be published separately.



1, R^1= The residual part of 3β-hydroxy-5-androstene-17-keto-16-oxime

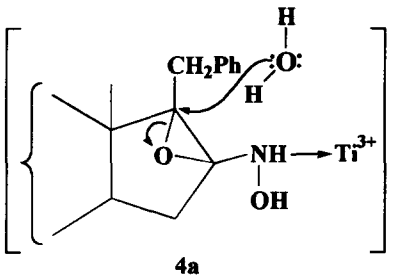
2, R^2= The residual part of 3-methoxy-estra-1,3,5(10)-triene-17-keto-16-oxime

3, R^1 series, R^3= CH_2Py (78%)
4, R^1 series, R^3= $CH_2C_6H_5$ (65%
5, R^2 series, R^3= $CH_2C_6H_5$ (68%

6, R^1 series, R_3= $CH_2C_6H_5$ (67%)
7, R^2 series, R_3= $CH_2C_6H_5$ (78%)

8, R^1 series, R_3= $CH_2C_6H_5$ (23%)
9, R^2 series, R_3= $CH_2C_6H_5$ (10%)
10, R^1 series, R_3= CH_2Py (53%)

Scheme 1 *Reagents:* a) α-$PyCH_2Li$, ether, THF, -10 -5°C;
b) $C_6H_5CH_2Li$, THF, -10°C;
c) $TiCl_3$ (4 mol equiv.), HCl-H_2O (1:1), EtOH, 25°C



4a

Scheme 2

We suggest that the observed rearrangement reaction occurs through the key intermediate having the structure of **4a** (Scheme 2). Thus, the hydrolysis of the 16-oximino function starts either by its protonation, or by its coordination with Ti^{3+} ion. This is followed by a neighbouring group participation of the 17β-hydroxy group affording the 16,17β-oxirane system. Quite likely, a complexed Ti^{3+} ion binds coordinatively an additional molecule of water, which *intra*molecularly attacks C_{17}-atom from the α-side, with an inversion of the configuration at C_{17}.

References

1. Miljković, D; Gaši, K, Bull. Soc. Chim., Belgrade, 1981, *46*, 263-268.

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