J.Serb.Chem.Soc. 68(4–5)303–312(2003)
JSCS – 3046

UDC 547.38:541.144+541.128
Original scientific paper

Acid-catalyzed and photolytic reactivity of some unsaturated B-nor-5,10-secosteroidal ketones*

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(Received 13 December 2002)

Abstract: The acid-catalyzed reaction of (*Z*)- and (*E*)-B-nor-5,10-seco-ketones **2** and **3** resulted in an intramolecular cyclization to give the 5-hydroxy-A-nor-1β,5β-10(19)-methylidene derivative **8**, the 5β-hydroxy-A-nor-1(10)-unsaturated compound **9** and the 5β,10α-dihydroxy-A-nor-product **10**, from the (*Z*)-isomer and the 5-hydroxy-A-nor-1α,5β-10(19)-methylidene product **11**, from the (*E*)-isomer. Upon UV-irradiation, the (*Z*)- and (*E*)-seco-ketones **2** and **3** underwent a reversible (*Z*)/(*E*) and (*E*)/(*Z*)-isomerization and in addition to a transannular photocyclization to afford the 10(19)-methylidene derivatives **8** and **11**, respectively, while photolysis of the 10(19)-methylidene-B-nor-5,10-seco-ketone **4** gave the oxetane derivative **12**.

Keywords: (*Z*)- and (*E*)-B-nor-5,10-secosteroidal ketones, 10(19)-methylidene-B-nor-5,10-secosteroidal ketone, acid-catalyzed reactions, photolytic reactions, mechanistic interpretation.

INTRODUCTION

As recently reported,[1] oxidative fragmentation of the C(5)–C(10) bond in 5α- and 5β-hydroxy-B-norcholestan-3β-yl acetates[2] (**1a** and **1b**) (Scheme 1) with lead tetraacetate (LTA) under photolytic conditions or with hypoiodite-forming reagents (LTA/I_2 or HgO/I_2 combinations),[3] afforded as the main products*** (*via* alkoxy **i** and alkyl radical **ii** intermediates) the isomeric (*Z*)- and (*E*)-1(10)-unsaturated and the methylidene-10(19)-unsaturated**** B-nor-5,10-secosteroidal ketones **2**–**4**, *i.e.*, a new type of modified steroids containing a nine-membered ring instead of the fused A,B-nor rings.

The conformations of the nine-membered rings of **2**–**4** in solution were deduced from their ^{1}H-NMR and ^{13}C-NMR spectral data and substantiated by calculation followed by

* Dedicated to Professor Miroslav J. Gašić on the occasion of his 70th birthday.

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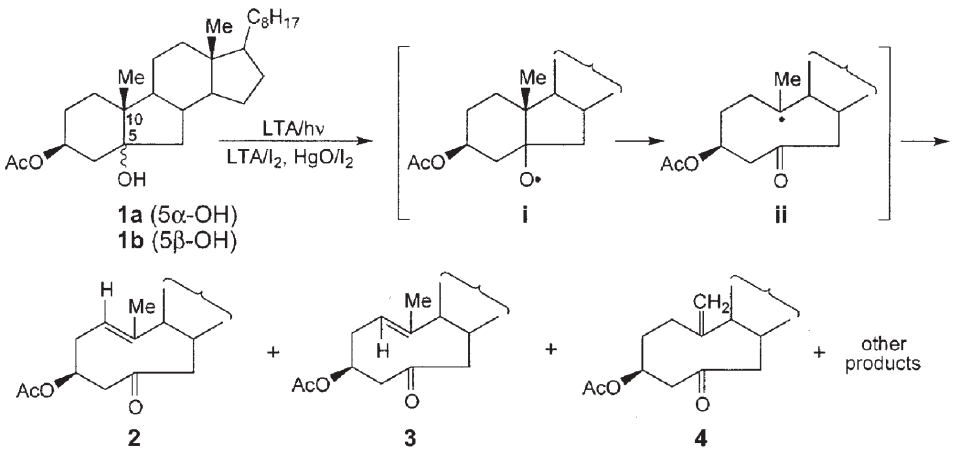
*** For information about other products isolated in these reactions see Ref. 1.

**** Obtained only with LTA under photolytic conditions.



Scheme 1.

geometry optimization using the MM+ program of HyperChem. The results indicated that the (*Z*)-stereoisomer **2** exists in solution in two conformational forms (Fig. 1), **A** (the major conformation) and **B** (the minor conformation), while the (*E*)-isomer **3** and 10(19)-methylidene derivative **4** are present in solution in only one conformation each, **C** (for the (*E*)-isomer **3**) and **D** (for the 10(19)-methylidene isomer **4**).

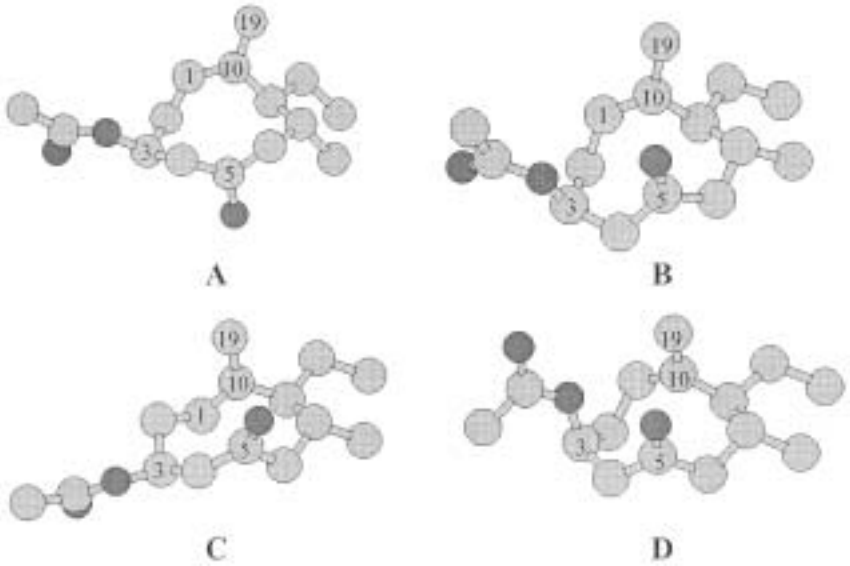
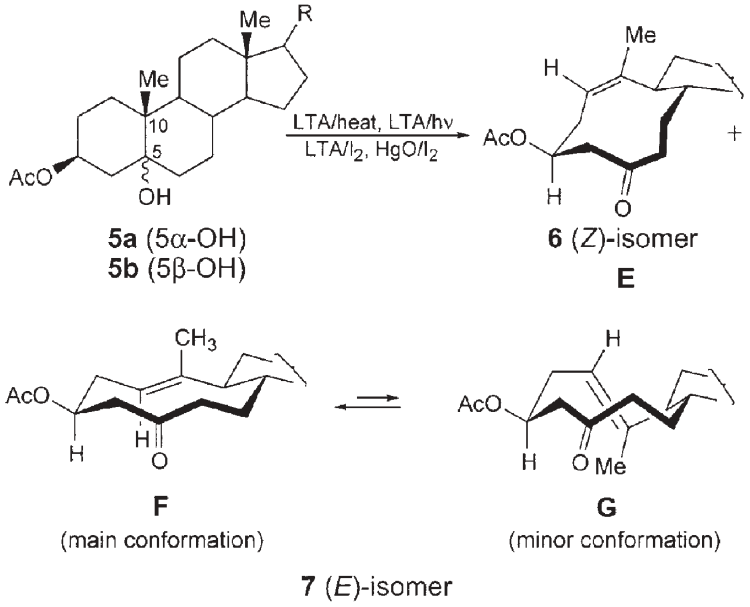


Fig.1 . The MM+ optimized conformations of the nine-membered ring in B-nor-5,10-seco-ketones **2** (**A** and **B**), **3** (**C**) and **4**(**D**).

Our previous investigations have shown that the ten-membered ring analogues of ketones **2** and **3**, *i.e.*, the (*Z*)- and (*E*)-1(10)-unsaturated steroidal cyclodecenones **6** and **7** (Scheme 2), obtained by similar fragmentation of the C(5)–C(10) bond in the non-modified 5α- and 5β-hydroxy steroids of type **5**,[4] behave differently towards reagent which can effect[5,6] or participate[7] in reactions involving bond formation across the ten-membered ring. This was explained by different stereochemical characteristics of the (*Z*)- and (*E*)-cyclodecenone system, which in solution exist in conformations **E** (the (*Z*) isomer **6**), and **F** (main) and **G** (minor) (the (*E*)-isomer **7**), respectively.



Scheme 2.

In connection with these results it was considered of interest to examine the possible transannular reactions of the B-nor-5,10-steroidal enones **2**–**4** too, for which differences characteristic for their respective nine-membered ring systems (shown in Fig. 1) could be expected.

In the present study the acid-catalyzed reactivity of the (*Z*)- and (*E*)-B-nor-5,10-seco-ketones **2** and **3** and in addition the photolytic behaviour of the B-nor-5,10-seco-ketones **2**–**4**, have been investigated.

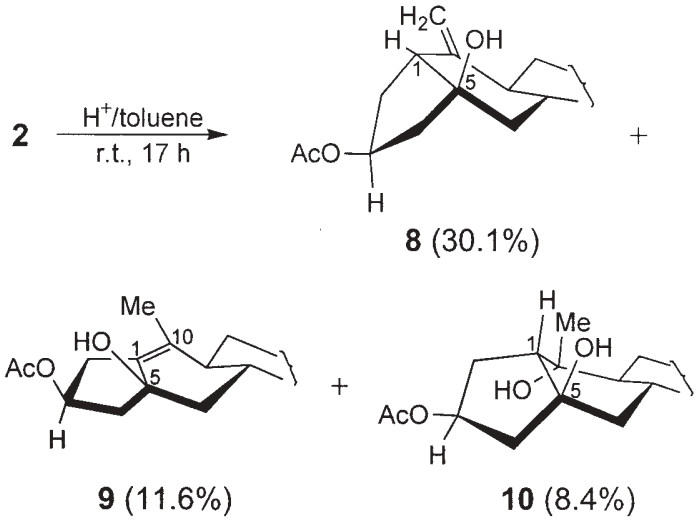
RESULTS AND DISCUSSION

The acid-catalyzed reactions of the (Z)- *and* (E)-*5-oxo-B-nor-5,10-secocholest-1(10)-en-3β-yl acetates (***2** *and* **3***).*

The acid-catalyzed reactions of **2** and **3**, respectively, were performed in a stirred toluene solution in the presence of catalytic amounts of toluene-*p*-sulphonic acid at room temperature until consumption of substrates (17 h for the (*Z*)- and 0.5 h for the (*E*)-isomer). Af-

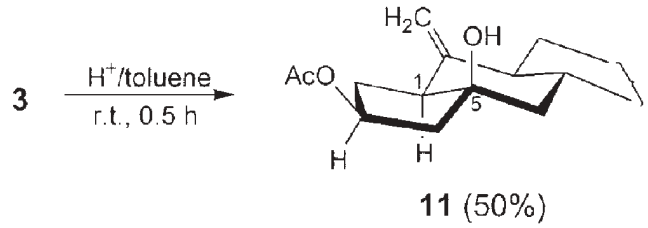
ter the usual work-up, the reaction mixtures were separated by column chromatography on silica gel.

Analysis of the products revealed that both the (*Z*)- and (*E*)-B-nor-5,10-seco-ketones **2** and **3**, respectively, undergo intramolecular cyclization. Thus, the (*Z*)-isomer (Scheme 3) afforded the 5-hydroxy-A-nor-1β,5β-10(19)-methylidene derivative **8** (in 30.1 % yield), the 5-hydroxy-A-nor-5β-1(10)-unsaturated compound **9** (in 11.6 % yield), and the 5,10-dihydroxy-A-nor-1β,5β,10α-product **10** (in 8.4 % yield).



Scheme 3.

On the other hand, the transannular cyclization of the (*E*)-5,10-seco-isomer **3** (Scheme 4) gave as the only product the methylidene derivative **11**, however with the 1α,5β-stereochemistry (in 50 % yield, while the rest was an unresolvable mixture of compounds).



Scheme 4.

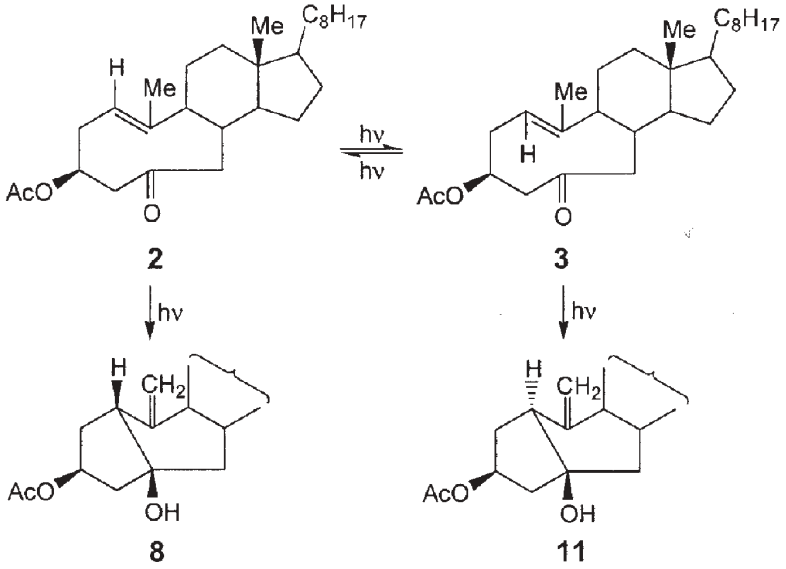
The A-nor derivatives **8**, **10** and **11** were identified by comparison with the samples isolated in the course of the HgO/I_2 oxidation of the 5α-alcohol **1a** as the secondary products arising from the primarily formed seco-ketones **2** and **3**, respectively.[1]

However, structure **9** was deduced on the basis of the physical data. In the IR spectrum of this compound, the absorption of the original 5-oxo function was replaced by a new absorption at 3447 cm^{-1} of a hydroxyl group. In its ^1H-NMR spectrum, a singlet at δ

= 1.65 ppm for the Me(19) group at the C=C bond and the absence of the olefinic proton indicated that, in this case, the intramolecular cyclization of **2** resulted in the formation of a tetrasubstituted olefinic double bond, involving the C(10) carbon. Its $\Delta^{1(10)}$-, rather than the Δ^{9}-position was suggested by the ^{13}C-NMR chemical shift of the C(8) carbon which appears as a doublet at 34.2 ppm (for the Δ^{9}-isomer, a value of about 43 ppm is to be expected).[8]

Photolytic reactions of the (Z)- *and* (E)-*5-oxo-B-nor-5,10-secocholest-1(10)-en-3β-yl acetates (***2** *and* **3***) and 5-oxo-B-nor-5,10-secocholest-10(19)-en-3β-yl acetate (***4***)*

Irradiation of the (*Z*)- and (*E*)-B-nor-5,10-seco-ketones **2** and **3** was carried out in a benzene solution with a high pressure mercury lamp Q81 at room temperature for 4 h.



Scheme 5.

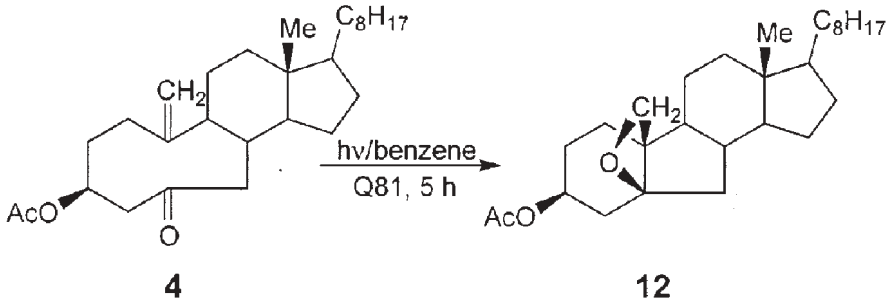
It was found (Scheme 5) that both stereoisomers **2** and **3** when exposed to UV light under these conditions underwent a reversible (*Z*)/(*E*) and (*E*)/(*Z*) isomerization, respectively, and, in addition, a transannular photocyclization to give the corresponding 10(19)-methylidene derivatives **8** and **11**, respectively.

The products formed in this reaction were separated by preparative thin-layer chromatography and identified by comparison with the corresponding authentic samples. The results are summarized in Table I.

Irradiation of the 10(19)-methylidene seco-ketone **4** was performed in benzene solution under similar experimental conditions as above until the starting material was consumed (about 5 h). After evaporation of solvent, the rest was dissolved in benzene/EtOAc (18:1) and purified by passing through a short SiO_2 column to afford the oxetane derivative **12** (in 90 % yield) (Scheme 6).

TABLE I. UV-Irradiation of the (*Z*)- and (*E*)-B-nor-5,10-seco-ketones **2** and **3** with a Q81 lamp in benzene solution for 4 h

Substrates	(*Z*)-isomer (**2**) yield in %	(*E*)-isomer (**3**) yield in %	Cyclization product **8** yield in %	Cyclization product **11** yield in %
(*Z*)-Isomer **2**	15.5	10.8	12.0	47.1
(*E*)-Isomer **3**	7.2	26.6	20.6	33.5



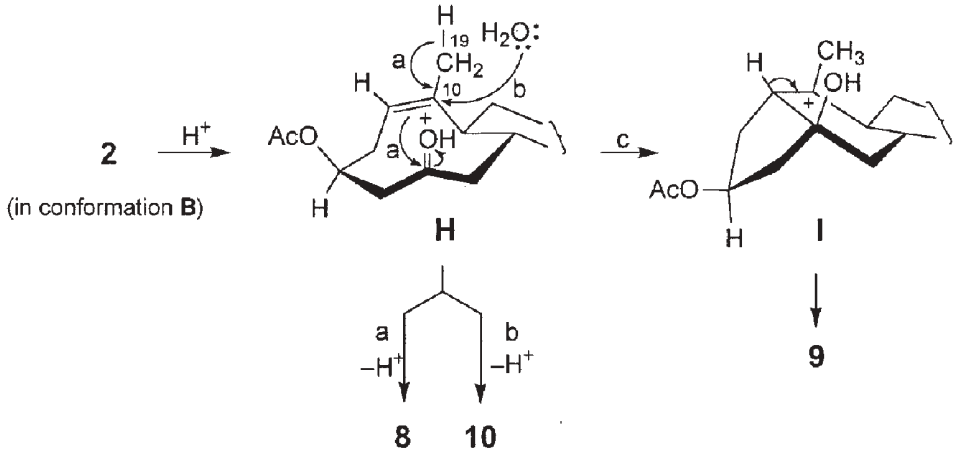
Scheme 6.

Identification of the photoproduct **12** was deduced from its spectral characteristics which were identical to the ones obtained for an authentic sample.[1]

From the results obtained it follows that the reactivity and stereochemical course in transannular acid-catalyzed and photolytic reactions of compounds **2**–**4** can be explained in terms of the deduced conformations of their respective nine-membered ring in solution shown in Fig. 1.

Thus, the intramolecular cyclization of the (*Z*)- and (*E*)-seco-ketones **2** and **3** with acid is initiated by protonation of the 5-oxo group and proceeds with participation of the π-electrons of the C(1)=C(10) bond.

In the (*Z*)-isomer, the interaction between the protonated carbonyl and olefinic double

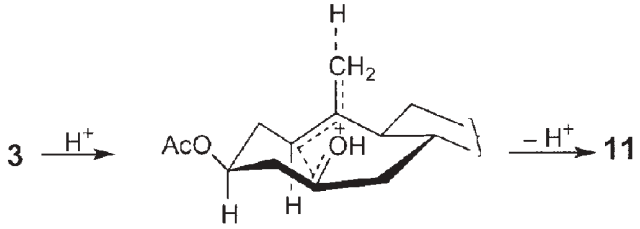


Scheme 7.

bond, due to steric reason, is possible only when the molecule assumes the minor conformation **B** (see Fig. 1).

Stabilization of the thus formed species **H** (Scheme 7) involves: (a) hydrogen elimination from the CH_3(19) group to give compound **8**; (b) water addition at C(10) followed by proton elimination to form the 10-hydroxy derivative **10**; or (c) proton elimination from C(1), which presumably proceeds *via* the carbo-cationic species I, affording the C(1)=C(10) unsaturated product **9**.

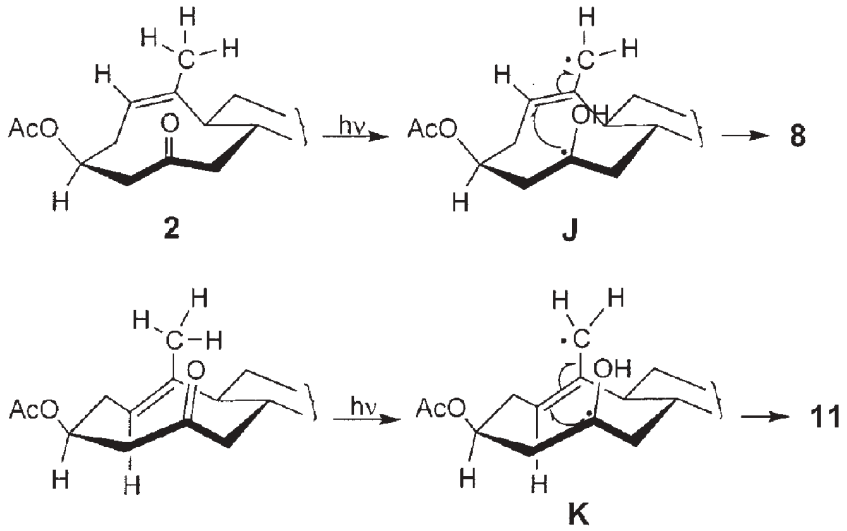
In the (*E*)-series, the reacting groups are favourably oriented to cyclize in the main conformation (Scheme 8).



Scheme 8.

As a consequence, the (*E*)-isomer reacts much faster than the (*Z*)-isomer. Under similar experimental conditions, the (*E*)-isomer **3** is consumed after 0.5 h, while the (*Z*)-isomer **2** only after 17 h.

On photolysis of **2** and **3**, the observed (*Z*)/(*E*) and (*E*)/(*Z*) isomerization of the olefinic C(1)=C(10) double bond, being incorporated in a medium-sized ring (such as the nine-membered ring in **2** and **3**) is a general photoreaction which can be effected by direct or sensitized excitation.[9]

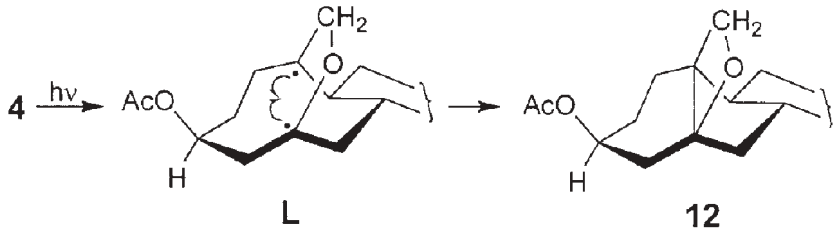


Scheme 9.

However, the photocyclization of **2** and **3** is an unusual process. It can be assumed that the reaction is initiated by abstraction of hydrogen from the CH_3(19) methyl group by the excited carbonyl[10] (Scheme 9), which is structurally determined by the proximity of the reacting groups.

Stabilization of the diradical **J** and **K**, respectively, proceeds by participation of the olefinic double bond and involves the formation of the transannular C(1)–C(5) bond. Which of the 10(19)-methylidene cyclization products (**8** or **11**) will be formed depends on the configuration of the $\Delta^{1(10)}$-double bond in the reacting diradical.

Finally, the high yield (90 %) of the oxetane **12** formed upon irradiation of the 10(19)-methylidene B-nor-seco-ketone **4** indicates that the excited carbonyl (which initiates the reaction) can easily reach the transannular methylene group to form the



Scheme 10.

biradical **L** (Scheme 10). On ring closure, this species gives the oxetane **12** (*i.e.*, the product of a transannular Paterno-Büchi reaction).[11]

EXPERIMENTAL

General

Column chromatography: silica gel 0.040–0.063 mm. TLC: control of reactions and separation of products on silica gel G (Stahl), detection with aq. 50 % H_2SO_4 soln. M.p.: uncorrected. IR Spectra: Perkin-Elmer-337 spectrophotometer; ν in cm^{-1}. NMR Spectra: Varian Gemini 200 (^1H at 200, ^{13}C at 50 MHz); $CDCl_3$ soln. At r.t.; $SiMe_4$ as internal standard; δ in ppm, *J* in Hz. Mass spectra: Finnigan-MAT 8230; *m/z* (rel. intensity in %); ionization energy 70 eV.

*Acid-catalyzed reaction of (Z)-5-oxo-B-nor-5,10-secocholest-1(10)-en-3β-yl acetate (**2**)*

A solution of **2** (100 mg, 0.232 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg) in toluene (40 ml) was stirred for 17 h, then diluted with Et_2O and washed with 5 % aq. $NaHCO_3$ soln. and H_2O. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on 30 g SiO_2 (0.040–0.063 mm). Elution with toluene/EtOAc (93:7) afforded first the 1β,5β-cyclization product **8** (30.1 mg, 30.1 %) and then the cyclization product **9** (11.6 mg, 11.6 %). Futher elution with toluene/EtOAc (50:50) gave the 3β,5β,10α-triol 3-acetate **10** (8.7 mg, 8.4 %). The IR, ^1H-NMR, ^{13}C-NMR and CI-MS of **8** and **10** were identical to those of the previously isolated compounds.[1]

5-Hydroxy-5(10→1)abeo-B-norcholest-1(10)-en-3β-yl acetate (**9**), oil. $[\alpha]_D = +2.20$ (c = 1.41, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 3447, 1739, 1248 cm^{-1}. ^1H-NMR ($CDCl_3$): δ = 0.77 (*s*, Me(18)), 0.86 (*d*, Me(26), Me(27)), 0.91 (*d*, Me(21)), 1.65 (*s*, Me(19)), 2.06 (*s*, AcO), 2.23 (*dd*, *J* = 6.9, 14.5, H_α–C(2)), 2.38 (*bd*, *J* = 14, H_β–C(4)), 2.53 (*dd*, *J* = 4, 14, H_α–C(4)), 5.07 (*dq*, *J* = 1.4, 4.7, H–C(3)). ^{13}C-NMR ($CDCl_3$): δ = 170.9 (*s*, Me*C*OO), 131.5 (*s*, C(10)), 124.2 (*s*, C(1)), 76.5 (*s*, C(5)), 73.,2 (*d*, C(3)), 56.5 (*d*, C(17)), 56.0 (*d*, C(14)), 50.9 (*t*, C(4)), 47.8 (*d*, C(9)), 42.3 (*s*, C(13)), 39.6 (*t*, C(6)), 39.4 (*t*, C(24)), 39.0 (*t*, C(12)), 38.6 (*t*, C(2)), 36.0 (*t*,

C(22)), 35.7 (*d*, C(20)), 34.2 (*d*, C(8)), 28.3 (*t*, C(16)), 27.9 (*d*, C(25)), 24.6 (*t*, C(11)), 24.4 (*t*, C(15)), 23.8 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.4 (*q*, *Me*COO), 18.6 (*q*, C(21)), 18.4 (*q*, C(19)), 11.1 (*q*, C(18)). MS: 412 (1 %, $M^+ - 18$), 352 (100 %, $M^+ - 60 - 18$).

*Acid-catalyzed reaction of (*E*)-5-oxo-B-nor-5,10-secocholest-1(10)-en-3β-yl acetate (***3***)*

A solution of **3** (20 mg, 0.046 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg) and toluene (8 ml) was stirred for 30 min. The mixture was worked up in the usual way and chromatographed on SiO_2 (2 g). Elution with toluene/EtOAc (95:5) gave the cyclization product **11** (10.0 mg, 50.0 %). For the IR, ^{1}H-NMR, ^{13}C-NMR and CI-MS of **11** see Ref. 1. The rest was a complex mixture which was not further investigated.

*UV-Irradiation of (*Z*)-5-oxo-B-nor-5,-10-secocholest-1(10)-en-3β-yl acetate (***2***)*

A solution of seco-ketone **2** (100 mg) in anh. benzene (25 ml) was irradiated with a high pressure mercury lamp Q81 at room temperature for 4 h. It was then evaporated *in vacuo* and the resulting mixture separated by preparative TLC (benzene/EtOAc (18:1)) to yield, in order of decreasing mobility: **2** (15.5 mg, 15.5 %), **3** (10.8 mg, 10.8 %), **11** (47.1 mg, 47.1 %) and **8** (12 mg, 12.0 %).

*UV-Irradiation of (*E*)-5-oxo-B-nor-5,10-secocholest-1(10)-en-3β-yl acetate (***3***)*

The UV-irradiation of **3** (100 mg) in anh. benzene was performed as above to give: **2** (7.2 mg, 7.2 %), **3** (26.6 mg, 26.6 %), **11** (33.5 mg, 33.5 %) and **8** (20.6 mg, 20.6 %).

*UV-Irradiation of 5-oxo-B-nor-5,10-secocholest-10(19)-en-3β-yl acetate (***4***)*

A solution of seco-ketone **4** (100 mg) in anh. benzene was irradiated with a high pressure mercury lamp Q81 at room temperature until the starting material was consumed (about 5 h). The resulting product obtained after evaporation of solvent was dissolved in benzene/EtOAc (18:1) and passed through a short SiO_2 column to give the 5β,19-epoxy-B-norcholestan-3β-yl acetate (**12**) (90 mg, 90 %). The spectral characteristics of **12** were identical to the ones obtained for an authentic sample.[1]

Acknowledgement: The authors acknowledge financial support by the Ministry of Science, Technology and Development of Serbia. (Part of the project "Synthesis and chemical transformations of steroidal and modified steroidal molecules" – Project Code 1702).

ИЗВОД

КИСЕЛО-КАТАЛИЗОВАНА И ФОТОЛИТИЧКА РЕАКТИВНОСТ НЕКИХ НЕЗАСИЋЕНИХ B-НОР-5,10-СЕКОСТЕРОИДНИХ КЕТОНА

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Кисело-катализована реакција (*Z*)- и (*E*)-B-нор-5,10-секо-кетона **2** и **3** резултује у интрамолекулској циклизацији дајући 5-хидрокси-A-нор-1β,5β-10(19)-метилиденски дериват **8**, 5β-хидрокси-A-нор-1(10)-незасићено једињење **9** и 5β,10α-дихидрокси-A-нор-производ **10**, из *Z*-изомера, и 5-хидрокси-A-нор-1α,5β-10(19)-метилиденски производ **11**, из *E*-изомера. (*Z*)- и (*E*)-Секо-кетони **2** и **3** UV-озрачивањем подлежу реверзибилној (*Z*)/(*E*) односно (*E*)/(*Z*) изомеризацији, као и трансануларној фотоциклизацији дајући 10(19)-метилиденске деривате **8** односно **11**, док се фотолизом 10(19)-метилиденског-5,10-секо-кетона **4** гради оксетански дериват **12**.

(Примљено 13. децембра 2002)

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