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

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

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, oxidative fragmentation of the C(5)–C(10) bond in 5α- and 5β-hydroxy-B-norcholestan-3β-yl acetates (1a and 1b) (Scheme 1) with lead tetraacetate (LTA) under photolytic conditions or with hypoidote-forming reagents (LTA/I2 or HgO/I2 combinations), afforded as the main products (via alkoxy and alkyl radical 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 1H-NMR and 13C-NMR spectral data and substantiated by calculation followed by...
geometry optimization using the MM+ program of HyperChem. The results indicated that the (Z)-stereoisomer \text{2} exists in solution in two conformational forms (Fig. 1), A (the major conformation) and B (the minor conformation), while the (E)-isomer \text{3} and 10(19)-methylidene derivative \text{4} are present in solution in only one conformation each, C (for the (E)-isomer \text{3}) and D (for the 10(19)-methylidene isomer \text{4}).

![Scheme 1.](image)

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 effect5,6 or participate7 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.

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-1\(\beta\),5\(\beta\)-10(19)-methylidene derivative 8 (in 30.1 % yield), the 5-hydroxy-A-nor-5\(\beta\)-1(10)-unsaturated compound 9 (in 11.6 % yield), and the 5,10-di-hydroxy-A-nor-1\(\beta\),5\(\beta\),10\(\alpha\)-product 10 (in 8.4 % yield).

![Scheme 3.](image)

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 1\(\alpha\),5\(\beta\)-stereochemistry (in 50 % yield, while the rest was an unresolvable mixture of compounds).

![Scheme 4.](image)

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 5\(\alpha\)-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 \(^1\)H-NMR spectrum, a singlet at \(\delta\)
= 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 Δ^{10(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)-methylene 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)-methylene 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

<table>
<thead>
<tr>
<th>Substrates</th>
<th>(Z)-isomer (2) yield in %</th>
<th>(E)-isomer (3) yield in %</th>
<th>Cyclization product 8 yield in %</th>
<th>Cyclization product 11 yield in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)-Isomer 2</td>
<td>15.5</td>
<td>10.8</td>
<td>12.0</td>
<td>47.1</td>
</tr>
<tr>
<td>(E)-Isomer 3</td>
<td>7.2</td>
<td>26.6</td>
<td>20.6</td>
<td>33.5</td>
</tr>
</tbody>
</table>

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 \( \pi \)-electrons of the \( C(1)=C(10) \) bond.

In the (Z)-isomer, the interaction between the protonated carbonyl and olefinic double
bond, due to steric reason, is possible only when the molecule assumes the minor conformation \textbf{B} (see Fig. 1).

Stabilization of the thus formed species \textbf{H} (Scheme 7) involves: (a) hydrogen elimination from the \( \text{CH}_3(19) \) group to give compound 8; (b) water addition at \( \text{C}(10) \) followed by proton elimination to form the 10-hydroxy derivative 10; or (c) proton elimination from \( \text{C}(1) \), which presumably proceeds via the carbo-cationic species 1, affording the \( \text{C}(1)=\text{C}(10) \) unsaturated product 9.

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

![Scheme 8](image)

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 \( \text{C}(1)=\text{C}(10) \) 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](image)
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 A$^{10(19)}$-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 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$_2$SO$_4$ soln. M.p.: uncorrected. IR Spectra: Perkin-Elmer-337 spectrophotometer; v in cm$^{-1}$. NMR Spectra: Varian Gemini 200 (H at 200, 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)-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$_2$O and washed with 5 % aq. NaHCO$_3$ soln. and H$_2$O. The organic layer was dried over Na$_2$SO$_4$ 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 1,5-cyclization product 8 (30.1 mg, 30.1 %) and then the cyclization product 9 (11.6 mg, 11.6 %). Further elution with toluene/EtOAc (50:50) gave the 3,5,10-triol 3-acetate 10 (8.7 mg, 8.4 %). The IR, $^1$H-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)-abeo-B-norcholest-1(10)-en-3β-yl acetate (9), oil, [α]$^D$_D = + 2.20 (c = 1.41, CHCl$_3$).

**IR (CHCl$_3$): v$_{max}$ = 3447, 1739, 1248 cm$^{-1}$.**

**$^1$H-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$_2$–C(2)), 2.38 (bd, J = 14, H$_2$–C(4)), 2.53 (dd, J = 4, 14, H$_2$–C(4)), 5.07 (dq, J = 1.4, 4.7, H–C(3)).

**$^{13}$C-NMR (CDCl$_3$):** δ = 170.9 (s, MeCOO), 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)), 38.5 (t, C(2)), 36.0 (t,
Acid-catalyzed reaction of (E)-5-oxo-B-nor-5,10-secocholest-1(10)-en-3-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 SiO2 (2 g). Elution with toluene/EtOAc (95:5) gave the cyclization product 11 (10.0 mg, 50.0 %). For the IR, 1H-NMR, 13C-NMR and CI-MS of 11 see Ref. 1. The rest was a complex mixture which was not further investigated.

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REFERENCES

3. J. Kalvoda, K. Heusler, Synthesis (1971) 525
10. Ref. 9, pp. 386–392
11. Ref. 9, p. 446.