CROATICA CHEMICA ACTA CCACAA 62 (1) 43—49 (1989)

CCA-1837

YU ISSN 0011-1643
UDC 541.7
Original Scientific Paper

Transannular Photocyclization of (*E*)-3β-Acetoxy-5,10-seco--1(10)-cholesten-5-one*

Ljubinka Lorenc, Vladimir Pavlović, and Mihailo Lj. Mihailović

Department of Chemistry, Faculty of Science, University of Belgrade, Studentski trg 16. P. O. Box 550, YU-11001 Belgrade, Yugoslavia, and Institute of Chemistry, Technology and Metallurgy, Belgrade

Bernard Tinant, Jean-Paul Declercq, and Maurice Van Meerssche

Laboratoire de Chimie physique et de Cristallographie, Université de Louvain, Bâtiment Lavoisier, Place Louis Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium

Received August 29, 1988

UV irradiation of the (*E*)-5,10-seco-steroidal ketone *1* in acetone solution results, in addition to the previously described *E*/*Z* isomerization and intramolecular Paterno-Büchi reaction (leading to the 1α,5α-oxetane *4* in about 42% yield and 1β,5β-oxetane *5* in 2—3% yield), in a transannular cyclization (accompanied by acetic acid elimination) producing the anthrasteroidal enone *3* (in about 7% yield). The structure of *3* was deduced from spectral data and confirmed by X-ray analysis.

INTRODUCTION

We reported previously that UV irradiation of (*E*)-3β-acetoxy-5,10-seco--1(10)-cholesten-5-one (*1*) in dioxane[2] or acetone solution[3] with a high pressure mercury lamp leads to an intramolecular Paterno-Büchi reaction (cycloaddition of the carbonyl chromophore to the olefinic double bond) to give two oxetane derivatives, one, *4*, with the 1α,5α-configuration, as the major product (in 32—42% yield), and the other, *5*, with the 1β,5β-configuration, as a minor component (in 2—3% yield); in addition, *E*/*Z* isomerization of the olefinic $\Delta^{1(10)}$-double bond was observed. In the present paper we investigated, in more detail, the photolytic behaviour of the (*E*)-5,10-seco-ketone *1* when subjected to UV irradiation in acetone solution.

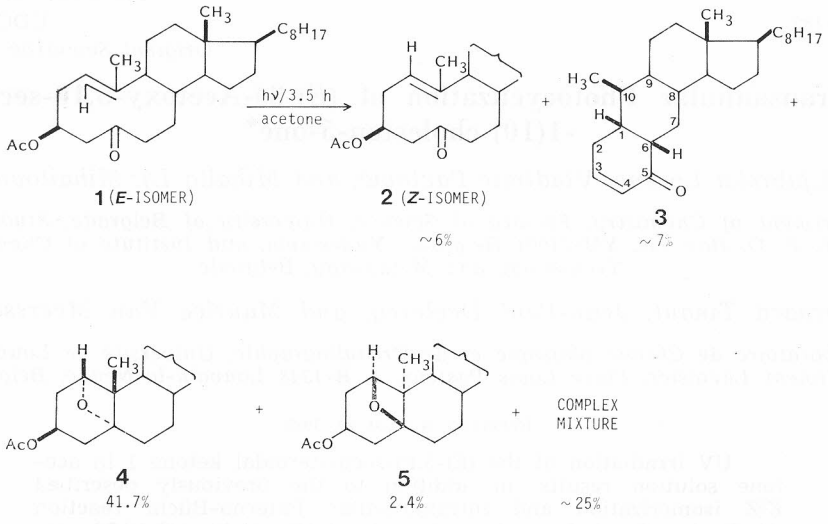
RESULTS AND DISCUSSION

A $\sim 0.9 \times 10^{-2}$ M acetone solution of the (*E*)-stereoisomeric 5,10-seco--ketone *1* was irradiated with a high pressure mercury lamp TQ 150 Z2 for 3.5 hours at room temperature. Product analysis revealed that under these conditions, besides the above mentioned transformations (*i. e.* *E*/*Z* isomerization and intramolecular Paterno-Büchi reaction), a transannular cycli-

* Part XXVIII in the series »*Synthesis structure and reactions of seco-steroids containing a medium-sized ring*«. For Part XXVII see reference 1.

zation (accompanied by acetic acid elimination) producing the anthrasteroidal enone *3* also took place as a minor process. The results are given in Scheme 1.*

Sheme 1



The photolysis products were separated by column chromatography Actually, due to similar adsorption properties, (Z)-3β-acetoxy-5,10-seco-ketone *2* and the anthrasteroidal enone *3* were eluted from the column as a mixture. Their successful separation (on a SiO_2 column) was performed only after the mixture was treated with a ~ 1% methanolic KOH solution, which transformed product *2* into its more polar derivative, *i. e.* (Z)-3β-hydroxy-5,10--seco-1(10)-cholesten-5-one[4], leaving *3* unchanged (see Experimental).

The structure of compound *3* was deduced from elemental microanalysis ($C_{27}H_{44}O$) and spectral data. Thus, MS (*m/z* 384), IR and ^{1}H-NMR spectra of *3* revealed that the 3β-OAc group present in *1* was lost during irradiation (in the form of acetic acid) to produce a conjugated enone function (UV maximum at 227 nm, IR absorption at 1670 and 1620 cm^{-1}, and signals at 5.97 and 6.95 ppm in the ^{1}H-NMR spectrum). Also, its ^{1}H-NMR and ^{1}H-decoupled ^{13}C-NMR spectra indicated that the original $\Delta^{1(10)}$-double bond was missing (no signals of the H—C(1) proton and the CH_3(19) group attached to an isolated olefinic bond). Moreover, the appearance of the CH_3(19) group as a doublet at 0.97 ppm in the ^{1}H-NMR spectrum of *3* and the number of primary, secondary, tertiary and H-free C-atoms detectable in the ^{1}H-decoupled ^{13}C-NMR spectrum of this compound (5 quartets, 9 triplets, 11 doublets and 2 singlets) strongly suggested that the olefinic $\Delta^{1(10)}$-double bond took part in an intramolecular cyclization leading to the anthrasteroidal structure *3*.

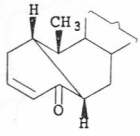
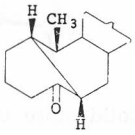
Catalytic hydrogenation of the olefinic double bond in *3* afforded the corresponding 3-saturated analogue *6*, the spectral characteristic of which were in complete agreement with the proposed structure (see Experimental).

* Yields refer to crude products (see Experimental).

In an attempt to determine the stereochemistry at the newly formed chiral centres of *3* (particularly at the C(1) and C(6) bridgehead positions), CD measurement was performed on compound *3* and its saturated derivative *6*. The CD maxima are summarized in Table I. However, they proved to be unsatisfactory for a precise configurational assignment of *3*. Namely, from the molecular models it follows that the enone moiety in configuration-

TABLE I

CD Data for the anthrasteroidal ketones 3 *and* 6 *(in acetonitrile)*[a]

Compound		λ_{max} ($\Delta\varepsilon$)
	3	351(+2.17), 339(+2.27), 254(-0.48) 224(-3.78), 216(-3.61), 194(+6.53)
	6	301(+2.69), 243(-0.34), 232(-0.46) 222(-0.53), 199(-1.92), 198(-1.86)

[a] λ given in nm

ally different anthrasteroid systems of type *3* is not, or at least not very strongly, twisted, making predictions of the Cotton-effect sign for the unsaturated molecules difficult; on the other hand, in the case of the saturated analogue *6* a positive CD for the $n \rightarrow \pi^*$ band (found experimentally, Table I) is consistent with the 6β-configuration in both the 1α,6β- and 1β,6β-stereoisomers. Thus, the 1β,6β,10β(CH_3)-configuration of the cyclization product *3* was determined by X-ray analysis.

X-Ray Analysis and Structure Determination of the Anthrasteroidal Enone 3

Crystal data of enone *3* are as follows: $C_{27}H_{44}O$, $M_r = 384.65$, orthorhombic, space group $P2_12_12_1$ with $a = 33.173(18)$, $b = 6.604(3)$, $c = 11.172(4)$ Å; $V = 2447(2)$ Å^3, $D_x = 1.04$ g cm^{-3} for $Z = 4$. The intensities of 1523 $h\,k\,l$ independent reflections were collected on a Huber four circle diffractometer using CuKα graphite monochromatized radiation ($\lambda = 1.54178$ Å) up to $2\Theta = 130°$. 739 reflections having $I \geqslant 2.5\sigma(I)$ were considered as observed and used in the structure refinement. The structure was solved by MULTAN 80[5] and refined using F values first with isotropic and then with anisotropic temperature factors for the non-H atoms with SHELX 76[6]. The positions of the H atoms were calculated with C—H distances of 1.08 Å and H—C—H angles of 109.4°. The final R value is 0.051 for 739 observed reflections. Lists of the atomic coordinates and of the geometrical parameters have been deposited with the Cambridge Crystallographic Data Centre.

Figure 1 is a stereoscopic view of molecule *3*, showing the numbering of the atoms (PLUTO[7]).

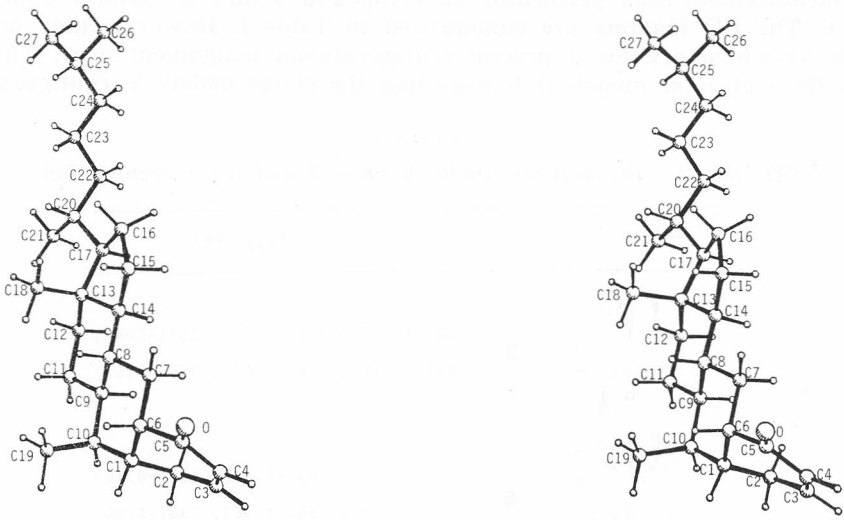
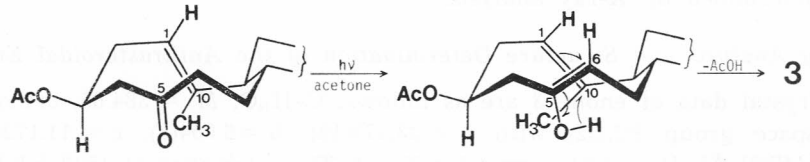


Figure 1. Stereoscopic view of enone *3* in its solid state conformation.

The C(1)—C(2)—C(3) = C(4)—C(5)—C(6) ring has a half-chair conformation with torsion angles 46, —22, 0, —2, 27 and — 49°. The two other 6-membered rings are in parallel chair conformations with an approximate local mirror plane containing C(8) and C(9). The pentagonal ring exhibits an envelope conformation with C(13) at the flap.

A plausible mechanistic course for the photochemically induced cyclization of the (*E*)-5,10-seco-ketone *1* to enone *3* is shown in Scheme 2.

Scheme 2



1 A

The first step involves photoenolization of ketone *1** (towards the C(6) atom) to produce species *A*, which then undergoes intramolecular rearrangement *via* a cyclic six-membered transition state (along with acetic acid elimination), resulting in the stereospecific formation of the 1β,6β,10β(CH_3)--anthrasteroidal enone *3* as the final product. Formally, this rearrangement can be considered as a retro-Norrish Typ II process, not observed as yet. In this case the reaction is possible, probably due to entropy factors.

* About photoenolization of saturated ketones see, for example, ref. 8.

EXPERIMENTAL

General

Prep. column chromatography: Silica gel 0.063—0.200 mm. TLC: control of reactions and separation of products on silica gel G (Stahl) with benzene/AcOEt 9 : 1, detection with 50% aq. H_2SO_4 soln. Melting points are uncorrected. CD spectra: ISA-Jobin-Yvon dichrograph model Mark III at room temperature in acetonitrile at conc. of approximately 0.2 mg/ml. UV spectra: Varian UV Super Scan 3 spectrophotometer: λ_{max} nm (ε). IR spectra: Perkin-Elmer-337 spectrophotometer; ν_{max} in cm^{-1}. NMR spectra: Bruker AM-360 (^1H at 360 MHz, ^{13}C at 90.55 MHz), $CDCl_3$ soln. at room temperature, TMS as internal standard; chemical shifts in ppm as δ values. Mass spectra (MS): Varian CH7 instrument; in *m/z*.

UV Irradiation of (E)-3β-Acetoxy-5,10-seco-1(10)-cholesten-5-one (1)[4]

A solution of the (*E*)-5,10-seco-ketone (*1*) (1.00 g) in acetone (250 ml) was irradiated with a high pressure mercury lamp TQ 150 Z2 (Hanau) at room temp for 3.5 hours. It was then evaporated *in vacuo* and the oily residue (1.2 g) chromatographed on silica gel (50 g). Benzene-diethyl ether (99 : 1) eluted a mixture of (*Z*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (*2*) and anthrasteroidal enone *3* (132 mg). Benzene-diethyl ether (98 : 2) eluates gave first 180 mg (18%) of unchanged (*E*)-seco-ketone *1*, *m.p.* 136 °C (from acetone-MeOH) (lit.[4] *m.p.* 136 °C), followed by 24 mg (2.4%) 19α-methyl-1β,5-epoxy-5β-cholestan-3β-ol acetate (*5*). Oxetane *5* was rechromatographed on SiO_2 column to afford a chromatographically (TLC) pure sample (16 mg, 1.6%), oil (lit.[2] oil); $[\alpha]_D^{20} = +32.5$ ($c = 1.93\%$, $CHCl_3$); IR (CH_2Cl_2): 1730, 1235, 1028; ^1H-NMR: 0.68 (s, CH_3-18), 0.84 (d, CH_3-26 and CH_3-27), 0.87 (d, CH_3-21), 0.88 (s, CH_3-19), 2.03 (s, AcO), 3.02 (m, H—C(1)), 5.10 (m, H—C(3)); ^{13}C-NMR: 171.2 (s, CH_3COO), 74.3 (d, C-3), 70.0 (s, C-5), 58.5 (d, C-1), 56.6 (d, C-17), 55.0 (d, C-14), 49.3 (d, C-9), 43.5 (s, C-13), 41.0 (s, C-10), 40.3 (t, C-12), 39.5 (t, C-24), 37.8 (d, C-8), 37.5 (t, C-4), 36.1 (t, C-22), 35.8 (d, C-20), 31.8 (t, C-6), 30.2 (t, C-7), 29.7 (t, C-2), 28.0 (d, C-25), 27.9 (t, C-16), 24.6 (t, C-11), 24.1 (t, C-15), 23.9 (t, C-23), 22.8 (q, C-27), 22.6 (q, C-26), 21.4 (q, CH_3COO), 18.6 (q, C-21), 16.5 (q, C-19), 12.4 (q, C-18). MS: $m/z = 444$ (M^+).

Anal. Calcd. for $C_{29}H_{48}O_3$ ($M_r = 444.70$): C 78.32, H 10.88%; found: C 78.17, H 10.64%.

Benzene-diethyl ether (97 : 3 and 96 : 4) eluted 1α,5-epoxy-5α-cholestan-3β-ol acetate (*4*)[2,3] (417 mg, 41.7%), *m.p.* 101—102 °C (from acetone) (lit.[2,3] *m.p.* 101—102 °C); $[\alpha]_D^{20} = +20.0$ ($c = 1.00\%$, $CHCl_3$); IR (CH_2Cl_2): 1732, 1238, 1025; ^1H-NMR: 0.66 (s, CH_3-18), 0.84 (s, CH_3-19), 0.85 (d, CH_3-26 and CH_3-27), 0.91 (d, CH_3-21), 2.01 (s, AcO), 3.94 (d, $J = 6$ Hz, H-C(1)), 5.20 (m, H-C(3)); ^{13}C-NMR: 170.5 (s, CH_3COO), 88.5 (s, C-5), 83.2 (d, C-1), 66.7 (d, C-3), 56.1 (d, C-14 and C-17), 47.0 (d, C-9), 45.5 (s, C-18), 42.5 (t, C-4), 39.9 (t, C-12), 39.5 (t, C-24), 38.7 (d, C-8), 36.2 (t, C-22), 35.8 (d, C-20), 34.2 (s, C-10), 31.6 (t, C-2), 31.0 (t, C-6), 28.1 (t, C-16), 28.0 (d, C-25), 27.8 (t, C-7), 24.4 (t, C-15), 23.9 (t, C-23), 23.1 (t, C-11), 22.8 (q, C-27), 22.6 (q, C-26), 21.2 (q, CH_3COO), 18.8 (q, C-21), 11.8 (q, C-18), 11.7 (q, C-19).

Anal. Calcd. for $C_{29}H_{48}O_3$ ($M_r = 444.70$): C 78.32, H 10.88%; found: C 78.18, H 10.87%.

Further elution with benzene-diethyl ether (95 : 5, 90 : 10 and 80 : 20) afforded a complex mixture (260 mg, about 25%), from which no definite product could be isolated.

Separation of the Anthrasteroidal Enone 3 from (Z)-3β-Acetoxy-5,10-seco-1(10)-cholesten-5-one (2)

A mixture of *2* and *3* (isolated with benzene-diethyl ether (99 : 1) in the above chromatography procedure) was dissolved in 5 ml MeOH to which 5% methanolic KOH (1 ml) was added, and the solution left overnight at room temperature. The residue (126 mg) obtained after the usual work-up was chromatographed on silica gel (5 g). Elution with benzene gave the anthrasteroidal enone *3* (62 mg, 7.2%),

which was twice recrystallized from acetone-MeOH (43 mg, 5.0%), *m. p.* 136—137 °C; $[\alpha]_D^{20} = +102.6$ ($c = 0.30\%$, $CHCl_3$); UV (EtOH): 227 (7700); IR (CH_2Cl_2): 1670, 1620; ^{1}H-NMR: 0.66 (s, CH_3-18), 0.86 (d, CH_3-26 and CH_3-27), 0.90 (d, CH_3-21), 0.97 (d, CH_3-19), 5.97 (d x d, $J = 10$, 2.4 Hz, H-C(4)), 6.95 (d x d x d, $J = 10$, 6.2, 2.8 Hz, H-C(3)); ^{13}C-NMR: 203.4 (s, C-5), 150.2 (d, C-3), 128.5 (d, C-4), 56.3 (d, C-17), 55.9 (d, C-14), 44.3 (d, C-6), 43.3 (s, C-13), 41.2 (d, C-1), 41.0 (d, C-9), 40.1 (t, C-12), 39.5 (t, C-24), 36.3 (d, C-8), 36.2 (t, C-22), 35.7 (d, C-20), 33.5 (d, C-10), 30.2 (t, C-7), 28.2 (t, C-16), 27.9 (d, C-25), 26.4 (t, C-11), 23.9 (t, C-15 and C-23), 23.8 (t, C-2), 22.8 (q, C-27), 22.6 (q, C-26), 18.7 (q, C-21), 14.5 (q, C-19), 12.0 (q, C-18). MS: *m/z* 384 (M^+).

Anal. Calcd. for $C_{27}H_{44}O$ ($M_r = 384.65$): C 84.31, H 11,53%; found: C 84.14, H 11.38%.

Benzene-diethyl ether (90 : 10) eluted (Z)-3β-hydroxy-5,10-seco-1(10)-cholesten--5-one (52 mg, 5.7%), *m. p.* 118 °C (from MeOH) (lit.[4] *m. p.* 116—118 °C), which was acetylated (with Ac_2O in pyridine) to (Z)-3β-acetoxy-5,10-seco-1(10)-cholesten-5--one (*2*), *m. p.* 138 °C (from acetone) (lit.[4] *m. p.* 138 °C).

Catalytic Hydrogenation of the Anthrasteroidal Enone 3

A solution of the anthrasteroidal enone *3* (100 mg) in ethanol (25 ml) was hydrogenated in the presence of Adams catalyst (10 mg) at room temp. for 1 hour. The mixture was filtered through a Celite mat and the filtrate evaporated under reduced pressure, to give the saturated anthrasteroidal ketone *6* (100 mg, 100%), which after recrystallization from acetone (91 mg, 90.5%) had *m. p.* 102—104 °C; $[\alpha]_D^{20} = +82.5$ ($c = 0.40\%$, $CHCl_3$); IR (KBr): 1705; ^{1}H-NMR: 0.66 (s, CH_3-18), 0.86 (d, CH_3-26 and CH_3-27), 0.91 (d, CH_3-21), 0.95 (d, CH_3-19); ^{13}C-NMR: 215.3 (s, C-5), 56.3 (d, C-17), 56.0 (d, C-14), 48.5 (d, C-6), 45.0 (d, C-1), 43.3 (s, C-13), 40.9 (d, C-9), 40.1 (t, C-12), 39.5 (t, C-24), 37.9 (t, C-4), 37.3 (d, C-8), 36.2 (t, C-22), 35.7 (d, C-20), 34.0 (d, C-10), 30.9 (t, C-7), 28.2 (t, C-16), 28.0 (d, C-25), 26.4 (t, C-3), 26.1 (t, C-11), 25.7 (t, C-2), 23.9 (t, C-15 and C-23), 22.8 (q, C-27), 22.6 (q, C-26), 18.7 (q, C-21), 14.7 (q, C-19), 12.0 (q, C-18).

Anal. Calcd. for $C_{27}H_{46}O$ ($M_r = 386.67$): C 83.87, H 11.99%; found: C 83.69, H 11.86%.

Acknowledgements. — The authors are grateful to Prof. G. Snatzke (Lehrstuhl für Strukturchemie, Ruhruniversität Bochum, West Germany) for his measurements and comments of CD spectra. The authors from Yugoslavia thank the *Serbian Academy of Sciences and Arts* and the *Serbian Research Fund,* and the authors from Belgium the SPPS (Belgium) for financial support.

REFERENCES

1. M. Lj. Mihailović, Lj. Lorenc, M. Rajković, I. Juranić, and A. Milovanović, *Heterocycles,* (in press).
2. M. Lj. Mihailović, Lj. Lorenc, N. Popov, and J. Kalvoda, *Helv. Chim. Acta* **54** (1971) 2281.
3. M. Lj. Mihailović, Lj. Lorenc, V. Pavlović, and J. Kalvoda, *Tetrahedron* **33** (1977) 441.
4. M. Lj. Mihailović, Lj. Lorenc, M. J. Gašić, M. Rogić, A. Melera, and M. Stefanović, *Tetrahedron* **22** (1966) 2345.
5. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq and M. M. Woolfson, (1980) MULTAN 80. A system of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data. Universities of York (England) and Louvain-la-Neuve (Belgium).
6. G. M. Sheldrick, (1976) SHELX 76. Program for Crystal Structure Determination. University of Cambridge, England.
7. S. Motherwell and W. Clegg, (1978) PLUTO, Univ. of Cambridge, England.
8. J. T. Przybytek, S. P. Singh, and J. Kagan, *Chem. Commun.* (1969) 1224.
9. M. Akhtar and S. Marsh, *J. Chem. Soc. (C)* (1966) 937.

IZVOD

Transanularna fotociklizacija kod (*E*)-3β-acetoksi-5,10-seko-1(10)-holesten-5-ona

Ljubinka Lorenc, Vladimir Pavlović, Mihailo Lj. Mihailović, Bernard Tinant, Jean-Paul Declercq i Maurice Van Meerssche

UV ozračivanjem (*E*)-5,10-seko-steroidnog ketona *1* u acetonskom rastvoru vrši se, pored ranije opisanih transformacija — tj. *E*/*Z*-izomerizacije i intramolekulske Paterno-Büchi-jeve reakcije (koja daje 1α,5α-oksetan *4* u prinosu od 42% i 1β,5β-oksetan *5* u prinosu od 2—3%) — još i transanularna ciklizacija (praćena eliminacijom sirćetne kiseline), pri čemu se gradi antrasteroidni enon *3* (u prinosu od oko 7%). Struktura proizvoda *3* izvedena je na osnovu spektralnih podataka a potvrđena je rendgenskom strukturnom analizom.