102. Synthesis, Structure, and Reactivity of Secosteroids Containing a Medium-Sized Ring

Part 36[1])

Transannular Photocyclization of Some Unsaturated 5,10-Secosteroidal Ketones: A Reevaluation

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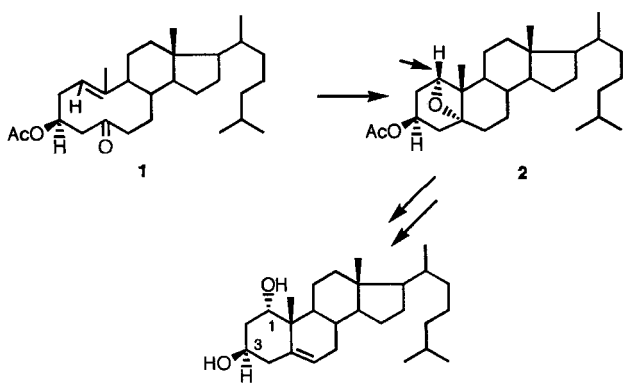
The structures **9** and **8** are proposed for the single isolated irradiation product of 5-oxo-5,10-secocholest-1(10)-en-3α-yl acetate (**6**) [2] and for the minor product of irradiation of 5-oxo-5,10-secocholest-1(10)-en-3β-yl acetate (**1**) [3], respectively. These compounds are formed in an alternative reaction with respect to the originally observed intramolecular *Paterno-Büchi* photoprocess (transformation of **1** to oxetane **2**). The formerly postulated 'active' conformations for **1** and **6** still allow explanation of their generation.

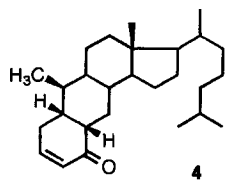
Introduction. – In the penultimate part of these series [2], we had summarized the results of the irradiation experiments on unsaturated 5,10-secosteroidal ketones and attempted to correlate the 'active' conformations of these medium-size-ring compounds with the structures of their photoproducts.

Scheme 1



[1]) Part 35: [1].

In a preliminary communication [3] as well as in more detailed papers [4] [5], the cyclization of the 3β-AcO derivative **1** to the oxetane **2** has been described (*Scheme 1*). The formation of this compound was interpreted as an intramolecular *Paterno-Büchi* reaction, and its structure was established by transformation into 1α-hydroxycholesterol (**3**) and by direct chemical correlation with the corresponding known saturated dihydroxycholestane [6]. In addition, an anthrasteroid (**4**) and a noncrystalline product, isomeric with **2**, were isolated in small amounts. In analogy to **2**, the oxetane structure **5** had been tentatively assigned [3] to the latter compound on the basis of its ^{1}H-NMR spectra.



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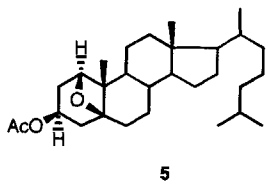
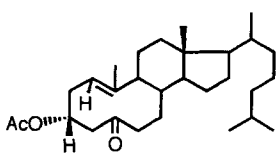


5

In [2], the photochemical transformation of a 3α-AcO secosteroid **6** to a single non-ketonic compound, epimeric at C(3) with **5**, was described. In analogy to **5**, the 1β,5β-oxido structure **7** was postulated for this photoproduct.



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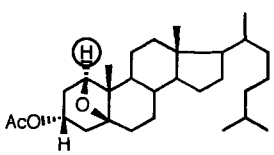


7

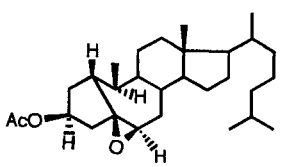
The unexpected high-field shift of the proton on the O-bearing C-atom in **5** and **7** compared to the chemical shift of the H_β–C(1) in oxetane **2** was explained by the missing deshielding effect of the C(9)–C(11) bond in these two compounds.

In connection with another project, one of the authors (*R.H.*) compared the chemical shifts of the α-protons of a series of steroidal *oxetanes* of an established structure (*cf. e.g.* [7] [8]), and noticed that all of them were in a narrow range of 4.4 ± 0.5 ppm, comparable to those observed for the oxetane **2** (3.95 ppm), and none at a field as high as for **5** and **7** (3.05 and 3.07 ppm, resp.). These last two values are, however, perfectly in accordance to the chemical-shifts values of *oxirane* protons.

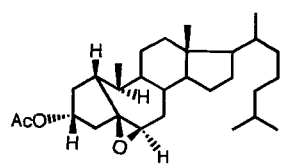
We decided, therefore, to reexamine the structure of the irradiation products, originally proposed as **5** and **7**, of the 3α-OH analogue of **7** as well as of the newly synthesized 3α-benzoate derivative (*cf. Exper. Part*) on the basis of a detailed interpretation of the ^{1}H- and ^{13}C-NMR spectra and of additional mechanistic considerations.

NMR Analysis. – The ^{1}H- and ^{13}C-NMR spectra of the deacetyl analogue of **7** and of the corresponding 3α-benzoate were recorded. Interpretation of the NMR data of the free OH compound afforded the following results: *1*) From the ^{13}C signals due to a DEPT spectrum follows that the 27 C-atoms of the molecule are subdivided into the following

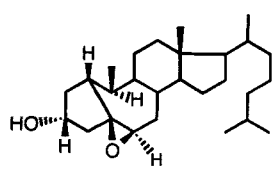
species: 5 Me, 10 CH_2, 10 CH, and 2 quaternary C-atoms. This finding is not in agreement with the originally proposed structure **7** for the Ac analogue of the compound. *2*) The ^1H chemical shift of the proton on the second O-bearing C-atom at 3.05 ppm is indeed not compatible with the presence of an oxetane ring. It corresponds, however, as mentioned above, to the expected position of an oxirane CH signal. The presence of an epoxide ring in the molecule is further supported by the ^{13}C-NMR data of the proton-bearing C-atom attached to an O-atom (δ(–O–CH–) = 59.4 ppm, $^1J(^{13}C,^1H)$ = 167 Hz). *3*) The five Me groups detected in the molecule can be again divided into two classes: 4 secondary Me groups (3 of them belonging to the cholestane side chain) and one tertiary Me group (the Me(18) signal). Therefore, the remaining secondary Me group has to correspond to Me(19). In the ^1H-NMR spectrum of the compound in $CDCl_3$ solution, the Me region of the spectrum is so heavily overlapped that the presence of an additional secondary Me *doublet*, instead of the usual *singlet* due to Me(19), cannot be detected. In the ^1H-NMR spectrum of the compound dissolved in a mixture (D_6)benzene/$CDCl_3$, however, 3 *doublets* (one due to the i-Pr group attached to C(25) (6 H), one due to the Me group attached to C(20), and finally the original Me(19) as a *secondary* Me group) could clearly be observed. *4*) Under the assumption that Me(19) does not migrate during the irradiation process and remains attached to C(10), and that an epoxide ring containing a methine C-atom and a quaternary C-atom is present in the molecule, a mechanistically plausible route to an isomeric structure fulfilling all the above conditions was proposed. This arrangement with a yet not established configuration at the four newly formed chiral centers is represented by structure **10**. *5*) With the help of extended NOE experiments, 2D-NMR spectra (*e.g.* E-COSY), we were finally able to propose also the given (relative) configuration for the free hydroxy compound **10**. In analogy, the structures **9**, **11**, and **8**



8 (originally **5**)



9 (originally **7**)



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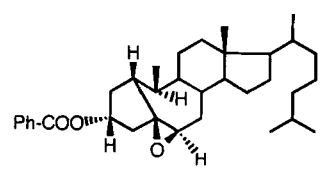

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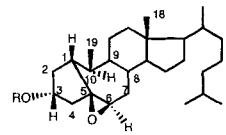
could be assigned to the corresponding acetate and benzoate derivatives, and to the epimeric 3β-acetate (originally **5**), respectively. *6*) In *Table 1*, selected ^1H- and ^{13}C-NMR chemical shifts of the compounds **10** and **11**, and in *Table 2* some characteristic NOE's are listed.

On the basis of a simple CAMM analysis, two preferred conformations (*cf.* **A** and **B** in *Fig. 1*) were taken into consideration for the seven-membered ring in compounds **8**–**11**.

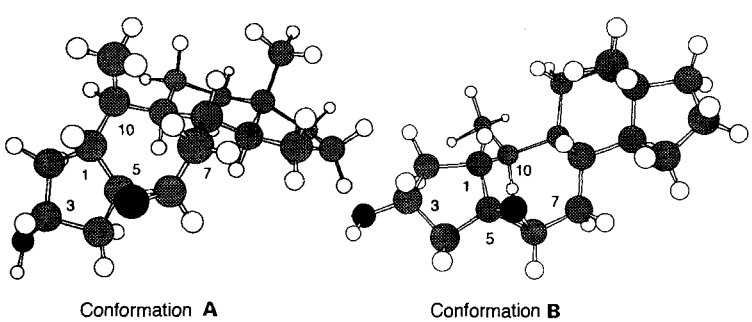
Table 1. *Selected ^{1}H- and ^{13}C-NMR Data* (in $CDCl_3$; for ^{1}H at 360.1 MHz, for ^{13}C at 90.6 MHz) *of Compounds* **10** *and* **11**



10 R = OH					**11** R = O–CO–Ph			
^{1}H	$\delta(^1H)$	^{13}C	$\delta(^{13}C)$	^1J(C,H)	^{1}H	$\delta(^1H)$	^{13}C	$\delta(^{13}C)$
H–C(1)	1.99 (*m*)	C(1)	41.1	128	H–C(1)	2.06	C(1)	42.1
H_β–C(2), H_α–C(2)	2.14 (*m*), 1.58 (*m*)	C(2)	40.4	132	H_β–C(2), H_α–C(2)	2.32 (*m*), 1.94 (*m*)	C(2)	36.9
H_β–C(3)	4.41 (*m*)	C(3)	71.5	146	H_β–C(3)	5.53 (*m*)	C(3)	75.4
H_β–C(4), H_α–C(4)	1.93, 1.87 (*ABC*)	C(4)	44.1	131	H_β–C(4), H_α–C(4)	2.21 (*d*)	C(4)	40.8
–	–	C(5)	70.1	–	–	–	C(5)	70.1
H_α–C(6)	3.04 (*dd*)	C(6)	59.4	167	H_α–C(6)	3.14 (*dd*)	C(6)	59.7
H_β–C(7), H_α–C(7)	1.84 (*m*), 1.75 (*m*)	C(7)	30.3	125	H_β–C(7), H_α–C(7)	1.52 (*m*)	C(7)	30.6
H–C(8)	1.95 (*m*)	C(8)	37.7	124	H–C(8)	1.98 (*m*)	C(8)	35.1
H–C(9)	1.22 (*m*)	C(9)	49.3	122	H–C(9)	1.35 (*m*)	C(9)	48.6
H–C(10)	1.45 (*m*)	C(10)	31.6	123	H–C(10)	1.51 (*m*)	C(10)	31.9
Me(18)	0.66 (*s*)	C(18)	12.2	124	Me(18)	0.69 (*s*)	C(18)	12.1
Me(19)	0.86 (*d*)	C(19)	16.8	127	Me(19)	0.88 (*d*)	C(19)	16.7

Table 2. *NOE Data for Compound* **10**

Irradiation of	NOE [%]
H_β–C(2)	H_α–C(2) (18), H_β–C(1) (6), H_β–C(3) (9.5)
H_β–C(1)	H_β–C(2) (6), Me(19) (5)
Me(19)	H_α–C(10) (5)
H_β–C(3)	H_β–C(2) (5), H_β–C(4) (6)
H_α–C(6)	H_β–C(4) and H_α–C(4) (7), H_β–C(7) (5)



Conformation **A** Conformation **B**

Fig. 1. *Preferred conformations of the seven-membered ring in compounds* **8**–**11**

X-Ray Crystal-Structure Analysis of Compound 10. – Crystal data[2]) are given in *Table 3*. Cell constants were determined by a least-squares fit to the Θ values of 25 independent reflections. Data were reduced, and *Lorentz*, polarization, and decomposition corrections were applied. The structure was solved by direct methods using program SHELXS-86 [9]. H-Atom positions were calculated assuming normal geometry.

Table 3. *Crystal Data for Compound* **10**

Formula	$C_{27}H_{46}O_2$	Radiation	graphite monochromated CuK_α
Mol. wt.	402.66	Wavelength [Å]	1.5418
Crystal system	monoclinic	Scan mode	Θ–2Θ
Space group	$P2_1$	Scan range (2Θ)	6–150
a [Å]	6.300(1)	No. of unique reflections	2888
b [Å]	8.166(1)	No. of observed reflections ($> 3\sigma(I)$)	2286
c [Å]	25.026(5)	Refinement method	full matrix
β [°]	91.47(1)	No. of parameters	262
V [Å^3]	1287(1)	R	0.083
Z	2	R_w	0.091
$D_{calc.}$ [g·cm^{-3}]	1.039	Weighting scheme	$1/\sigma^2(F)$
Crystal size [mm]	0.65 × 0.65 × 0.02	Max/min density in final	0.451/−0.349
Diffractometer	*Enraf-Nonius CAD4*	difference map [eÅ^{-3}]	

The drawing was prepared by the program SCHAKAL 92 [10]. Tables of coordinates, bond lengths, and angles were deposited with the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EW, England.

The X-ray structure analysis of compound **10** (*Fig. 2*) performed in our laboratories[3]) confirmed the structures proposed for the compounds **8**–**11**. The steric arrangement of the ring *B* was shown to be similar to conformation *B* in *Fig. 1*.

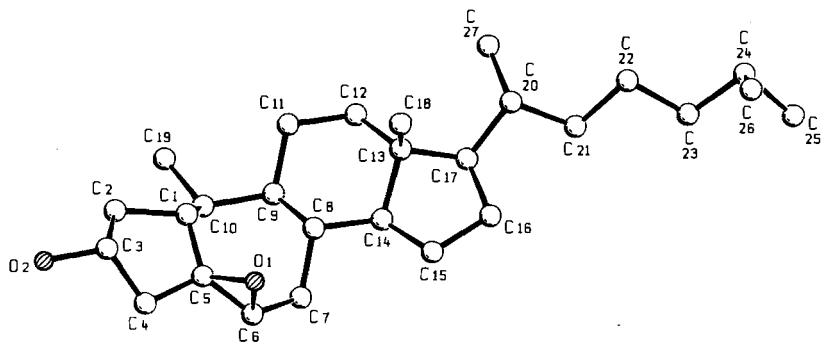


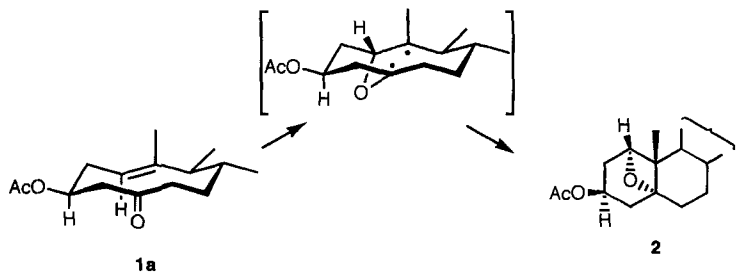
Fig. 2. *X-Ray structure of compound* **10**

[2]) For analytical data, *cf.* [2].

[3]) We would like to acknowledge the important contribution of the X-Ray Laboratories of *Ciba-Geigy* to the final evidence for the proposed structure.

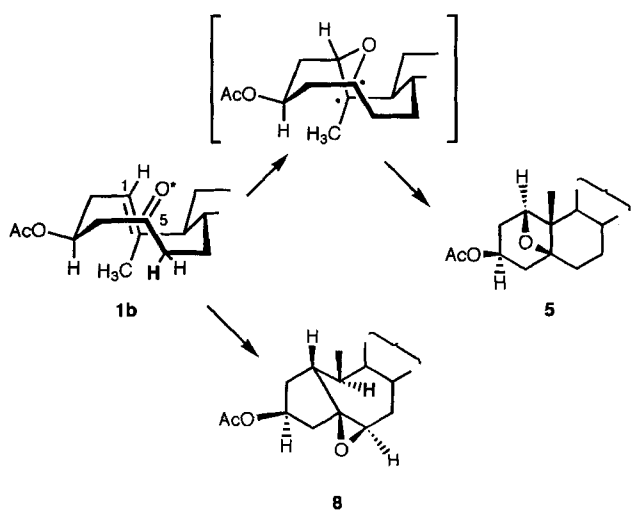
Discussion. – The formation of compound **2** and its configuration have been originally [1] explained by '... an initial attack of the O-atom of the excited carbonyl in its n,π^* singlet or triplet state at the transannular 1(10)-olefinic π-system...' in its preferred ground-state conformation **1a** (*Scheme 2*).

Scheme 2



On the other hand, conformation **1b**[4]) was postulated to be involved in the formation of the erroneous, not yet isolated structure **5** (*Scheme 3*).

Scheme 3



The same conformation **1b** may, indeed, explain the generation of the epoxide structure **8**, although, in this case, a primary attack of a C(5)-centered radical at the C(1) end of the C(1)=C(2) bond would have to be postulated, followed by a shift of the (*pro-S*)-H-atom at C(6) to C(10) and by the formation of the oxirane ring.

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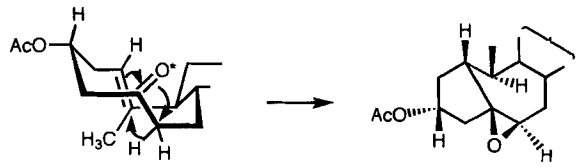
[4]) Structure **1b** has not been detected in solution but represents the main (calculated) conformation in the gas phase [11].

The preferred conformation of the 3α-acetoxy-5,10-secosteroid ketone **6** in solution was deduced [12] to be **6a**. As shown in *Scheme 4*, it could also explain the stereochemical aspects of the formation of **9**.

Scheme 4



6a **9**

Experimental Part

*Preparation of 5,6β-Epoxy-5(10→1)*abeo-*1β*H,*10α*H-*5β-cholestan-3α-yl Benzoate* (**11**). To a soln. of *5,6β-epoxy-5(10→1)*abeo-*1β*H,*10α*H-*5β-cholestan-3α-ol* (**10**; 100 mg) in dry pyridine (2 ml), an excess of benzoyl chloride (1.22 ml) was added. After standing overnight at r.t., the mixture was poured into ice-cold water, the precipitate filtered off, washed with H_2O, and air-dried. The rest was dissolved in benzene, the resulting soln. passed through a short SiO_2 column, evaporated *in vacuo* to dryness, and the residue (115 mg, 91.4%) was recrystallized from acetone/MeOH to give **11** (86 mg, 68.3%). M.p. 136–136.5°. $[\alpha]_D = +53.3$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3061*w*, 2950*s*, 2861*s*, 1714*s*, 1602*w*, 1585*w*, 1278*s*, 1117*s*, 707*s*. For ^{1}H- and ^{13}C-NMR, *cf. Table 1*. Anal. calc. for $C_{34}H_{50}O_3$ (506.774): C 80.58, H 9.95; found: C 80.31, H 9.78.

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