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

Part 32[1])

Conformations and Photochemical Reactivity of Some Unsaturated 5,10-Secosteroidal Ketones

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Dedicated to Professor *Kurt Schaffner* on the occasion of his 60th birthday

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UV irradiation of the unsaturated (*E*)-5,10-secosteroidal ketones **1** and **6** results, in addition to (*E*/*Z*)-isomerization, in an intramolecular *Paterno-Büchi* reaction and, in the case of **1**, in transannular cyclization (along with AcOH elimination). The stereochemistry of the observed intramolecular photoprocesses can be explained in terms of ground-state conformations of the (*E*)-seco-ketones **1** and **6** in solution.

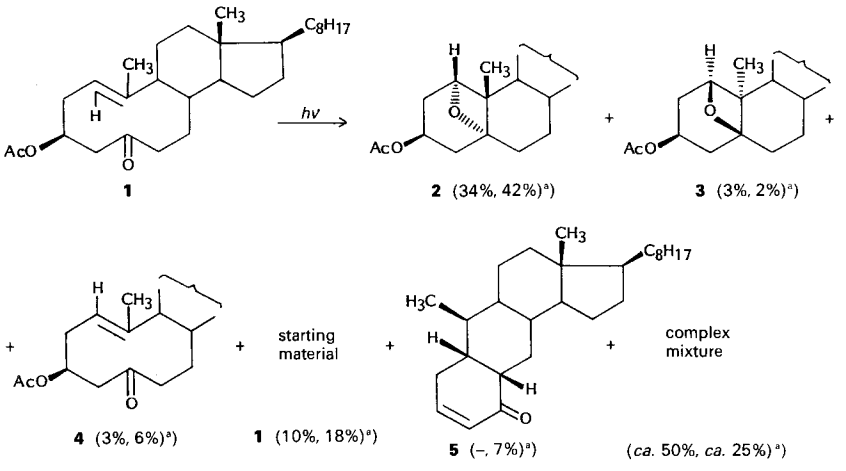
Introduction. – The effect of ground-state conformations on the photochemical reactivity and product distribution is a subject of considerable interest [2]. In this paper, we wish to report on the photochemical behaviour of some unconjugated bichromophoric systems containing a keto group and olefinic double bond incorporated in the ten-membered ring of 5,10-secosteroids **1** and **6** (*Schemes 1* and *2*, resp.). Since, on the basis of ^{1}H-NMR and ^{13}C-NMR spectral data, the main conformational forms of the medium-sized ring in 5,10-secosteroids have been determined in solution [3] [4], it was possible to correlate the ground-state conformations of these molecules with their photoproducts.

As previously reported [5], UV irradiation of (*E*)-5-oxo-5,10-secocholest-1(10)-en-3β-yl acetate (**1**) in dioxane or acetone solution with a high-pressure mercury lamp (*TQ 150 Z2*) for 3.5 h resulted in an intramolecular *Paterno-Büchi* reaction to give a 1α,5α-epoxy derivative **2** (main product) and its 1β,5β-isomer **3** (minor component). Concomitant photochemical transformations were (*E*/*Z*)-isomerization (→**4**) and, in acetone solution, transannular cyclization accompanied by AcOH elimination to produce a 1β,6β,10β(CH_3)-anthrasteroidal enone **5** (*Scheme 1*).

In the present study, we investigated the photolysis of the corresponding 3α-epimer, *i.e.* (*E*)-5-oxo-5,10-secocholest-1(10)-en-3α-yl acetate (**6**) [4].

[1]) Part 31: [1].

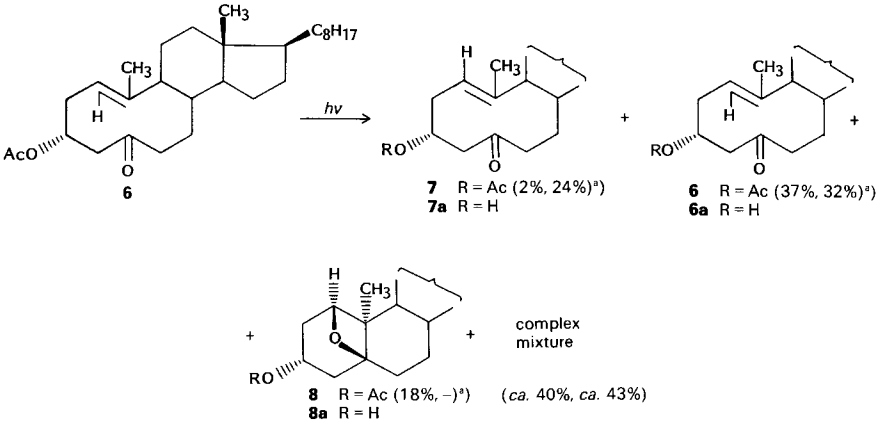
Scheme 1



a) The first value refers to irradiation in dioxane, the second one to irradiation in acetone.

Results and Discussion. – For comparison purposes, (*E*)-3α-acetate **6** was irradiated under conditions similar to those previously applied to the isomeric (*E*)-3β-acetate **1** (see above). It was found that **6** also underwent (*E*/*Z*)-isomerization (to give (*Z*)-3α-acetate **7**)[2]) and, in dioxane solution, intramolecular oxetane formation; but in this case, only the 1β,5β-configurated isomer **8** was obtained (*Scheme 2*)[3]).

Scheme 2



a) See *Footnote a* in *Scheme 1*.

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[2]) When (*Z*)-5-oxo-5,10-secocholest-1(10)-en-3α-yl acetate (**7**) was exposed to UV light under analogous experimental conditions, it was first isomerized to the (*E*)-derivative **6**, which reacted further as shown in *Scheme 2*.

[3]) (*Z*)- and (*E*)-3α-acetates **6**/**7** were separated in the form of the corresponding 3α-hydroxy compounds **6a** and **7a**.

The structure of (*Z*)-3α-acetate **7** was determined by direct comparison with an authentic sample [6], while that of compound **8** was established by elemental microanalysis and spectral data. Saponification of epoxy-3α-acetate **8** gave the corresponding 3α-hydroxy compound **8a** (*Scheme 2*), which was reacetylated to **8**.

The configuration of the epoxy bridge in **8** and **8a** was deduced from their ^{1}H- and ^{13}C-NMR spectral data, which were compared with those of the corresponding epoxy-3β-acetates **2** and **3** of known configuration. Thus, the ^{1}H-NMR signal of H–C(1) of **8** and **8a** appears at δ 3.08 and 3.06, respectively, close to δ 3.05, observed for H–C(1) of **3** (H_β–C(1) of **2** is deshielded by the C(9)–C(11) bond and appears at considerably lower field (3.95 ppm)). Similarity in spatial orientation of the epoxy bridge in **3** and **8a** is also evident from their ^{13}C-NMR spectra (*Table*).

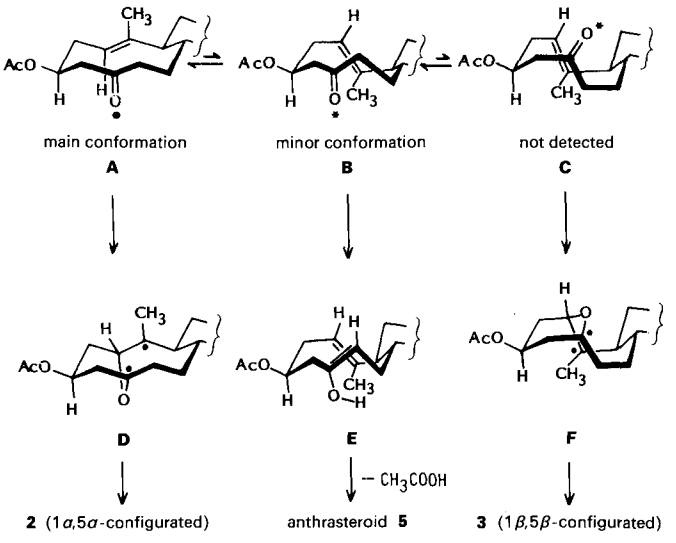
Table. *Selected ^{13}C-NMR Chemical Shifts* (ppm rel. to TMS) *of* **2**, **3**, *and* **8a**[a])

	1α,5α-Epoxy-3β-acetate	1β,5β-Epoxy-3β-acetate	1β,5β-Epoxy-3α-ol		1α,5α-Epoxy-3β-acetate	1β,5β-Epoxy-3β-acetate	1β,5β-Epoxy-3α-ol
C(1)	83.2	58.5	59.5	C(7)	27.8	30.2	30.2
C(2)	31.6	29.7	37.6	C(8)	38.7	37.8	40.4
C(3)	66.7	74.3	71.3	C(9)	47.0	49.3	49.3
C(4)	42.5	37.5	44.0	C(10)	34.2	41.0	41.0
C(5)	88.5	70.0	70.2	C(18)	11.8	12.4	12.2
C(6)	31.0	31.8	31.6	C(19)	11.7	16.5	16.8

[a]) Measured in $CDCl_3$ at 25.2 MHz.

The stereochemistry of these transannular photoprocesses leading to oxetanes **2**/**3** and **8** can be explained in terms of the ground-state conformation of the (*E*)-seco-ketones **1** and **6**, respectively, in solution. In accordance with the stepwise mechanism suggested for similar examples of the *Paterno-Büchi* reaction [7], an initial attack of the O-atom of the excited carbonyl group in its n,π^* singlet or triplet state at the transannular 1(10)-olefinic π-system is assumed, producing a thermodynamically more stable C(5),C(10)-biradical.

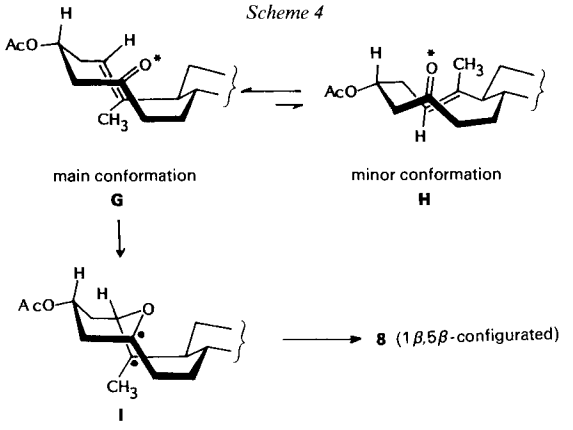
Scheme 3



The stereochemical course of this and also of the next cyclization step (which can occur either directly or after spin inversion, depending on the spin multiplicity) is determined by the conformations **A**–**C** and **G** and **H** of the ten-membered ring in **1** and **6**, respectively. ^{1}H- and ^{13}C-NMR studies have shown that (*E*)-3β-acetate **1** exists in solution predominantly (*ca.* 85%) in conformation **A** (*Scheme 3*) [3]. A conformation of this type could produce (*via* the 5,10-biradical **D**) an oxetane with 1α,5α-configuration; actually, 1α,5α-derivative **2** was the major photoproduct of **1** (isolated in 34 and 42% yield in dioxane and acetone, resp.). The other detected, but less populated (*ca.* 15%) conformer **B** of **1** in solution is obviously unfavourable for closure to the oxetane ring; however, it can explain the stereospecific formation of the 1β,6β,10β(CH_3)-anthrasteroidal enone **5** (*ca.* 7% yield). This transannular cyclization most probably involves photoenolization towards the C(6)-atom (→**E**), followed by intramolecular rearrangement *via* a cyclic six-membered species (along with AcOH elimination; see *Scheme 3*). The minor 1β,5β-derivative **3** (only 2–3% yield) can be correlated (*via* 5,10-biradical **F**) with conformer **C**, although the latter was not observed in solution by NMR techniques.

The (*E*)-3α-acetate **6** which, according to NMR analysis, exists in solution in the two conformations **G** and **H** (*ca.* 6:1) [4] undergoes transannular *Paterno-Büchi* reaction only in its main conformation **G**, producing thus (in dioxane solution *via* **I**) the 1β,5β-derivative **8** as the sole transannular photoproduct (*ca.* 18% yield; *Scheme 4*).

Scheme 4



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Experimental Part

1. *General.* Prep. column chromatography (CC): 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. M.p.: uncorrected. IR spectra: *Perkin-Elmer-337* spectrophotometer; in cm^{-1}. NMR spectra: ^{1}H (360 MHz), *Bruker HX-360;* noise-decoupled ^{13}C (25.15 MHz), *Varian XL-100* spectrometer equipped with a *Fourier*-transform accessory; $CDCl_3$ soln. at r.t., TMS as internal standard; chemical shifts in ppm as δ values.

2. *UV Irradiation of* **6** *in Acetone.* A soln. of **6** (250 mg) in acetone (250 ml) was irradiated with a high-pressure mercury lamp *TQ 150 Z2* (*Hanau*) at r.t. for 3.5 h. The mixture was then evaporated and the oily residue (286 mg)

submitted to CC (silica gel (15 g), benzene/Et_2O 97:3): crystalline **6**/**7** (148 mg). Further elution with benzene/Et_2O 95:5, 90:10, and 80:20 afforded an unresolvable mixture (106 mg, *ca.* 42%), which was not further investigated.

Separation of **6**/**7**. To the above mixture **6**/**7** (148 mg) in MeOH (30 ml), 15 ml of 5% KOH/MeOH were added. The resulting soln. was left for 12 h in a refrigerator, concentrated *in vacuo* at r.t. to *ca.* 15 ml, diluted with H_2O, and extracted with Et_2O. The org. layer was washed with H_2O until neutral, dried (Na_2SO_4), and evaporated. CC (silica gel (7.5 g), benzene/Et_2O 90:10) yielded 57 mg of *(Z)-3α-hydroxy-5,10-secocholest-1(10)-en-5-one* (**7a**; m.p. 114–116°; [5]: m.p. 116°). Acetylation (Ac_2O/pyridine 1:1 (2 ml), overnight at r.t.) gave, after usual workup, *(Z)-5-oxo-5,10-secocholest-1(10)-en-3α-yl acetate* (**7**; 60 mg, 24.0% rel. to starting **6**). M.p. 138° (from acetone/MeOH; [6]: m.p. 138°). Spectral data of **7**: identical with those of an authentic sample.

Further elution with benzene/Et_2O 85:15 afforded 77 mg of *(E)-3α-hydroxy-5,10-secocholest-1(10)-en-5-one* (**6a**) as an oil ([4]: oil). It was acetylated as described above: *(E)-5-oxo-5,10-secocholest-1(10)-en-3α-yl acetate* (**6**) (81 mg, 32.4% rel. to starting **6**).

3. *UV Irradiation of* **6** *in Dioxane.* A soln. of **6** (250 mg) in dioxane (250 ml) was irradiated and worked up as described in *Exper. 2*. CC (silica gel (15 g), benzene/Et_2O 97:3) of the oily residue (263 mg) yielded **6**/**7**/**8** (160 mg). Further elution with benzene/Et_2O 95:5, 90:10, and 80:20 gave fractions containing a complex mixture (99 mg, *ca.* 40%) which was not further investigated.

Separation of **6**/**7**/**8**. To a stirred and cooled (0–5°) soln. of **6**/**7**/**8** (160 mg) in MeOH (12 ml), $NaBH_4$ (65 mg) was gradually added. After 0.5 h, the mixture was diluted with H_2O, acidified with 10% aq. H_2SO_4 soln., and extracted with Et_2O. The org. layer was washed with H_2O, sat. aq. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated. The residue (164 mg) was chromatographed on silica gel (7.5 g). Elution with benzene/Et_2O 97:3 afforded *1β,5-epoxy-5β,10α-cholestan-3α-yl acetate* (**8**; 45 mg, 18% rel. to starting **6**). Oil. $[\alpha]_D^{20} = +21.7$ ($c = 0.92$, $CHCl_3$). IR (CCl_4): 1738*s*, 1240*s*, 1040*s*. ^{1}H-NMR: 0.70 (*s*, CH_3(18)); 0.87 (*d*, CH_3(26), CH_3(27)); 0.89 (*d*, CH_3(21)); 0.91 (*s*, CH_3(19)); 1.97 (*s*, AcO); 3.08 (*dd*, $J = 6$, 2.4, H–C(1)); 5.18 (*m*, H–C(3)). Anal. calc. for $C_{29}H_{48}O_3$ (444.70): C 78.33, H 10.88; found: C 78.13, H 10.64.

Benzene/Et_2O 95:5 eluted a mixture (108 mg), which was oxidized with a slight excess of *Kiliani*'s CrO_3 soln. [8]. The resulting mixture **6**/**7** (104 mg), isolated after usual workup, was dissolved in MeOH (20 ml) and hydrolyzed with a 5% KOH/MeOH (10 ml) affording **6a**/**7a** (94 mg). Separation by CC (silica gel (7.5 g)) and acetylation as described above gave 6 mg (2.4%) of **7** and 92 mg (36.8%) of **6** (yields rel. to starting **6**).

4. *UV Irradiation of* **7** *in Acetone or Dioxane.* A soln. of **7** (250 mg) in acetone (250 ml) or dioxane (250 ml) was irradiated and worked up as described in *Exper. 2* and *3*, resp. Acetone soln.: 53 mg (21.2%) of **7**, 76 mg (30.4%) of **6**, and 112 mg (*ca.* 45%) of a complex mixture. Dioxane soln.: 32 mg (12.8%) of **8**, 5 mg (2.0%) of **7**, 106 mg (42.4%) of **6**, and 102 mg (*ca.* 40%) of a complex mixture.

5. *Alkaline Hydrolysis of* **8**. A soln. of **8** (175 mg) in MeOH (30 ml) was treated with 5 ml of 5% KOH/MeOH and worked up as described in *Exper. 2* (overnight at r.t.) (concentration to *ca.* 10 ml). CC (silica gel (5 g), benzene/Et_2O 9:1) of the oil (160 mg) gave *1β,5-epoxy-5β,10α-cholestan-3α-ol* (**8a**; 115 mg, 72.8%). M.p. 104–106° (from acetone/MeOH). $[\alpha]_D^{20} = +40.2$ ($c = 1.00$, $CHCl_3$). IR (KBr): 3460*s*, 1070*s*. ^{1}H-NMR: 0.68 (*s*, CH_3(18)); 0.86 (*d*, CH_3(26), CH_3(27)); 0.89 (*d*, CH_3(21)); 0.91 (*s*, CH_3(19)); 1.97 (*s*, AcO); 3.06 (*dd*, $J = 6$, 2.4, H–C(1)). Anal. calc. for $C_{27}H_{46}O_2$ (402.6): C 80.54, H 11.51; found: C 80.38, H 11.33.

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