185. Conformations of the 10-membered Ring in 5,10-Secosteroids. II[1])[2]). (*E*)-3α-Acetoxy-5,10-*seco*-1(10)-cholesten-5-one and (*E*)-5,10-*seco*-1(10)-cholestene-3,5-dione

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Summary

(*E*)-3α-Acetoxy-5,10-*seco*-1(10)-cholesten-5-one (**3**) was synthesized by fragmentation of 3α-acetoxy-5α-cholestan-5-ol (**1**) using the photochemical version [3] of the lead tetraacetate reaction [4], and transformed into the corresponding 3-oxo-compound (**5**). Two conformations ($\mathbf{A}_2^{\alpha}$ and $\mathbf{B}_1^{\alpha}$) were deduced for the 10-membered ring of **3** by analysis of the ^{1}H- and ^{13}C-NMR. spectra in toluene. The major conformation ($\mathbf{A}_2^{\alpha}$) corresponds to that found in the solid state by X-ray analysis. According to its NMR. spectra in toluene, the medium-sized ring of the diketone **5** exists also predominantly in two conformations, the major one being analogous to $\mathbf{A}_1^{\beta}$ (the solid-state conformation of the 3β-acetoxy isomer (**9**) [1]) and the minor one to $\mathbf{A}_2^{\alpha}$ (see above). The stereochemistry of the acid-catalyzed and thermal cyclisations of **3** as well as of the corresponding 5-oxime is discussed in terms of conformational factors.

Introduction. - In the first paper of this series [1] we have discussed the conformations of the 10-membered ring of (*E*)-3β-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (**9**) and the corresponding 3β-*p*-bromobenzoate ester. By postulating an *equatorial* arrangement for the 3-acetoxy group or deducing it from the spectral parameters, the number of formally acceptable conformations was reduced to a set of four ($\mathbf{A}_1^{\beta}$, $\mathbf{A}_2^{\beta}$, $\mathbf{B}_1^{\beta}$ and $\mathbf{B}_2^{\beta}$, *cf. Scheme 1*). It could be shown by NMR. spectroscopy of **9** that in chloroform and toluene the compound exists in at least two forms, a major conformation corresponding to the 'crown'-type $\mathbf{A}_1^{\beta}$, and a minor one of type $\mathbf{B}_2^{\beta}$. Interestingly, in the solid state, the $\mathbf{A}_1^{\beta}$ conformation was again found for the ring-AB portion of the molecule. Transannular interactions of the double bond with the carbonyl group have been postulated to explain the unexpected thermodynamic stability of the 'crown'-type arrangement.

1) Part I: [1].
2) Part XV in the series 'Synthesis, Structure and Reactions of Secosteroids Containing a medium-sized Ring'. Part XIV: [2].
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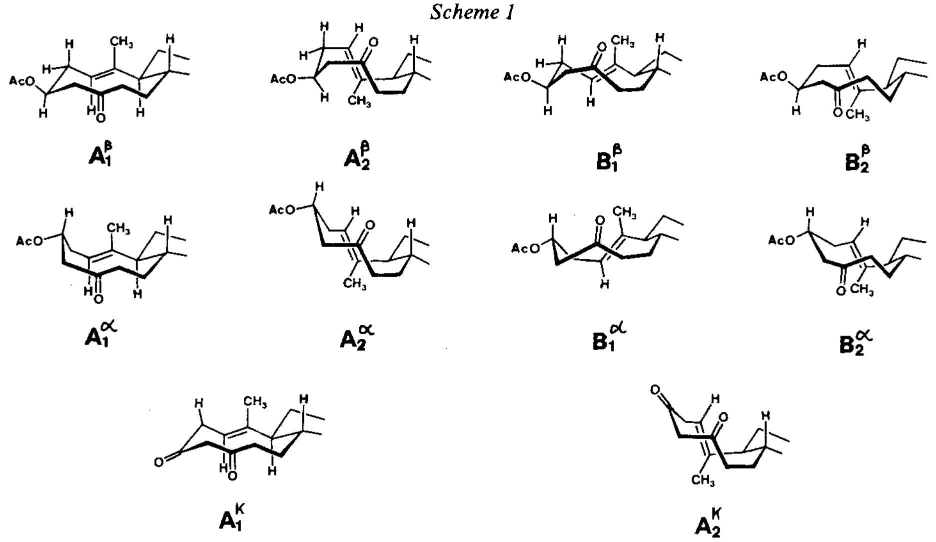
Scheme 1



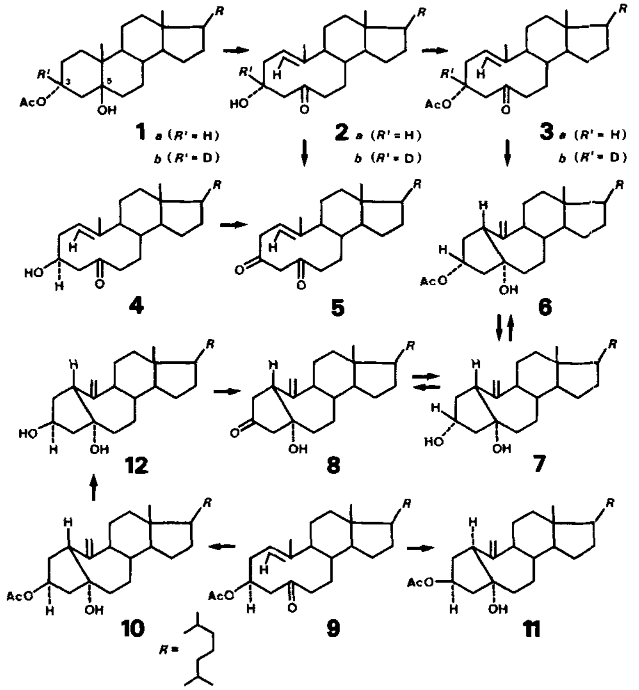
Pursuing our work in the field of the secosteroids containing a medium-sized ring (*e.g.* [1] [2]), we wished to synthesize the 3α-acetoxy and 3-oxo analogues **3** and **5** of the above 5,10-seco compound **9**, in order to examine their respective ground state conformations and to study their reactivity.

1. Chemistry. - The easily available 5β-hydroxy-compound **1a** [5] was the most adequate starting material for the planned synthesis. The lead tetraacetate reaction [6], as well as the hypoiodite reaction [7] have been used for the fragmentation of 5-hydroxy-steroids to the corresponding 5,10-*seco*-compounds. Since the mild photochemical version [3] of the lead tetraacetate reaction has advantages over the usual thermal procedure, the 5-hydroxy compound **1a** was irradiated in benzene solution, in the presence of lead tetraacetate. The crude reaction mixture consisting of both the (*Z*)- and (*E*)-isomers was hydrolyzed, and subsequently separated by column chromatography, affording the desired (*E*)-3α-hydroxy-5,10-*seco*-1(10)-cholesten-5-one (**2a**) *(Scheme 2)* in 36% yield. Under the usual acetylation conditions **2a** was transformed into the corresponding 3α-acetate **3a**. For NMR. studies (*cf.* p. 1776) the deuteriated analogue **3b** was prepared by a similar procedure, starting from the known 5-hydroxy-5β-cholestan-3-one [5], *via* **1b** and **2b**.

On the other hand, **2a** was oxidized by chromic acid/pyridine, affording the diketone **5**. The same compound was obtained by oxidation of the known epimeric 3β-hydroxy analogue **4** [6b], thus confirming the postulated structures of **2** and **3**.

Since (*E*)-cyclodecenones of similar type easily undergo thermal and acid-catalyzed cyclisations [6b] [8], compound **3a** was treated under both conditions. The acid-catalyzed cyclisation using hydrochloric acid in chloroform (4 h at 0°) afforded the expected 5(10→1βH)*abeo*-5α-cholest-1(19)-ene-3α,5α-diol 3-acetate **6** in a yield of *ca.* 37%. Under thermal conditions, refluxing **3a** in toluene or ethanol, a maximum of 18% of the same compound could be obtained.

Scheme 2



To determine the configuration at the junction of the 5- and 7-membered ring of **6**, this hydroxy acetate was saponified to the diol **7** and the latter oxidized to give the hydroxy ketone **8**. This compound was obtained previously by oxidation of the known $3\beta,5\beta$-diol **12** [8]. Since the two envisaged centres, C(1) and C(5), were not involved in the reactions, the configuration at these two carbon atoms must be identical in both series, *i.e.* in compounds **6** and **7** as well as in **10** and **12**.

In *Table 1* the course of the thermal and acid-catalyzed cyclisations of the 3α- and 3β-acyloxy analogues **3** and **9** are compared[6]).

Another reaction sequence known from the 3β-series [6b] [9], the cyclization of **9** to the isoxazolidine **13** (*via* intramolecular 1,3-dipolar cycloaddition of a nitrone-type intermediate to the 1(10)-double bond), was also applied to the 3α-isomer **3a** *(Scheme 3)* [9].

Upon refluxing a solution of the 3α-acetoxy-secosteroid **3a** in ethanol/pyridine in presence of an excess of hydroxylamine hydrochloride for 14 h, a mixture containing 39% of the isoxazolidine **17** and 27% of the oxime of **3a** was obtained and separated by chromatography (the 3β-acetoxy-*seco*-ketone **9**, under the same conditions but after only 5 h of reflux, afforded 97% of the corresponding isoxazolidine **13** (see *Table 1*)). To confirm the postulated structure for **17**, it was *N*-acetylated and the acetamide **18** thus formed hydrolyzed to give the free alcohol **19**. Subsequent oxidation (chromic acid/pyridine) generated a ketone with the

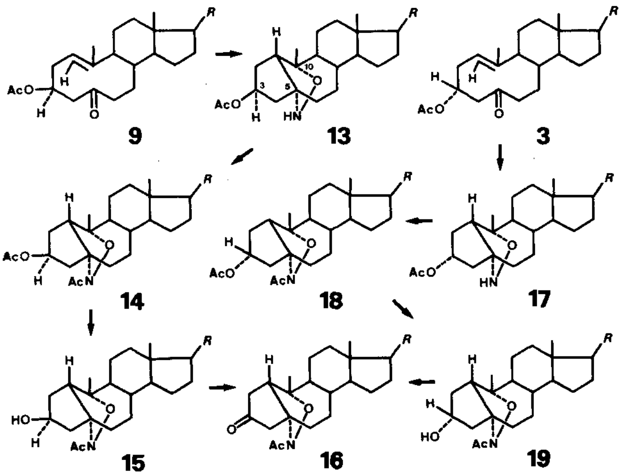
[6]) For the discussion of the results *cf.* p. 1780.

Table 1. *Conditions and yield of the thermal and acid-catalyzed cyclisation of compounds* **3a** *and* **9**

Starting compound	Conditions	Composition of the product
9 (3β)	Toluene reflux, 16 h	**10** (44%) + **9** (41%)
	Ethanol reflux, 36 h	**10** (31%) + **9** (62%)
	$CHCl_3$/HCl 0°, 4 h	**10** (81%) + **11** (9%) + **9** (< 5%)
	$NH_2OH \cdot HCl$ ethanol/pyridine reflux, 5 h	**13** (97%)
3a (3α)	Toluene reflux, 16 h	**6** (18%) + **3a** (82%)
	Ethanol reflux, 36 h	**6** (8%) + **3a** (92%)
	$CHCl_3$/HCl, 0°, 4 h	**6** (37.5%) + **3a** (61%)
	$NH_2OH \cdot HCl$ ethanol/pyridine reflux, 14 h	**17** (39%) + oxime of **3a** (27%)[a]

[a]) The rest consisted of a complex mixture, not further investigated.

Scheme 3

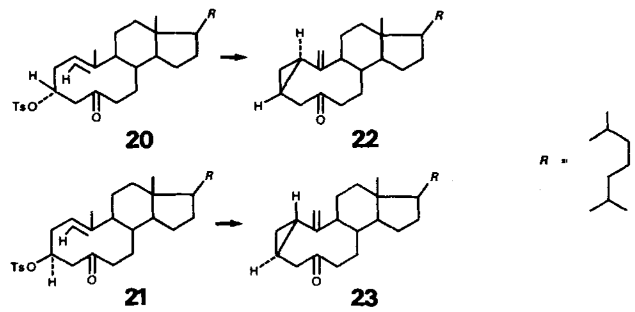


expected characteristics. By direct comparison it was shown to be identical with the known ketone **16** formed from the 3β-acetate **9** [9] *via* **13**, **14** and **15** by an analogous series of reactions *(Scheme 3)*.

Compounds **3** and **9** contain a homoallylic system, which could possibly participate in an *i*-steroid-type rearrangement. The corresponding tosylates **20** and **21** were therefore solvolyzed under reflux in acetone/water 9:1 in the presence of anhydrous potassium acetate. The respective cyclopropane derivatives **22** and **23** were thereby obtained (among other products) and their molecular structures determined by X-ray analysis[7]).

[7]) Experimental details of these reactions and crystallographic data of the cyclopropane products will be presented in separate papers. Preliminary communication: [2].

Scheme 4



By the described transformations the general features of the structure of compound **3** (and **5**), as well as its chemical behaviour were sufficiently characterized. The preferred conformation of the 10-membered ring could now be studied by X-ray analysis and NMR. spectroscopy.

2. X-Ray analysis of compound 3a. – 2.1. *Crystal data.* Crystals are monoclinic, space group $P2_1$, $a = 6.080$ (3), $b = 10.515$ (7), $c = 22.827$ (14) Å, $\beta = 105.87$ (5)°, U = 1403 Å^3, $D_c = 1.052$ g/cm^3, $D_m = 1.065$ g/cm^3.

2.2. *Intensity data, structure determination and refinement.* A *Picker* FACS-I automatic diffractometer was used for data collection with Mo*Kα̂* radiation and graphite monochromator. The intensities of 1785 independent reflections with $\theta \leqslant 25°$ were measured, of which 1645 were classified as observed with $I \geqslant 2\sigma$ (I).

The structure was solved by direct methods using the MULTAN 71 Program [10]. The positions of the H-atoms of the steroid skeleton were found by a difference *Fourier* synthesis, while the coordinates of the H-atoms of the cholestane side-chain were calculated assuming tetrahedral geometry. The structure was refined by full-matrix least squares calculations with anisotropic (isotropic for H-atoms) thermal parameters to a final R value of 0.058.

2.3. *Results and discussion.* Final atomic coordinates with their standard deviations are given in *Table 2*. The molecular structure is illustrated in *Figures 1* and *2*. The bond lengths are listed in *Table 3*. They agree in general with the standard values quoted in the literature. C_{sp^3}–C_{sp^3} bonds are in the range of 1.513–1.566 Å with a mean value of 1.534 Å. The C=C double bond has a length of 1.318 Å and the two C=O bonds of 1.206 (at C(5)) and 1.211 Å (at C(29)).

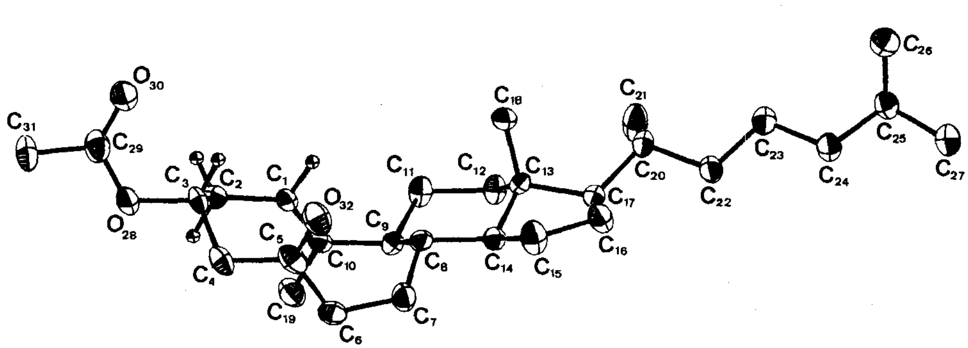


Fig. 1. *Perspective view of the molecule.* The thermal ellipsoids are scaled to include 20% probability. For clarity only the hydrogen atoms used for NMR. calcuations are drawn.

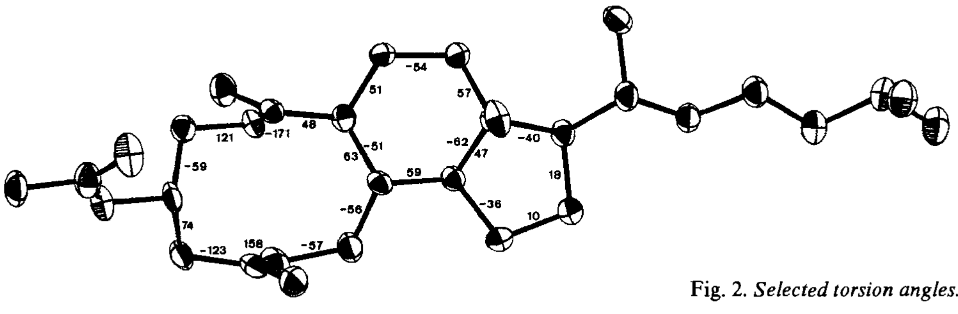


Fig. 2. *Selected torsion angles.*

Figure 2 shows the torsion angles [11] of the steroid skeleton. The 10-membered ring has the A_2^a conformation *(Scheme 1)* with approximate C_s-symmetry. C(19) and O(32) assume pseudo-axial, C(11), C(14) and O(28) pseudo-equatorial positions. Ring C adopts the normal chair conformation with an average torsion angle of 55.7°.

Table 2. *Fractional atomic coordinates*

	x	*y*	*z*
C(1)	0.6695 (9)	0.3029 (7)	0.8791 (2)
C(2)	0.7872 (10)	0.2972 (6)	0.9459 (2)
C(3)	0.8674 (10)	0.1630 (7)	0.9650 (2)
C(4)	0.6710 (11)	0.0659 (7)	0.9507 (2)
C(5)	0.5854 (11)	0.0389 (6)	0.8837 (2)
C(6)	0.3332 (10)	0.0605 (7)	0.8531 (2)
C(7)	0.2738 (12)	0.0803 (7)	0.7838 (2)
C(8)	0.3910 (9)	0.1892 (6)	0.7592 (2)
C(9)	0.3583 (10)	0.3207 (6)	0.7848 (2)
C(10)	0.4583 (9)	0.3389 (6)	0.8522 (2)
C(11)	0.4432 (11)	0.4290 (6)	0.7506 (2)
C(12)	0.3448 (11)	0.4222 (6)	0.6803 (2)
C(13)	0.3918 (9)	0.2922 (6)	0.6569 (2)
C(14)	0.2889 (9)	0.1931 (6)	0.6897 (2)
C(15)	0.2955 (13)	0.0694 (7)	0.6537 (2)
C(16)	0.2448 (12)	0.1140 (8)	0.5878 (2)
C(17)	0.2567 (9)	0.2622 (6)	0.5894 (2)
C(18)	0.6460 (10)	0.2736 (7)	0.6643 (2)
C(19)	0.2976 (12)	0.3993 (7)	0.8849 (2)
C(20)	0.3382 (11)	0.3168 (7)	0.5355 (2)
C(21)	0.3511 (14)	0.4633 (8)	0.5385 (3)
C(22)	0.1714 (11)	0.2763 (6)	0.4751 (2)
C(23)	0.2435 (11)	0.3102 (7)	0.4182 (2)
C(24)	0.0918 (10)	0.2433 (7)	0.3615 (2)
C(25)	0.1275 (11)	0.2913 (7)	0.3019 (2)
C(26)	0.3644 (12)	0.2628 (8)	0.2952 (3)
C(27)	−0.0521 (12)	0.2356 (8)	0.2486 (2)
O(28)	0.9683 (7)	0.1577 (5)	1.0303 (1)
C(29)	1.1848 (12)	0.1876 (8)	1.0517 (2)
O(30)	1.3029 (8)	0.2198 (6)	1.0193 (1)
C(31)	1.2683 (13)	0.1774 (8)	1.1193 (2)
O(32)	0.7104 (8)	−0.0058 (4)	0.8562 (1)

Table 3. *Bond lengths (Å)*

C(1)–C(2)	1.497 (8)	C(13)–C(14)	1.515 (9)
C(1)–C(10)	1.318 (8)	C(13)–C(17)	1.566 (8)
C(2)–C(3)	1.517 (10)	C(13)–C(18)	1.521 (8)
C(3)–C(4)	1.537 (10)	C(14)–C(15)	1.545 (10)
C(3)–O(28)	1.450 (6)	C(15)–C(16)	1.524 (9)
C(4)–C(5)	1.502 (9)	C(16)–C(17)	1.560 (10)
C(5)–C(6)	1.518 (10)	C(17)–C(20)	1.556 (8)
C(5)–O(32)	1.206 (8)	C(20)–C(21)	1.542 (9)
C(6)–C(7)	1.539 (9)	C(20)–C(22)	1.532 (9)
C(7)–C(8)	1.534 (10)	C(22)–C(23)	1.521 (9)
C(8)–C(9)	1.535 (9)	C(23)–C(24)	1.539 (9)
C(8)–C(14)	1.538 (8)	C(24)–C(25)	1.520 (9)
C(9)–C(10)	1.504 (8)	C(25)–C(26)	1.519 (10)
C(9)–C(11)	1.547 (9)	C(25)–C(27)	1.514 (10)
C(10)–C(19)	1.521 (10)	O(28)–C(29)	1.310 (9)
C(11)–C(12)	1.553 (8)	C(29)–O(30)	1.211 (8)
C(12)–C(13)	1.522 (9)	C(29)–C(31)	1.491 (9)

The conformation of ring D is between a C(13) envelope and a C(16) half-chair, with *Romers* [12] ring parameters $\varphi_m = 47°$ and $\Delta = 8.5°$. The side-chain is in an extented conformation; all torsion angles lie within $180 \pm 11°$ or $60 \pm 5°$.

3. NMR. studies of the conformations in solution of the 10-membered ring in the two secosteroids 3 and 5. – The conformations of the secosteroids **3a** and **5** were determined by an NMR. analysis[8]) similar to the one described [1]. The rough features of the steroid conformations can be deduced from the ^{13}C-NMR. spectra of these compounds. For finer details one has to consult the ^{1}H-NMR. parameters. The chemical shifts and coupling patterns of H–C(1) and H–C(3) of **3**, **5** and the 3β-isomer **9** are collected in *Tables 4* and *5*. The chemical shifts of the ^{13}C-nuclei in the 10-membered ring are listed and assigned in *Table 6*. Each of the three compounds exhibits two sets of NMR. resonances at lower temperatures (0° to −40°), one set being always dominant and corresponding to the major conformation. Therefore these (*E*)-5, 10-*seco*-1(10)-cholestanones coexist in at least two stable conformations on the NMR. time scale.

3.1. *3a-Acetoxy ketone* **3a**. The NMR. parameters suggest a conformation $\mathbf{A}_2^a$ for the major component while the minor conformation most likely has a spatial arrangement closely resembling $\mathbf{B}_1^a$ *(Scheme 1)*. The following NMR. arguments support the proposed conformations.

3.1.1. *^{1}H-NMR. Spectrum.* The 3α-acetoxy group has to be in an equatorial position in the major as well as in the minor conformation, since the multiplet structure of H_β–C(3) is typical for coupling with two axial and two equatorial vicinal protons.

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[8]) *Experimental.* – Noise decoupled ^{13}C-NMR. spectra were recorded at 25.2 MHz and ^{1}H-NMR. spectra at 100 MHz on a *Varian* XL-100 spectrometer equipped with a *Fourier* transform accessory. Deuterions of the $CDCl_3$ and (D_8) toluene were used for a 15.4 MHz ^{2}H-lock during ^{13}C-work. In order to achieve higher resolution some ^{1}H-experiments were repeated at 360 MHz on a *Bruker* HX-360 spectrometer (Mr. *P. Hug*, Laboratory of Dr. *H. Fritz*).

Table 4. *Chemical shift parameters of H–C(1) and H–C(3) of* **9**, **3a** *and* **5**[1])

Solvent	**9**				**3a**				**5**		
	Main component		Minor component		Main component		Minor component		Main component	Minor component	
	H–C(1)	H–C(3)	H–C(1)	H–C(3)	H–C(1)	H–C(3)	H–C(1)	H–C(3)	H–C(1)	H–C(1)	–
$CDCl_3$	4.82	5.35	5.10 ...	5.40	4.88	5.30	5.10 ...	5.40	–	–	–
(D_8) Toluene	4.80	5.60	5.20 ...	5.30	4.85[2])	5.58[2])	5.19[2])	5.26[2])	4.80[3])	4.89[3])	–

[1]) Chemical shift values in ppm/TMS.
[2]) From a ^{1}H-360 MHz spectrum at $-40°$ (In the 3β-deuteriated compound **3b** the H–C(1) signals from the major and minor conformer were found at 4.80 and 5.09 ppm respectively).
[3]) Values from a ^{1}H-360 MHz spectrum at $-30°$.

The coupling parameters of the H–C(1) resonance in the spectrum of the main component *(cf. Table 5)* suggest a dihedral angle of approximately 180° between H–C(1) and H_{ax}–C(2) [13]. The signal assigned to H–C(1) of the minor component is a triplet. The dihedral angle [13] of H–C(1) and H_{ax}–C(2) is approximately 0°, while the angle of H–C(1) and H_{eq}–C(2) is about 120°.

The vinylic resonances of the major and minor conformations of product **3a** are nicely separated in the 360 MHz spectrum of a toluene solution at $-30°$. The intensity ratio of the resonances of major to minor conformation is approximately 6:1. This ratio corresponds to an energy difference between the two conformations of approximately 1 kcal/mol.

We assume that the shielding influence of the carbonyl group at position 5 causes a high field shift of the H–C(1) resonance in the main conformation. This influence is not operative for the minor conformation, where the keto group and the vinylic proton are anti-parallel to each other.

3.1.2. *^{13}C-NMR. Spectrum.* The conformations of the 3β-isomer **9** have been originally determined uniquely from the ^{1}H-NMR. data [1]. *Table 6* additionally relates ^{13}C-chemical shifts with different spatial arrangement of $H_3C(19)$ and OC(5). Using the relationship established for **9** the ^{13}C-shifts of **3** yield data which are in good agreement with the conformations deduced above.

The resonance at 19.2 ppm assigned to $H_3C(19)$ of the main component is characteristic for a methyl group located on the α-side of the steroid skeleton. The chemical shift of the $H_3C(19)$ resonance of the minor conformation is 12.7 ppm. As a consequence, the CH_3 group must be on the β-side (*cf.* with the values for $H_3C(19)$ of $\mathbf{A}_1^{\beta}$).

Other resonances, *e.g.* those assigned to C(1), C(9), C(10) and C(11) of both conformations are in good agreement with the proposed $\mathbf{A}_2^{\alpha}$ and $\mathbf{B}_1^{\alpha}$ arrangements. The main conformation is interestingly enough very close to that determined in the solid state by X-ray analysis (*cf.* p. 1774).

3.2. *Diketone* **5**. The ^{1}H- and ^{13}C-NMR. parameters of **5** suggest conformations $\mathbf{A}_1^{\kappa}$ for the main and $\mathbf{A}_2^{\kappa}$ for the minor component *(Scheme 1)*. These conformations closely resemble the main conformations of **9** and **3a**, *i.e.* $\mathbf{A}_1^{\beta}$ and $\mathbf{S}_2^{\alpha}$.

3.2.1. *^{1}H-NMR. Spectrum.* The 360 MHz spectrum of **5** in toluene at $-30°$ shows the resonances of H–C(1) of both conformers clearly separated. From the

Table 5. *Theoretical and experimental coupling constants* (Hz) *of the H–C(1) signals*

9				**3a**				**5**			
Theoretical coupling constans[a]		Experimental coupling constants		Theoretical coupling constants[a]		Experimental coupling constants		Theoretical coupling constants[a]		Experimental coupling constants	
Conform. $\mathbf{A}_1^{\beta}, \mathbf{B}_1^{\beta}$[f]	Conform. $\mathbf{A}_2^{\beta}, \mathbf{B}_2^{\beta}$[f]	Main. comp.	Minor comp.	Conform. $\mathbf{A}_1^{a}, \mathbf{B}_1^{a}$[f]	Conform. $\mathbf{A}_2^{a}, \mathbf{B}_2^{a}$[f]	Main comp.	Minor comp.	Conform. $\mathbf{A}_1^{\kappa}$[f]	Conform. $\mathbf{A}_2^{\kappa}$[f]	Main comp.	Minor comp.
$\emptyset_1$[b] = 180°	$\emptyset_1$[b] = 0°	$d \times d$[g]	t[h]	$\emptyset_1$[b] = 0°	$\emptyset_1$[b] = 180°	$d \times d$[f]	t[h]	$\emptyset_1$[b] = 150°	$\emptyset_1$[b] = 30°	$d \times d$[g]	$d \times d$[g]
$\emptyset_2$[b] = 60°	$\emptyset_2$[b] = 120°			$\emptyset_2$[b] = 120°	$\emptyset_2$[b] = 60°			$\emptyset_2$[b] = 30°	$\emptyset_2$[b] = 150°		
$J_1 = 11.6$	$J_1 = 6.6$	$J_1 \sim 11$	J_1[d] ~ 7.5	$J_1 = 6.6$	$J_1 = 11.6$	$J_1 \sim 11$	J_1[c] ~ 7.5	$J_1 = 8.6$	$J_1 = 4.8$	$J_1 = 9.6$[e]	$J_1 = 5.6$[e]
$J_2 = 3.6$	$J_2 = 4.8$	$J_2 \sim 5$	J_2[d] ~ 7.5	$J_2 = 4.8$	$J_2 = 3.6$	$J_2 \sim 5$	J_2[c] ~ 7.5	$J_2 = 4.8$	$J_2 = 8.6$	$J_2 = 5.6$[e]	$J_2 = 9.6$[e]

a) According to *Karplus* rule.
b) Dihedral angle of H–C(1) with the H at C(2).
c) 3β-Deuteriated compound **3b** and 180-90° pulse experiments.
d) 180-90° pulse experiments.
e) ^{1}H-360 MHz spectrum at 0°.
f) See *Figure 1*.
g) $d \times d$ = doublet of doublets.
h) t = triplet.

Table 6. *[13]C-Chemical shift parameters of compounds* **9**, **3a** *and* **5**[a])

Carbon	**9**[b])		**3a**[b])		**5**[c])	
	Main conformation[d])	Minor conformation[e])	Main conformation[f])	Minor conformation[g])	Main conformation[h])	Minor conformation[i])
C(1)	123.9	116.5	119.0	120.8	119.2	115.2
C(2)	34.0	–	34.2	34.2	39.3	42.0
C(3)	74.4	71.3	73.9	71.0	–	–
C(4)	47.7	48.5	48.2	47.4	57.1	57.9
C(5)	–	–	–	–	–	–
C(6)	42.7	–	41.4	42.5	42.7	43.8
C(7)	28.6	–	28.6	27.2	28.4	25.0
C(8)	38.2	–	35.6	37.5	38.2	36.7
C(9)	54.9	51.6	51.1	55.0	54.8	51.6
C(10)	138.8	146.5	143.7	149.0	143.2	147.1
C(11)	26.6	31.4	31.4	26.6	27.0	31.2
C(19)	12.8	19.5	19.2	12.7	12.5	19.0

a) In ppm/TMS.
b) At +30° in toluene-d_8.
c) At −30° in (D_8) toluene.
d) $\mathbf{A}_1^{\beta}$ conformation.
e) $\mathbf{B}_2^{\beta}$ conformation.
f) $\mathbf{A}_2^{\alpha}$ conformation.
g) $\mathbf{B}_1^{\alpha}$ conformation.
h) $\mathbf{A}_1^{\kappa}$ conformation.
i) $\mathbf{A}_2^{\kappa}$ conformation.

magnitude of the chemical shift and the very small shift difference between these resonances, the H–C(1) proton in both conformers must be in the shielding region of the carbonyl group in position 5. The coupling patterns of the H–C(1) vinylic resonances are similar but slightly different from those encountered in the main components of **3a** and **9**. This may be interpreted by slightly different dihedral angles between H–C(1) and H_{ax}–C(2) and H–C(1) and H_{eq}–C(2). Very likely $\mathbf{A}_1^{\kappa}$ is slightly flattened in comparison to $\mathbf{A}_1^{\beta}$ and the same is probably true for $\mathbf{A}_2^{\kappa}$ in respect to $\mathbf{A}_2^{\alpha}$. The intensity differences of the two conformations in the [1]H-NMR. spectrum of 6:4 indicate, according to *Boltzmann* distribution, an energy difference between $\mathbf{A}_1^{\kappa}$ and $\mathbf{A}_2^{\kappa}$ of approximately 0.25 kcal/mol.

3.2.2. *[13]C-NMR. Spectrum.* The [13]C-NMR. parameters of the main conformations of **5** and of **9** are quite close. Their spatial arrangement therefore must be very similar. For the same reasons the minor conformation of **5** must resemble the main conformation of **3a**. Exceptions concerning the relationship between $\mathbf{A}_1^{\kappa}$ and $\mathbf{A}_1^{\beta}$, and $\mathbf{A}_2^{\kappa}$ and $\mathbf{A}_2^{\alpha}$, mentioned above, are the chemical shift values of C(1) and C(10). If we make the reasonable assumption that the introduction of a keto group in position 3 changes the chemical shift values of C(1) and C(10) by −4 ppm and +4 ppm respectively, compared with the situation of the 3-acetoxy compounds **3a** and **9**, the correspondence holds for all assigned resonances of the 10-membered ring.

3.3. *Discussion.* As mentioned in [1], a crucial point for deducing the conformations of **9** is the selection of a representative set of conformations as a basis for the discussion, since the limited number of experimental parameters does not allow for determination of all dihedral angles in the 10-membered ring. The same approach had to be used also in the case of **3a**.

Once the equatorial position of the 3-acetoxy group is either assumed or determined from the H–C(3) splitting pattern, four conformations with the carbonyl group OC(5) and the methyl group $H_3C(19)$ in either α or β positions seem to form a reasonable basis for an approximative description of **3a** and **9**. For the deduction of the conformations of **5** the close correspondence of ^{13}C-data discussed in 3.2.2. indicates that the same basic set of conformations may be used.

Our experimental results only give an idea about the two most populated conformations of **3a**, **5** and **9**. The actual time-dependent spatial arrangement is certainly much more complicated. Conformations with relative populations of a few percent affect the NRM. spectra only slightly but might be important in a particular chemical reaction.

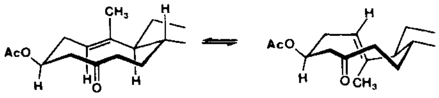
The change in the configuration of the 3-acetoxy-group from α to β (**3**→**9**) leads to inversion of OC(5) and $H_3C(19)$ between α and β positions for both conformations. This behaviour indicates that the energy difference between the two types of conformations, *i.e.* **A** and **B**, is small compared to the energy difference between an axial and an equatorial acetoxy group.

Calculation of the chemical shifts of the olefinic carbons according to the phenomenological parameters of *Horsley & Sternlicht* [14] leads to the following values:

$$\delta(C(1)) = 124.5 \text{ ppm} \qquad \delta(C(10)) = 137.1 \text{ ppm}$$

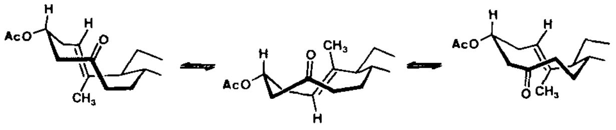
No conformational parameters are included in these rules and the γ-increment of the β-acetoxy group at C(3) is assumed to be $\Delta\delta\gamma = -1.5$ ppm. These values agree much better with those measured for the main components $\mathbf{A}_1^\beta$ and $\mathbf{A}_2^\alpha$ than with the values for the respective minor components $\mathbf{B}_2^\beta$ and $\mathbf{B}_1^\alpha$. In the **B**-type conformations the orientation of the C(1)–C(10) double bond is such that it may be slightly influenced by the dipolar electric field of the OC(5) keto group. If such an electric field effect is operative, the C(10) resonance should shift towards higher field. This is indeed observed for both C(1) and C(10) of **9** and for C(10) of **3a**. In both examples the difference between the two chemical shift values is increased.

4. General discussion. – (*E*)-3β-Acetoxy-5, 10-*seco*-1(10)-cholesten-5-one **9** exists in conformations **9**-$\mathbf{A}_1^\beta$ (solid state conformation and major conformation in solution) and **9**-$\mathbf{B}_2^\beta$ (minor conformation in solution) [1].



9-A_1^β 9-B_2^β

In the present study, for the epimeric (*E*)-3α-acetoxy-5, 10-*seco*-1(10)-cholesten-5-one (**3a**), the solid state conformation and major conformation in solution was found to be **3**-$\mathbf{A}_2^\alpha$, and the minor conformation in solution **3**-$\mathbf{B}_1^\alpha$.



3a-A$_2^\alpha$ **3a-B$_1^\alpha$** **3a-B$_2^\alpha$**

Both epimers (**9** and **3**) and their oximes undergo cyclisations involving intramolecular C(1)–C(5) bond formation (see *Scheme 2*)[9]), to give always A- nor-B-homo-derivatives with the *same* configuration at C(1) and C(5), namely with the *trans*-1β,5α-configuration (these products being of the 5(10→1βH)-*abeo*-5α-steroid type). That means that in the case of **9**, the conformation involved in these cyclizations must be of the **9-B$_2^\beta$** type [1] [8] [9][10]), while in the case of **3** it should be of the **3-B$_2^\alpha$** type, although such a conformation was not found (by NMR.) in solution (in the ground state). However, it should be stressed that in all these internal ring closures the 3β-acetate **9** is considerably more reactive than the 3α-epimer **3** (see *Table 1* and *Schemes 2* and *3*).

Another cyclization, involving intramolecular C(1)–C(3) bond formation, is the solvolysis of the epimeric 3-tosylates **20** and **21** *(Scheme 4)* [2] [15]. Both compounds react in the same way, *i.e.* afford cyclopropane derivatives, but whereas the 3β-tosylate **21** is converted to the 1α,3β-cyclo-5,10-secosteroid **23**, the 3α-tosylate **20** cyclizes to the 1β,3α-cyclo-5,10-secosteroid **22** with the opposite configuration at the junction carbon atoms C(1) and C(3)[11]). These results indicate that in the solvolysis of the 3β-tosylate **21** the conformation controlling the stereochemical course is of the **B$_2^\beta$** type, while in the case of the 3α-tosylate **20** it must be of the **B$_1^\alpha$** type.

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Experimental Part[12])

Melting points (m.p.) are not corrected. Optical rotations were measured at 20° in $CHCl_3$. Routine ^{1}H-NMR. spectra were recorded at 100 MHz on a *Varian* HD-100 spectrometer, in $CDCl_3$ at RT., using TMS as internal standard; chemical shifts are expressed in ppm (δ scale). IR. spectra were determined on a *Perkin-Elmer* instrument, Model 337 ($\tilde{\nu}_{max}$ cm^{-1}). UV. spectra were obtained

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9) For internal ring-closure reactions of **9** see [6b] and [8] (acid catalyzed and thermal cyclisations), and [9] (thermal cyclisation of the oxime of **9**); for similar reactions of **3a** see [9] (thermal cyclisation of the oxime of **3a**), and the present paper (acid catalyzed and thermal cyclisations).

10) In the acid catalyzed cyclization of **9**, a minor A- nor-B-homo-product (**11**, *Scheme 2*) with the *cis*-1α,5α configuration was also formed [8], which is derived from the major **9-A$_1^\beta$** conformation [1] [8].

11) 1β,3α-Cyclo-... in **22**, and 1α,3β-cyclo-... in **23** refer to the configuration of the new C(1)–C(3) cyclopropane bond (and *not* to the configuration of H–C(1) and H–C(3)), as required by the IUPAC-rules for nomenclature of steroids [16].

12) IR. and UV. spectral measurements were performed in the Laboratories for Instrumental Analysis (directed by Prof. *D. Jeremić*), and elemental microanalyses in the Microanalytical Laboratory (Dr. *R. Tasovac*) of the Department of Chemistry, Faculty of Science, Belgrade.

on a *Perkin Elmer* 137 UV. spectrophotometer (λ_{max} nm, ε in parentheses). Silica gel 0.05-0.20 was used for preparative column chromatography. The separation of products was controlled by TLC. on silica gel G *(Stahl)* using benzene/ethyl acetate 9:1, 7:3 or 1:1 for development and 50% aqueous sulfuric acid for detection.

Preparation of (*E*)-3α-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (3a). - a) *(E)-3α-Hydroxy-5,10-*seco*-1(10)-cholesten-5-one* (**2a**). To a solution of 5β-cholestane-3α,5-diol 3-acetate (**1a**) [5] (4.0 g, 0.009 mol) in anhydrous benzene (250 ml), placed in a quartz cylindrical irradiation vessel, lead tretraacetate (13.3 g, 0.03 mol) and dry $CaCO_3$ (4.0 g, 0.04 mol) were added. The vigorously stirred mixture was irradiated at RT. with a high pressure Hg-lamp (TQ 150 Z2, *Hanau*), contained in a central, water-cooled jacket. After 1 h the starting material had disappeared (TLC.) and excess lead tetra-acetate was destroyed by the addition of a few drops of ethylene glycol. The precipitate was removed by fitration, and the filtrate washed with aqueous $NaHCO_3$-solution and water, dried ($MgSO_4$) and evaporated *in vacuo*, to give a mixture which was chromatographed on silica gel (120 g). Benzene and benzene/ether 99:1 eluted 490 mg of a non-identified product, then benzene/ether 97:3 eluted a crystalline mixture (3.0 g) mainly of (*Z*)- and (*E*)-3α-acetoxy-5,10-*seco*-1(10)-cholesten-5-one. To this mixture in MeOH (120 ml), 30 ml of 5% methanolic KOH was added, the resulting solution left for 12 h in a refrigerator, concentrated *in vacuo* at RT. to about 50 ml, diluted with water and extracted with ether. The organic layer was washed with water until neutral, dried ($MgSO_4$) and evaporated *in vacuo*. The products obtained were chromatographed on silica gel (95 g); benzene eluted a mixture (1.35 g) of (*Z*)-3α-hydroxy-5,10-*seco*-1(10)-cholesten-5-one and 2 non identified compounds, while benzene/ether 85:15 eluted 1.30 g (35.9%) of (*E*)-3α-hydroxy-5,10-*seco*-1(10)-cholesten-5-one (**2a**), as an oil or glassy substance (single spot on TLC.); $[\alpha]_D = -30°$ ($c = 0.55$). - IR. (CCl_4): 3620, 3470, 1702, 1692. - NMR.: 0.74 (*s*, $H_3C(18)$); 0.88 (*d*, $H_3C(26) + H_3C(27)$); 0.92 (*d*, $H_3C(21)$); 1.70 (*d*, $H_3C(19)$); *ca.* 3.8 (*m*, H-C(3)); about 4.8 and 5.1 (*m*, H-C(1) of both conformers).

$C_{27}H_{46}O_2$ (402.64) Calc. C 80.54 H 11.52% Found C 80.19 H 11.28%

b) *(E)-3α-Acetoxy-5,10-*seco*-1(10)-cholesten-5-one* (**3a**). A mixture of alcohol **2a** (1.6 g, 0.004 mol) and Ac_2O (10 ml) in dry pyridine (15 ml) was allowed to stand 24 h at RT. Light petroleum (b.p. 40-60°) and MeOH were then added, and the mixture was evaporated to dryness, this process being repeated several times. The solid residue (1.6 g), recrystallized from acetone/MeOH, afforded (*E*)-3α-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (**3a**) (1.45 g, 81%), m.p. 102°; $[\alpha]_D = +13°$ ($c = 0.86$). - UV. (EtOH): 223 (2530). - IR. (KBr): 1738, 1704, 1250. - NMR.: 0.70 (*s*, $H_3C(18)$); 0.86 (*d*, $H_3C(26) + H_3C(27)$); 0.90 (*d*, $H_3C(21)$); 1.78 (*d*, $H_3C(19)$); 2.02 (*s*, AcO); about 4.9 (*m*, H-C(1) of one conformer); 5-5.3 (*m*, H-C(1) of the other conformer + *m*, H-C(3) of both conformers).

$C_{29}H_{48}O_3$ (444.67) Calc. C 78.32 H 10.88% Found C 78.10 H 11.02%

Preparation of (*E*)-3β-D-3α-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (3b). - a) *3β-D-5β-cholestane-3α,5-diol-3-acetate* (**1b**). The usual reduction of 5-hydroxy-5β-cholestan-3-one [5] [17] (7.25 g, 0.018 mol) in dry ether (120 ml) with $LiAlD_4$ (1.0 g, 0.024 mol) in ether (60 ml), followed by column chromatography on silica gel (140 g), afforded 2 epimers. The first, 3α-D-5β-cholestane-3β,5-diol (3.82 g, 52.3%) was eluted with benzene/ether 60:40 and recrystallized from acetone (3.58 g, 49%), m.p. 147-149°. - IR. (KBr): 3300, 1170, 1065, 885.

$C_{27}H_{47}DO_2$ (405.66) Calc. C 79.94 H+D 12.17% Found C 80.07 H+D 11.93%

The second product (2.46 g, 33.7%), eluted with ether, was 3β-D-5β-cholestane-3α,5-diol; it was recrystallized from acetone/MeOH: 2.24 g (30.7%), m.p. 191-193°. - IR. (KBr): 3420, 1130, 1055, 940.

$C_{27}H_{47}DO_2$ (405.66) Calc. C 79.94 H+D 12.17% Found C 79.82 H+D 11.96%

Acetylation of 3β-D-5β-cholestane-3α,5-diol (2.03 g, 0.005 mol) with Ac_2O (20 ml) in dry pyridine (20 ml) at RT. for 24 h, followed by the usual work-up, afforded, upon recrystallization from acetone/MeOH, 3*β*-D-5*β*-cholestane-3*α*,5-diol 3-acetate (**1b**): 2.10 g (93.7%), m.p. 146–148°. – IR. (KBr): 3540, 1730, 1275.

$C_{29}H_{49}DO_3$ (447.70) Calc. C 77.80 H+D 11.48% Found C 77.84 H+D 11.26%

b) *(E)-3β-D-3α-Acetoxy-5,10-*seco*-1(10)-cholesten-5-one* (**3b**). This compound **3b** was obtained from **1b** (2.01 g, 0.0045 mol) in the same way as described above for the corresponding non-deuteriated *seco*-ketone (*i.e.* **1a**→**3a**), except that the originally produced (*ca.* 1:1) mixture of (*Z*)- and (*E*)-3*β*-D-3*α*-acetoxy-5,10-*seco*-1(10)-cholesten-5-ones, prior to saponification, was UV.-irradiated in benzene for 2 h, in order to affect as much as possible $Z \rightarrow E$ isomerisation. The pure (*E*)-3*β*-D-3*α*-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (**3b**), obtained after 3 crystallisations from acetone (300 mg, 15% overall yield from **1b**), had m.p. 102°. – IR. (KBr): 1740, 1708, 1260. – NMR.: 0.70 (*s*, $H_3C(18)$); 0.86 (*d*, $H_3C(26)+H_3C(27)$); 0.89 (*d*, $H_3C(21)$); 1.78 (*d*, $H_3C(19)$); 2.01 (*s*, AcO); 4.75–5.35 (*m*, H–C(1) of both conformers).

$C_{29}H_{47}DO_3$ (445.68) Calc. C 78.15 H+D 11.08% Found C 78.34 H+D 11.38%

Preparation of (*E*)-5,10-*seco*-1(10)-cholestene-3,5-dione (5). – A solution of (*E*)-3*β*-hydroxy-5,10-*seco*-1(10)-cholesten-5-one (**4**) [6] (201 mg, 0.5 mmol) or its 3*α*-epimer **2a** (see above) in dry pyridine (2.5 ml) was added to a slurry of CrO_3 (200 mg) in dry pyridine (2 ml). The mixture was left 24 h at RT., then diluted with ether and filtered. The filtrate was washed with dilute acetic acid, aqueous $NaHCO_3$-solution and water, and dried ($MgSO_4$). Removal of the solvent afforded 190 mg (95%) of (*E*)-5,10-*seco*-1(10)-cholestene-3,5-dione (**5**), which was recrystallized from acetone, m.p. 104°, $[\alpha]_D = -30°$ (c = 1.0). – IR. (KBr): 1712, 1708. – NMR.: 0.69 (*s*, $H_3C(18)$); 0.84 (*d*, $H_3C(26)+H_3C(27)$); 0.88 (*d*, $H_3C(21)$); 1.67 (*d*, $H_3C(19)$); 5.04 (*m*, H–C(1)).

$C_{27}H_{44}O_2$ (400.62) Calc. C 80.94 H 11.07% Found C 81.20 H 11.18%

Cyclisations of (*E*)-3α-acetoxy-5,10-*seco*-1(10)-cholesten-5-one (3a). – A) *Acid catalyzed cyclization.* A saturated solution of HCl in $CHCl_3$ (4 ml) was slowly added at 0° to the (*E*)-3*α*-acetoxy-ketone **3a** (80 mg) dissolved in $CHCl_3$ (4 ml). The resulting solution was kept at 0° for 4 h, then diluted with ether, washed with water, aqueous $NaHCO_3$-solution and water, dried ($MgSO_4$) and evaporated *in vacuo.* The residue (80 mg) was chromatographed on silica gel (5 g); benzene/ether 99:1 eluted unchanged **3a** (49 mg, 61%), while benzene/ether 98:2 eluted 5(10→1*β*H)*abeo*-5*α*-cholest-1(19)-ene-3*α*,5*α*-diol 3-acetate (**6**) (30 mg, 37.5%), which was recrystallized from MeOH, m.p. 70–72°; $[\alpha]_D = +51.5°$ (c = 0.5). – IR. (CCl_4): 3560, 1750, 1640, 1250, 905. – NMR.: 0.69 (*s*, $H_3C(18)$); 0.86 (*d*, $H_3C(26)+H_3C(27)$); 0.88 (*d*, $H_3C(21)$); 2.02 (*s*, AcO); 2.67 (*qa*, H–C(1)); 5.01 and 5.14 (2 exocyclic vinyls H at C(19)); *ca.* 5.2 (*m*, H–C(3)).

$C_{29}H_{48}O_3$ (444.67) Calc. C 78.32 H 10.88% Found C 78.44 H 10.73%

Under the same conditions, the (*E*)-3*β*-acetoxy-ketone **9** underwent this type of cyclization to the extent of over 90% [6] [8].

B) *Thermal cyclisations.* a) *In toluene.* A solution of the (*E*)-3*α*-acetoxy-ketone **3a** (100 mg) in dry toluene (10 ml) was refluxed 16 h and then evaporated to dryness. The residue, upon chromatography on silica gel (5 g) as described above, afforded 82 mg (82%) of unchanged **3a** and 18 mg (18%) of **6** (see above).

Under the same thermal conditions, the (*E*)-3*β*-acetoxy-ketone **9** underwent cyclization to the extent of 44% [8].

b) *In ethanol.* Heating at reflux 100 mg of the (*E*)-3*α*-acetoxy-ketone **3a** in 10 ml of EtOH for 36 h gave, upon chromatography on silica gel (as described above), 92 mg (92%) of unchanged **3a** and 8 mg (8%) of **6**.

Under the same thermal conditions, the (*E*)-3*β*-acetoxy-ketone **9** underwent this type of cyclisation in 31% yield [8].

C) *Configurational assignment at C(1) and C(5) in the cyclization product* **6**. Compound **6** (64 mg) was saponified with 5% methanolic KOH in the usual way [8] to the corresponding diol **7**, which was oxidized in acetone, without further purification, with a slight excess of *Jones* reagent (as described previously [8]), to give the known 5-hydroxy-5(10→1*β*H)*abeo*-5*α*-cholest-10(19)-en-3-*one*

(**8**) (60 mg, 93.7%), identical (m.p., mixed m.p., TLC., IR., NMR.) with the ketone **8** obtained previously by a similar oxidation of 5(10→1βH)*abeo*-5α-cholest-10(19)-ene-3β,5α-diol (**12**) [8] (the latter compound resulting from cyclization of **9** to **10** followed by saponification).

When diol **7** was prepared, following **12**→**8**→**7** [8], it afforded, upon acetylation with Ac_2O in pyridine (in the usual way), 5(10→1βH)*abeo*-5α-cholest-10(19)-ene-3α,5α-diol 3-acetate (**6**), which was identical to the cyclization product **6** formed from the (*E*)-3α-acetoxy-ketone **3a** (see above).

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