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STRUCTURE-REACTIVITY RELATIONSHIP IN THE SOLVOLYSIS OF 5,10-SECOSTEROIDAL 5-*p*-NITROBENZOATES[1]

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Abstract—The solvolysis of (*Z*)- and (*E*)-3β-acyloxy-5,10-seco-1(10)-cholesten-5β-ol *p*-nitrobenzoates 4 and 5 has been investigated and compared with the solvolytic reactivity of the epimeric (*Z*)- and (*E*)-5α-*p*-nitrobenzoates 1 and 2, as well as of the reference compound, i.e. the 1,10-saturated 5α-*p*-nitrobenzoate. Kinetic data and product analysis revealed that the relative spatial orientation of the 1(10)-olefinic double bond and the chiral center at C(5) in the 10-membered ring, which these secosteroidal 5-*p*-nitrobenzoates can adopt in the transition state, is the main factor which determines their solvolytic behaviour, so that the esters 1, 2 and 5 solvolyse with transannular double bond participation, while such an interaction is not present in the case of the (*Z*)-5β-ester 4.

In our previous communication on the solvolytic reactivity of 5,10-seco-steroids,[2,3] it was reported that both (*Z*)- and (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5α-ol *p*-nitrobenzoates (1 and 2, Scheme 1) undergo solvolysis with considerable participation of the 1(10)-double bond in the transition state, giving as the only transannular cyclization product 5(10→1β*H*)*abeo*-5β-cholest-10(19)-en-3β-ol acetate (3). From kinetic data it was concluded that anchimeric assistance is more pronounced in the *E* isomer 2, indicating that the stereochemistry around the 1(10)-double bond affects the overall conformation of the 10-membered ring and, therefore, is one of the factors which determines the solvolytic behaviour of these esters. However, since such transannular assistance requires the two reacting centers, i.e. the double bond and the C(5) chiral carbon, to attain a favourable relative spatial arrangement for back-side π-bond internal attack, it seemed justifiable to examine the solvolytic reactivity also in relation to the orientation of the ester group at C(5). For that reason, in the present work, the solvolysis of the 5β-*p*-nitrobenzoate esters in the *Z* and *E* series (4[b] and 5, Scheme 2)[4] was studied and compared with the solvolytic behaviour of the 5α-epimers 1 and 2.

In this way it was possible to correlate the reactivity of a full set of stereoisomers and to obtain useful information on the stereochemical (configurational and conformational) features affecting transannular interaction in the 10-membered ring in such systems.

Solvolysis of p-*nitrobenzoates* 4 *and* 5. In order to ensure proper comparison of the solvolytic reactivity of all four isomeric 5-*p*-nitrobenzoates, solvolysis of 4 and

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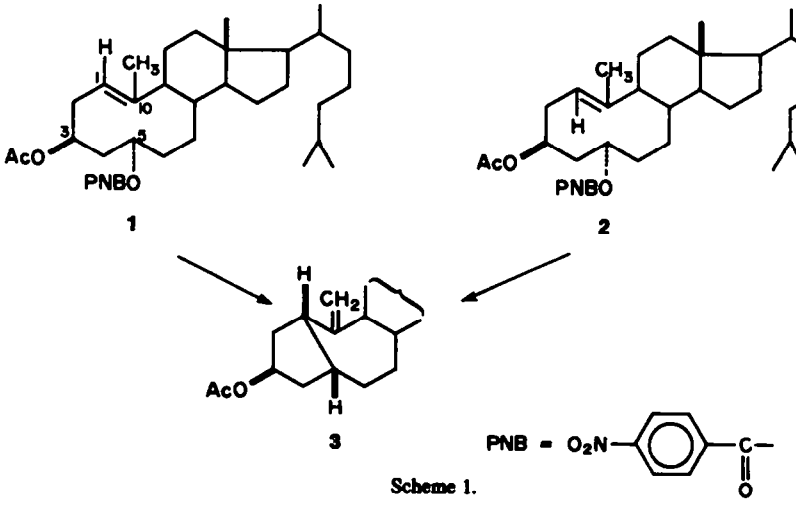
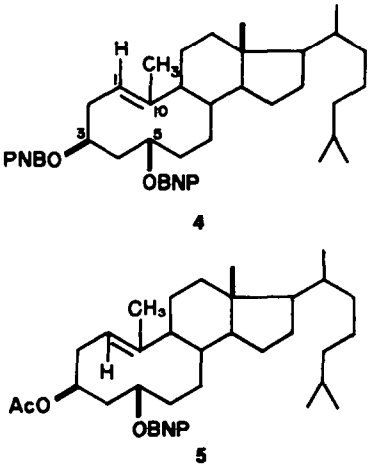
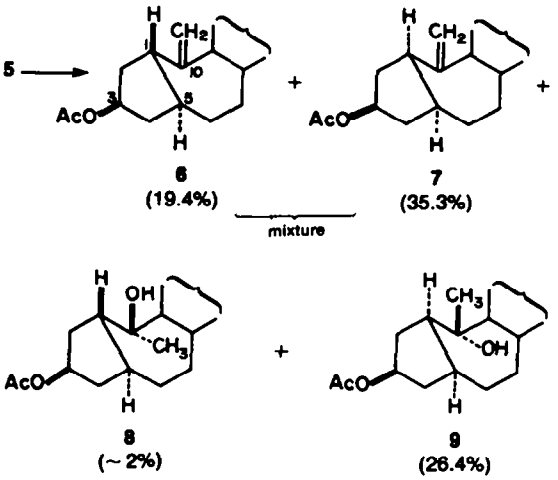
[b]Since (*Z*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5β-ol *p*-nitrobenzoate could not be prepared in pure form, the corresponding (*Z*)-3β,5β-di-*p*-nitrobenzoate 4 was used instead in the solvolysis experiment. Inclusion of this compound seemed justified because it was previously established that the 3β-*p*-nitrobenzoyloxy group in 5,10-seco-steroid derivatives is practically inert to solvolysis, and therefore cannot interfere in the solvolysis reactions performed under the conditions described in this paper.



Scheme 1.



Scheme 2.



Scheme 3.

5 was carried out under the experimental conditions previously used for the *p*-nitrobenzoates in the 5α-series (1 and 2[2,3]), i.e. in acetone–water (90:10, v/v) solution in sealed tubes at 125°. It was found that under these conditions (*Z*)-di-*p*-nitrobenzoate 4 remained practically unchanged even after 240 hr.. The solvolysis rate of (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5β-ol *p*-nitrobenzoate 5 was followed up to about 85% completion by potentiometric titration of the liberated *p*-nitrobenzoic acid with 0.022 M KOH using a least squares computer program to calculate first-order rate constant. These results and kinetic data obtained earlier for the solvolysis reactions of the 5α-*p*-nitrobenzoates 1 and 2, as well as of the 5α-*p*-nitrobenzoate of the 1,10-saturated alcohol (obtained by catalytic hydrogenation of the (*E*)-1(10)-unsaturated analogue[3]) are presented in Table 1.

A large scale experiment for product analysis performed with ester 5 was carried out under similar solvolytic conditions described for rate determination, i.e. a 90% aqueous acetone solution of *p*-nitrobenzoate 5 was heated at 100° until practically all starting material was consumed. The solvolysis products formed were isolated and separated by column chromatography on silica gel. The results showed that the ester 7 solvolyses to give (Scheme 3) a mixture of the following cyclization products: 5(10→1βH)*abeo*-5α-cholest-10(19)-en-3β-ol acetate (6) (19.4%), 5(10→1αH)*abeo*-5α-cholest-10(19)-en-3β-ol-acetate (7) (35.3%), 5(10→1βH)*abeo*-5α-cholestane-3β,10β-diol 3-acetate (8) (about 2%) and 5(10→1αH)*abeo*-5α-cholestane-3β,10α-diol 3-acetate[c] (9) (24.6%), the rest (about 16%) being a complex mixture which was not further investigated.

Actually, due to similar adsorption properties, cyclization products 6 and 7 were eluted from the column as a mixture. Their successful separation (on SiO_2 column) was performed only after saponification to the corresponding alcohols 10 and 11, which eventually were reacetylated to the primary formed products 6 and 7, respectively.

On the other hand, the 10-hydroxy compounds 8 and 9 were dehydrated with mesyl chloride in dimethylformamide and pyridine solution to the 10(19)-unsaturated cyclization products 6 and 7, respectively, showing that the solvolysis products 6 and 8 and the corresponding isomeric solvolysis products 7 and 9 represent pairs with the same configuration at the ring junction C atoms C(1) and C(5).

The constitution and stereochemistry of all solvolysis products was established on the basis of elemental micro-analysis, spectral data (IR, NMR, CD and mass spectra) and by chemical transformations described above and outlined in Scheme 5. It should be noted that since separate experiments have shown that all of these products are stable under the reaction conditions, the relative yields obtained reflect the original product distribution in the solvolysis process.

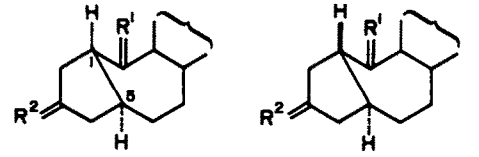
Configuration at C(1) *and* C(5) junction atoms in the *solvolysis products* (6, 7, 8 *and* 9). From spectral data and other characteristics it follows that the 10-hydroxy

[c]The configuration at C(10) in the hydroxylated solvolysis products 8 and 9 was deduced by assuming a synchronous mechanism involving *trans*-addition of C(5) and water across the $\Delta^{1(10)}$-double bond.

Table 1. Solvolysis rates of the 5-*p*-nitrobenzoates 1, 2, 4 and 5 and of the 1,10-saturated 5α-ester

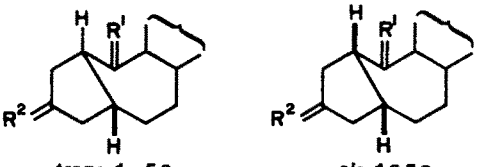
5-*p*-nitrobenzoate	k (sec^{-1})	relative rates
1 1(10)-Z-5α	1.20×10^{-6}	1,200
2 1(10)-E-5α	1.85×10^{-5}	18,500
4 1(10)-Z-5β	0	
5 1(10)-E-5β	2.58×10^{-4}	258,000
1,10-saturated-5α	1×10^{-9}	1

cyclization compound **8** and its dehydration 10(19)-olefinic analogue **6** are configurationally different from the corresponding products **9** and **7**. Also, 10(9)-unsaturated compounds **6** and **7** were found to be different from the 1β,5β-cyclization product **3**, earlier obtained in the solvolysis of (*Z*)- and (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5α-ol *p*-nitrobenzoates **1** and **2** (Scheme 1).[2,3] Since a 5-membered and 7-membered ring can be either *cis*- or *trans*-fused, 5(10→1)*abeo*-steroid derivatives can exist in four stereoisomeric forms (two with the B-homo/A-nor *cis*-configuration, **A** and **D**, and two with the B-homo/A-nor *trans*-configuration, **B** and **C**, Scheme 4), and therefore three of these (i.e. one *cis* **A** and both *trans* **B** and **C**) can be considered as possible structures



cis-1α,5α
A

trans-1β,5α
B



trans-1α,5β
C

cis-1β,5β
D

Ketones type (I): $R^1 = CH_2$, $R^2 = O$

Ketones type (II): $R^1 = O$, $R^2 =$ 

Scheme 4.

[4]The *cis* 1β,5β-configuration of the earlier obtained cyclization product **3** was determined in a similar way.[5] The corresponding 5- and 7-membered ring ketones were prepared from **3** by the same reaction sequence as shown in Scheme 5.[3,5]

of the cyclization products formed in the solvolysis of (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5β-ol *p*-nitrobenzoate **5**. That compounds **6** and **8** have the *trans* 1β,5α-configuration **B** and compounds **7** and **9** the *cis* 1α,5α-configuration **A** was determined on the basis of CD data obtained for the 5-membered and 7-membered ring ketones, i.e. the 3-keto-derivatives **12** and **15** and the 10-keto-derivatives **14** and **17**, which were prepared from **6** and **7**, respectively, by the reaction sequences outlined in Scheme 5.

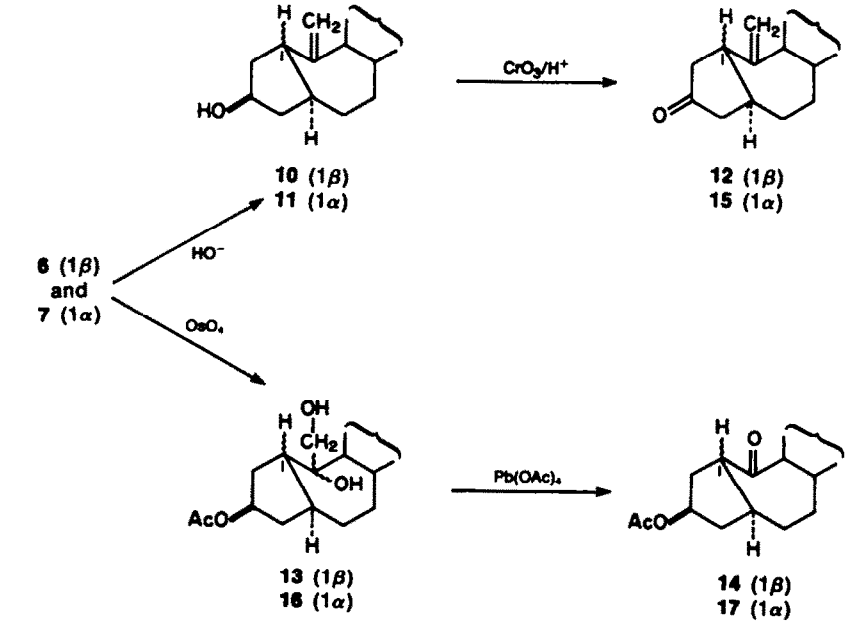
In these 5(10→1)*abeo*-steroid compounds, the 7-membered ring B can adopt several conformations, and for all four possible configurational isomers (**A-D**, Scheme 4) of general structure I (5-membered ring ketones) and II (7-membered ring ketones) Snatzke *et al.* have estimated relative stabilities, and also predicted $\Delta\epsilon_{max}$-values for the most stable conformations of the ketones of both types.[5] These values are presented in Table 2.[4]

By comparing the estimated values (Table 2) with the measured data (Table 3), it was possible to sort out the ketonic pairs which give consistent results.

According to Scheme 5, the pairs **12/14** and **15/17** should have the same configurations at the C(1) and C(5) ring junction C atoms. The positive CD values for the

Table 2. Estimated $\Delta\epsilon_{max}$-values for the ketone R-band in ketones of type I and II (Scheme 4). Uncertainty, about ± 1

Stereochemistry (see Scheme 4)	Ketones of Type I	Ketones of Type II
1α,5α (A, cis)	+ 0.4	0
1β,5α (B, trans)	+ 2.5	+ 6.0
1α,5β (C, trans)	- 1.1	+ 0.3
1β,5β (D, cis)	0	+ 2.1



Scheme 5.

Table 3. CD-values of 5(10→1)*abeo*-steroidal ketones

Compound	Solvent	$\lambda_{(nm)}$ ($\Delta\varepsilon_{max}$)
1β,5α-3-keto (12)	Dioxan	315i(+1.36), 305(+2.51), 295(+2.64), 265i(+0.51)
1β,5α-10-keto (14)	Dioxan	305i(+1.95), 295(+2.44), 290i(+2.29), 220(+0.13)
1α,5α-3-keto (15)	Dioxan	318(+0.46), 306.5(+0.87) 296(+0.87), 287(+0.65)
1α,5α-10-keto (17)	Dioxan	313.5(+0.09), 302(+0.13), 292.5(+0.13), 282(+0.11), 240(−0.02)

ketonic pair 12/14 indicates that these compounds should have the *trans*-1β,5α-configuration (B), while for the pair 15/17 the *cis*-1α,5α-configuration (A) fits best. Since these keto-derivatives originate from the solvolysis products 6 and 7, respectively, which were also correlated with the 10-hydroxy compounds 8 and 9, the configuration of all the solvolysis products is thus assigned.

DISCUSSION

From the data in Table 1 it can be seen that the (*E*)-isomer 5 readily solvolyses according to the first-order rate law, while its (*Z*) counterpart 4, under the same reaction conditions, remains unchanged. Since the aim of this work is to explore the structure-reactivity relationship in the solvolysis of 10-membered ring seco-steroid esters, the present discussion will also include the results obtained earlier for the remaining stereoisomers 1 and 2, as well as for the reference compound, i.e. the 1(10)-saturated 5α-*p*-nitrobenzoate.

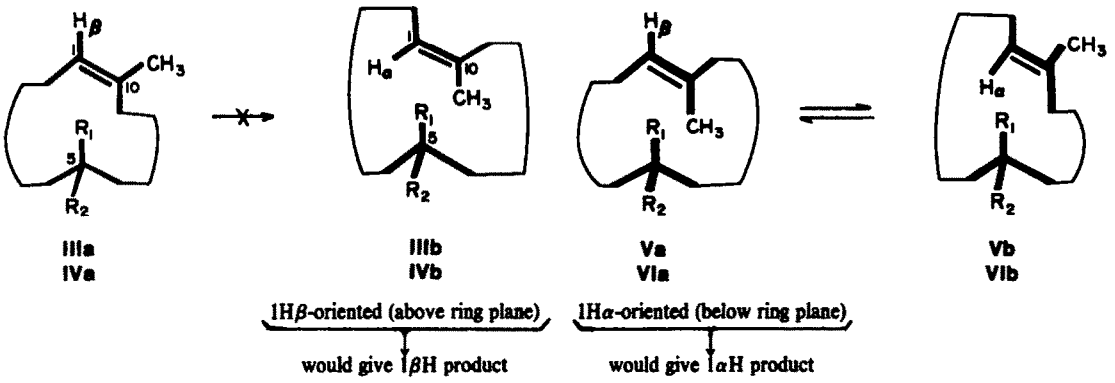
Kinetic measurements (Table 1) point to the following order of reactivity: (*E*)-5β > (*E*)-5α > (*Z*)-5α > 1,10-saturated-5α ≫ (*Z*)-5β, the approximate ratio of solvolysis rates of the four reactive esters being 258000:18500:1200:1 ((*Z*)-5β, $k \sim 0$). It seems unlikely that the difference in reactivity between the *p*-nitrobenzoates 1, 2 and 5 on one hand, and the (*Z*)-5β-ester 4 on the other hand can be ascribed to their ground-state energy differences; rather, for all four compounds similar ground-state energies should be envisaged.[a] Therefore, this result shows that mutual spatial orientation of the 1(10)-olefinic double bond and the chiral center at C(5) in the 10-membered ring, which the stereoisomeric 5-*p*-nitrobenzoates can adopt in the transition state, is the main factor which determines their solvolytic behaviour, so that the esters 1, 2 and 5 solvolyse with transannular double bond participation, while such interaction is not present in the case of the (*Z*)-5β-ester 4. This finding is further substantiated by the fact that of all four unsaturated esters, only the (*Z*)-5β-*p*-nitrobenzoate 4 is less reactive than the reference compound, i.e. the 1,10-saturated 5α-ester. Namely, since the change of hybridization of the two C atoms C(1) and C(10) (from sp^3 to sp^2) stabilizes the 10-membered ring,[8] in the absence of other factors one should expect a slower reaction for an unsaturated ester than for the corresponding saturated analogue.[9]

Product analysis also strongly indicates that in the solvolysis reactions of the reactive 1(10)-unsaturated esters anchimeric assistance by the olefinic double bond is involved. Namely, since such a transannular assistance requires that the two reacting centers, i.e. the 1(10)-double bond and carbon C(5), attain a favourable relative spatial arrangement for back-side internal attack which would enable a maximum overlap of the π-electrons of the double bond with the incipient *p*-orbital at C(5), a nucleophilic displacement with inversion of configuration at C(5) is expected. In the above examples, the stereochemistry at the C(5) ring junction position in the solvolysis products is determined by the original configuration at C(5) in the starting esters. Thus, both the (*Z*)- and (*E*)-5α-*p*-nitrobenzoates 1 and 2 solvolyse stereoselectively giving one and the same cyclization product with the 5β-configuration, i.e. 5(10→1βH)-*abeo*-5β-cholest-10(19)-en-3β-ol acetate 3, and the most reactive (*E*)-5β-isomer solvolyses non-stereoselectively forming several cyclization products, which, however, have all the same α-configuration at C(5), these products being the 1β,5α- and 1α,5α-derivatives 6, 7, 8 and 9 (Scheme 3).

On the other hand, the configuration at C(1) will depend on the way in which the olefinic double bond (either *Z* or *E*) can approach the reaction center from the rear. A schematic representation of these approaches, which would eventually result in 1αH or 1βH product formation is shown in Scheme 6. By considering the mutual orientation of the reacting groups necessary to enhance the solvolysis rate and on the basis of conformational analysis, the difference in reactivity of the four 1(10)-unsaturated esters can be understood.

Inspection of Dreiding models reveals that the *Z*-$\Delta^{1(10)}$-double bond in 5,10-seco-steroids is relatively fixed, because conformational changes involving reorientation of the double bond from IIIa to IIIb, or IVa to IVb (Scheme 6) would be associated with a very strong increase in I-strain. For that reason, molecules of the (*Z*)-5-esters, 1 and 4, respectively, are restricted to conformations from which only the 1βH configurational isomers can be derived. However, in the (*Z*)-5α-ester 1,

[a] Although the unsaturated (*Z*)-cyclodecene ring is about 3.3 kcal/mol more stable that the corresponding (*E*)-isomer,[6] the presence of other substituents in the unsaturated 10-membered ring of the 5,10-seco-steroid molecules, including steroid rings C and D, should cause lowering of this ground-state energy difference. This will be discussed in more detail in the paper to follow.[7]

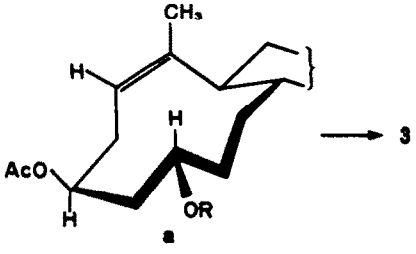


III and V: $R_1 = H$, $R_2 = PNBO$
IV and VI: $R_1 = PNBO$, $R_2 = H$

Scheme 6.

which in solution exists in conformation **a**[f] (Scheme 7), the relative orientation of the double bond with respect to the leaving group (corresponding to IIIa, Scheme 6) is such as to provide efficient π-electron participation and the exclusive formation of the 1β,5β-cyclization product **3**, while in the (*Z*)-5β-ester **4**, a similar orientation (corresponding to IVa, Scheme 6) places the double bond too far and/or ill-oriented with respect to the *p*-nitrobenzoate group to enhance its reactivity. Since such an arrangement exists in the most stable conformation of the 5β-ester **4** (**b**, Scheme 8) (and also in any less stable conformation which would precede cyclization), it is understandable why this isomer is extremely unreactive under solvolytic conditions.

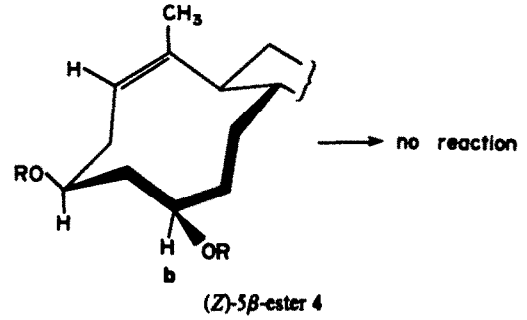
On the other hand, the $\Delta^{1(10)}$-double bond in the (*E*)-series is more flexible, and by rotation around the C(9)-C(10) and C(1)-C(2) single bonds can change its orientation so that both spatial relationships (corresponding to Va and Vb, and VIa and VIb, respectively, Scheme 6),



(*Z*)-5α-ester **1**

Scheme 7.

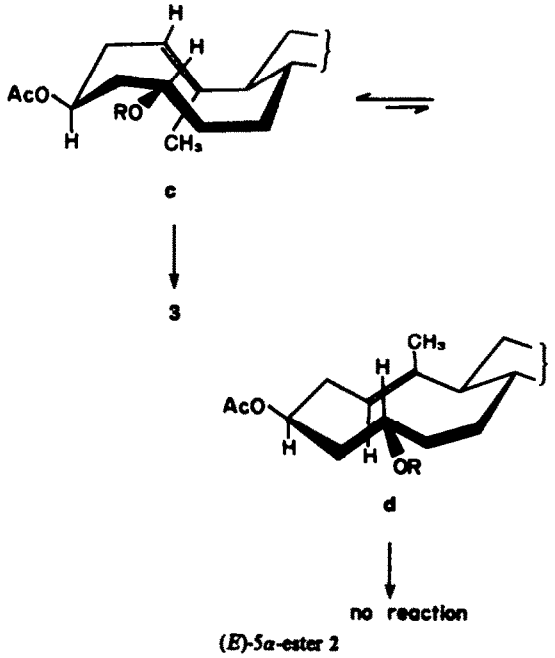
are interconvertible without major increase in I-strain in the 10-membered ring of the 5,10-seco-steroid molecules. Moreover, conformational analysis confirms such prediction, because it is found that the (*E*)-1(10)-unsaturated esters **2** and **5** exist in solution in at least two discrete



(*Z*)-5β-ester **4**

Scheme 8

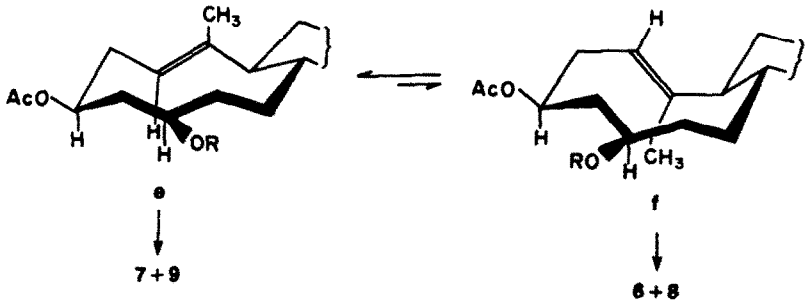
conformational forms, which differ in orientation of the olefinic double bond.[10] For the 5α-ester **2** (Scheme 9) these are conformations **c** (major) and **d** (minor), and for the 5β-ester **5** (Scheme 10) these are conformations **e** (major) and **f** (minor). Therefore, the fact that the (*E*)-



(*E*)-5α-ester **2**

Scheme 9

[f]The preferred conformations of the four 1(10)-unsaturated esters of type **1**, **2**, **4** and **5** in solution were deduced on the basis of ^{1}H NMR and ^{13}C NMR data.[10] It should be noted that although the ground-state conformations of the esters **1**, **2** and **5** should not necessarily be the same as the respective transition-state conformations, they correctly represent spatial relationships of the reacting centers in the transition states which lead to the corresponding cyclization products.



(*E*)-5β-ester 5

Scheme 10.

5α-*p*-nitrobenzoate 2 solvolyses stereoselectively, yielding exclusively the 5β(10→1β*H*)*abeo*-cyclization product 3, indicates that the reaction is conformationally controlled, so that effective transannular double bond participation can be exerted only when molecules are in conformation e. However, since the (*E*)-5β-*p*-nitrobenzoate 5 during solvolysis forms cyclization products with the 1α,5α-, as well as 1β,5α-configuration, it follows that in this case ionization is assisted by the double bond in both conformational forms. Thus, transannular π-electron participation in the major conformation e can result exclusively in the formation of the 5α(10→1α*H*)*abeo*-derivatives 7 and 9, while a similar interaction in the minor conformation f can lead exclusively to the 5β(10→1α*H*)*abeo*-derivatives 6 and 8 (Scheme 10). Moreover, since the relative ratio of the cyclization products with the 1α,5α- and 1β,5α-configuration formed in the solvolysis (~3:1) closely parallels the conformational population of e and f,[10] it may be assumed that both conformational forms are of alike reactivity.

Although the above results are unequivocally informative regarding the stereochemical (configurational and conformational) features of the solvolyses studied, on the basis of these data only it is not possible to present a precise picture concerning the nature of the reaction intermediate(s). However, it seems reasonable to assume that a not fully symmetrical distribution of the positive charge at the three reaction centers, i.e. C(1), C(5) and C(10) (Schemes 7, 9 and 10), occurs in the rate determining step; further, the reaction pathway leads to the formation of the most stable tertiary carbonium ion at C(10), which undergoes water addition and/or proton elimination to give the corresponding transannular solvolysis products.

EXPERIMENTAL[a]

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln. CD measurements were carried out with a JASCO J-20 Spectropolarimeter in dioxan soln at 20° and concentrations about 0.1%, using cells of path-lengths of 0.01–0.1 cm. NMR spectra were obtained at 100 MHz with a Varian HA-100 spectrometer in $CDCl_3$ soln at room temp using TMS as internal standard; chemical shifts are reported in δ values; abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were determined on a Perkin–Elmer double-beam instrument, model 337. Mass spectra were taken on an Atlas CH4 mass spectrometer. Silica gel (0.05–0.2) was used for preparative column chromatography. The separation of products was monitored by tlc on silica gel G (Stahl) with benzene–AcOEt (9:1 or 7:3), detection being effected with 50% H_2SO_4. Light petroleum refers to the fraction b.p. 40–60°.

Preparation of 5α-p-*nitrobenzoates* 1 and 2 from (*Z*)-and (*E*)-5,10-seco-1(10)-cholestene-3β,5α-diol 3-acetates[11] and their solvolysis to the cyclization product 3 was reported previously.[3] (*Z*)-5α-p-*Nitrobenzoate* 1, m.p. 168° (with sublimation); $[\alpha]_D^{20}$ + 37° (*c* = 0.51); IR (KBr): ν_{max} 1738, 1725, 1610, 1538, 1275, 1240 cm^{-1}; NMR: δ 0.71 (Me-18, s), 0.86 (Me-26 and Me-27, d), 0.89 (Me-21, d), 1.70 (Me-19, d), 1.92 (AcO-3, s), 4.90, 5.27 and 5.41 (H-1, H-3 and H-5, m), 8.19 (4 aromatic H, m). (Found: C, 72.35; H, 9.05; N, 2.29. Calc. for $C_{36}H_{53}O_6N$: C, 72.57; H, 8.97: N, 2.35%). (*E*)-5α-p-*Nitrobenzoate* 2, m.p. 132°; $[\alpha]_D^{20}$ −20° (*c* = 0.45); IR (KBr): ν_{max} 1734, 1720, 1605, 1532, 1270, 1238 cm^{-1}; NMR: δ 0.82 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.87 (Me-21, d), 1.76 (Me-19, d), 1.79 (AcO-3, s), between 5.00 and 5.65 (H-1, H-3 and H-5, m), 8.22 (4 aromatic H, m). (Found: C, 72.69; H, 8.91; N, 2.56. Calc. for $C_{36}H_{53}O_6N$: C, 72.57; H, 8.97; N, 2.35%). 5(10→1β*H*)abeo-5β-*Cholest*-10(19)-*en*-3β-*ol acetate* 3, m.p. 89–90°; $[\alpha]_D^{20}$ + 3° (*c* = 1.25); IR (KBr): ν_{max} 1742, 1635, 1242 cm^{-1}; NMR: δ 0.73 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.88 (Me-21, d), 2.01 (AcO-3, s), 2.35 (H-5, m), 3.08 (H-1, m), 4.66 and 4.84 (2 exocyclic vinyl H at C-19), 5.18 (H-3, m). (Found: C, 81.20; H, 11.01. Calc. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29%).

Preparation of (*Z*)- and (*E*)-5β-p-*nitrobenzoates* 4 and 5 was described previously[4] (*Z*)-5,10-*Seco*-1(10)-*cholestene*-3β,5β-*diol di*-p-*nitrobenzoate* 4, m.p. 65°; $[\alpha]_D^{20}$ + 92° (*c* = 1.0, dioxan); IR (KBr): ν_{max} 3110, 1720, 1600, 1520, 1270, 1100, 715 cm^{-1}; NMR: δ 0.72 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.87 (Me-21, d), 1.72 (Me-19, s), about 5.20 (H-1, H-3 and H-5, m), 7.95 (8 aromatic H, s). (Found: C, 69.82; H, 7.84; N, 4.03. Calc. for $C_{41}H_{54}O_8N_2$: C, 70.6; H, 7.74; N, 3.99%). (*E*)-5,10-*Seco*-1(10)-*cholestene*-3β,5β-*diol* 3-*acetate* 5-p-*nitrobenzoate* 5, m.p. 106–108°; $[\alpha]_D^{20}$ + 72° (*c* = 1.02); IR (CCl_4): ν_{max} 1735, 1720, 1595, 1520, 1265, 1230, 1095 cm^{-1}; NMR: δ 0.68 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.90 (Me-21, d), 1.70 (Me-19, s), 1.98 (AcO-3, s), about 5.10 (H-3 and H-5, m), about 5.30 (H-1, m), 8.20 (4 aromatic H, q). (Found: C, 72.71; H, 8.92; N, 2.50. Calc. for $C_{36}H_{53}O_6N$: C, 72.57; H, 8.97; N, 2.35%).

Solvolysis of (E)-5,10-*seco*-1(10)-*cholestene*-3β,5β-*diol* 3-*acetate* 5-p-*nitrobenzoate* 5

Kinetics. Acetone was purified by heating at reflux with a small quantity of $KMnO_4$, followed by drying over $CaSO_4$ and distillation at atmospheric pressure. Water used in the kinetic studies was doubly distilled.

For kinetic studies a 0.0168 M soln of 5 (containing 1.0009 g ester in 100 ml soln) in 90% aqueous acetone was prepared at 20°. Aliquots of the soln (5 ml) were sealed off in glass ampoules and placed in a thermostat heated at 125° ± 0.2° for appropriate time periods. On removal from the thermostat the ampoules were chilled in ice-water and the contents were analysed. The rate of acid formation was measured by potentiometric titration with 0.022 M KOH, using a pH-meter "22-Radiometer". The first-

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order rate constant, shown in Table 1, was calculated from the rate of *p*-nitrobenzoic acid formation in the usual manner and represents the average value of two separate experiments.

Solvolysis products. A soln of **5** (1.00 g) in aqueous acetone (90:10 v/v) (100 ml) was sealed off in a tube and heated for 24 hr at 100°. The content of the tube was poured into H_2O, extracted with ether, the ethereal layer washed with sat. $NaHCO_3$ aq and H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness. The residue (780 mg) was chromatographed on silica gel (40 g). Elution with benzene gave a mixture of **6** and **7** (468 mg, about 65%).

Benzene–ether (98:2, 96:4 and 94:6) afforded a complex mixture (45 mg) which was not further investigated. Benzene–ether (90:10) eluted first 16 mg (2.1%) of **8**; IR (CCl_4): ν_{max} 3620, 1742, 1245, 1030 cm^{-1}; M^+ 446. The next benzene–ether (90:10) eluates contained **9** (198 mg, 26.4%), m.p. 73–75° from acetone (181 mg, 24.1%); $[\alpha]_D^{20}$ + 21° (*c* = 1.50); IR (CCl_4): ν_{max} 3620, 3590, 1730, 1240, 1040 cm^{-1}; NMR: δ 0.68 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.90 (Me-21, d), 1.20 (Me-19, s), 2.00 (AcO-3, s), 4.95 (H-3, m). (Found: C, 77.78; H, 11.26. Calc. for $C_{29}H_{50}O_3$: 77.97; H, 11.28%).

Separation of the solvolysis products **6** *and* **7**. The oily mixture of **6** and **7** (468 mg) was hydrolysed with 5% methanolic KOH (50 ml) at room temp. for 2 hr and worked up in the usual way. The residue (416 mg) was then chromatographed on 20 g of silica gel. Benzene–ether (90:10) eluted first 124 mg (19.4%, calculated on the starting ester **5**) of **10**, m.p. 131–132° from acetone (108 mg, 16.9%); $[\alpha]_D^{20}$ + 35° (*c* = 0.20); IR (CCl_4): ν_{max} 3630, 1630, 1000, 886 cm^{-1}. (Found: C, 83.68; H, 11.90. Calc. for $C_{27}H_{46}O$: C, 83.87; H, 11.99%). It was acetylated with Ac_2O in pyridine soln in the usual way to give **6**, m.p. 67° from acetone–methanol; $[\alpha]_D^{20}$ + 55° (*c* = 0.20); IR (CCl_4): ν_{max} 1740, 1638, 1245, 890 cm^{-1}; NMR: δ 0.70 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.90 (Me-21, d), 2.02 (AcO-3, s), 4.74 and 4.86 (2 exocyclic vinyl H at C-19), 5.15 (H-3, m). (Found: C, 81.36; H, 11.23. Calc. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29%).

The next benzene–ether (90:10) eluates contained **10**, **11** and a complex mixture which was not further investigated (62 mg). Benzene–ether (85:15) afforded 226 mg (35.3% calculated on the starting ester **5**) of **11**, m.p. 107–108° from acetone (207 mg, 32.3%); $[\alpha]_D^{20}$ ~ 0° (*c* = 0.20); IR (CCl_4): ν_{max} 3640, 1640, 1070, 890 cm^{-1}. (Found: C, 83.91; H, 12.06. Calc. for $C_{27}H_{46}O$: C, 83.87; H, 11.99%). Acetylation of **11** with Ac_2O in pyridine gave **7** as an oil; $[\alpha]_D^{20}$ + 5° (*c* = 0.96); IR (CCl_4): ν_{max} 1745, 1640, 1245, 890 cm^{-1}. NMR: δ 0.70 (Me-18, s), 0.84 (Me-26 and Me-27, d), 0.90 (Me-21, d), 2.00 (AcO-3, s), 2.70 (H-1, m), 4.84 and 4.98 (2 exocyclic vinyl H at C-19), about 5.00 (H-3, m). (Found: C, 81.30; H, 11.49. Calc. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29%).

Dehydration of 5(10→1α*H*)*abeo-5α-cholestane-3β,10α-diol* 3-*acetate* **9**. A soln of **9** (95 mg) in DMF (1.2 ml) and anhyd pyridine (0.12 ml) was dehydrated with mesyl chloride (0.06 ml) at room temp. for 24 hr. The product (91 mg, 100%) obtained after the usual work up was dissolved in benzene and the soln passed through a SiO_2 column. Evaporation *in vacuo* to dryness gave **7** (78 mg, 85.6%) as an oil (IR and NMR spectra were identical with spectra of authentic **7**).

Dehydration of 5(10→1β*H*)*abeo-5α-cholestane-3β,10β-diol* 3-*acetate* **8**. Product **8** (14 mg) was treated with mesyl chloride in DMF and pyridine as described to give **6** (12 mg, 89.6%), IR spectrum was identical with spectrum of authentic **6**.

Oxidation of 5(10→1β*H*)abeo-5α-*cholest*-10(19)-*en*-3β-*ol* **10**. To a cooled (5°) soln of **10** (50 mg) in acetone (10 ml) a slight excess of Jones reagent[12] was added with stirring. After 5 min the mixture was poured into ice-water and extracted with ether. The ethereal layer was washed with H_2O, sat. $NaHCO_3$ aq, H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness, affording **12** (50 mg, 100%), which was dissolved in benzene, passed through a SiO_2 column, evaporated *in vacuo* to dryness and recrystallized from acetone-methanol (yield 40 mg, 80.4%), m.p. 69–71°; $[\alpha]_D^{20}$ + 73 (*c* = 0.30); IR (CCl_4): ν_{max} 1750, 1630, 890 cm^{-1}; NMR: δ 0.70 (Me-18, s), 0.86 (Me-26 and Me-27, d), 0.91 (Me-21, d), 4.90 and 4.94 (2 exocyclic vinyl H at C-19). (Found: C, 84.19; H, 11.60. Calc. for $C_{27}H_{44}O$: C, 84.31; H, 11.53%).

Oxidation of 5(10→1α*H*)abeo-5α-*cholest*-10(19)-*en*-3β-*ol* **11**. Alcohol **11** (65 mg) in acetone (13 ml) was oxidized as described above to give **15**, m.p. 88° from acetone–methanol (54 mg, 83.5%); $[\alpha_D^{20}$ + 28° (*c* = 0.3); IR (CCl_4): ν_{max} 1740, 1640, 895 cm^{-1}; NMR: δ 0.72 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.93 (Me-21, d), 4.63 and 5.00 (2 exocyclic vinyl H at C-19). (Found: C, 84.27; H, 11.56. Calc. for $C_{27}H_{44}O$: C, 84.31; H, 11.53%).

Hydroxylation of 5(10→1β*H*)abeo-5α-*cholest*-10(19)-*en*-3β-*ol acetate* **6** *and glycol cleavage of* 5(10→1β*H*)abeo-5α-cholestane-3β,10ξ,19-*triol* 3-*acetate* **13** *with lead tetraacetate.* Osmium tetroxide (58 mg) was added to a soln of **6** (85 mg) in thiophene-free benzene (2.5 ml) and pyridine (2.2 ml). After standing at room temp. for 24 hr the mixture was diluted with AcOEt (15 ml). H_2S was then bubbled through the soln for 1 hr and the insoluble salts were removed by filtration through a Celite mat. Evaporation of the solvents gave **13** (67 mg, 73.0%), which was used without further purification. Lead tetraacetate (80 mg) and **13** (67 mg) in dry benzene (10 ml) were heated under reflux for 0.5 hr. The mixture was cooled, diluted with ether, filtered through a Celite mat and the insoluble ppt thoroughly washed with ether. The organic soln was washed with H_2O, sat $NaHCO_3$ aq and H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to dryness, affording **14** (41 mg, 65.8%), m.p. 103–105° from MeOH (35 mg, 56.1%); $[\alpha]_D^{20}$ + 45° (*c* = 0.7); IR (KBr); ν_{max} 1740, 1695, 1245, 1177 and 1020 cm^{-1}; NMR: δ 0.76 (Me-18, s), 0.86 (Me-26 and Me-27, d), 0.91 (Me-21, d), 2.03 (AcO-3, s), ~3.20 (H-1, m), ~5.15 (H-3, m). (Found: C, 77.95; H, 10.83. Calc. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77%).

Hydroxylation of 5(10→1α*H*)abeo-5α-*cholest*-10(19)-*en*-3β-*ol acetate* **7** *and glycol cleavage of* 5(10→1α*H*)abeo-5α-*cholestane*-3β,10ξ,19-*triol* 3-*acetate* **16** *with lead tetraacetate.* Compound **7** (130 mg) was treated with osmium tetroxide (91 mg) in benzene (4 ml) and pyridine (3.5 ml) as described to give 108 mg (77.0%) of **16**. It was oxidized with lead tetraacetate (150 mg) in benzene (15 ml) as above, affording 77 mg (76.6%) of **17**, m.p. 100–102° from MeOH (70 mg, 69.6%); $[\alpha]_D^{20}$ + 11° (*c* = 0.5); IR (KBr): ν_{max} 1740, 1700, 1235, 1050 cm^{-1}; NMR: δ 0.72 (Me-18, s), 0.85 (Me-26 and Me-27, d), 0.92 (Me-21, d), 2.00 (AcO-3, s), ~3.15 (H-1, m), ~5.00 (H-3, m). (Found: C, 77.90; H, 10.89. Calc. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77%).

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