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CONFIGURATIONAL AND CONFORMATIONAL STUDIES OF SOME B-HOMO-A-NOR-STEROIDS[1,2]

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Abstract—Cyclization of (E)-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (**1**) by treatment with $H^{\oplus}$ in aprotic solvents leads to a mixture of two 1,5-stereoisomeric 5(10 → 1)*abeo*-cholest-10(19)-ene-3β,5-diol 3-acetates **2** (major product) and **3**, whereas the thermal cyclization of **1** affords exclusively product **2**. On the basis of chemical transformations and interpretation of physical measurements, particularly of CD data of 5-membered and 7-membered ring ketones derived from products **2** and **3**, it was possible to assign the *trans* 1β,5α-configuration to the 5(10 → 1)*abeo*-steroid **2**, and the *cis* 1α,5α-configuration to the stereoisomeric product **3**. The stereochemical course of these cyclization reactions is discussed in terms of possible transition state (and ground state) conformations of the *trans*-cyclodecene ring in the starting 5,10-seco-1(10)-en-5-one **1** (and its protonated intermediate).

INTRODUCTION

As reported previously,[3,4] the lead tetraacetate oxidation of either 5α-cholestane-3β,5-diol 3-acetate or its 5β-epimer affords mainly fragmentation products containing a ten-membered ring instead of the two fused cyclohexane rings A and B, namely (E)-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (**1**) and the corresponding (Z)-stereoisomer [(E) and (Z) referring to the C_1-H/C_{10}-CH_3 *trans*- and *cis*-configuration, respectively, around the 1(10)-double bond].‡ When treated with $H^{\oplus}$ in aprotic solvents the (E)-5,10-seco-enone **1** (Scheme 1) undergoes intramolecular cyclization (in 70–75% yield), to give a mixture of two 1,5-stereoisomeric 5(10 → 1)*abeo*-cholest-10(19)-ene-3β,5-diol 3-acetates‡ **2** and **3**, in a molar ratio of 9:1.[4] Transannular cyclization of the (E)-5,10-seco-1(10)-en-5-one **1** can be also achieved thermally, in the absence of $H^{\oplus}$, whereby only isomer **2** (Scheme 1) is obtained (in 40–45% yield when a solution of **1** in toluene is heated to reflux for 16 hr, and in about 30% yield when refluxing is carried out in ethanol solution). The stereoisomeric (Z)-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate, however, does not cyclize and remains unchanged under similar (acidic or thermal) reaction conditions.¶

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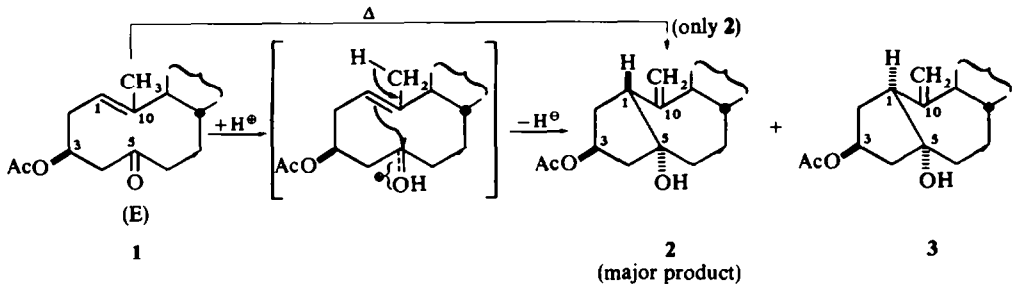
‡ All names according to IUPAC-IUB 1967 Revised Tentative Rules for Steroid Nomenclature (*IUPAC Information Bull.* 33,453 (1968)). (E)/(Z)-Nomenclature according to IUPAC 1968 Tentative Rules, Section E, Fundamental Stereochemistry (*Ibid.* 35, 36 (1969)).

¶ Inspection of Dreiding models shows that because of the favourable distance and orientation of the 5-CO group with respect to the 1(10)-olefinic bond, the (E)-5,10-seco-1(10)-en-5-one **1** in its stable conformations would be expected to undergo readily transannular reactions[5] with participation of the C=C double b... [3,4] whereas the stable conformations of the stereoisomeric (Z)-5,10-seco-1(10)-en-5-one, with the 1(10)-carbon-carbon double bond far away from the 5-CO group, should not favour intramolecular cyclization of this kind.[4]



SCHEME 1

By treating **1** with acid Akhtar and Marsh[6] have obtained only one compound (**2**), and mainly from consideration of IR spectra have deduced the 1β,5α-stereochemistry for it. We have now converted alcohols **2** and **3** into various ketones and other products (Schemes 2, 3 and 5), and on the basis of spectral data and particularly of CD measurements have proved the configuration of **2** and determined that of **3**, as well as the configurations of their respective derivatives.

CHEMICAL TRANSFORMATIONS

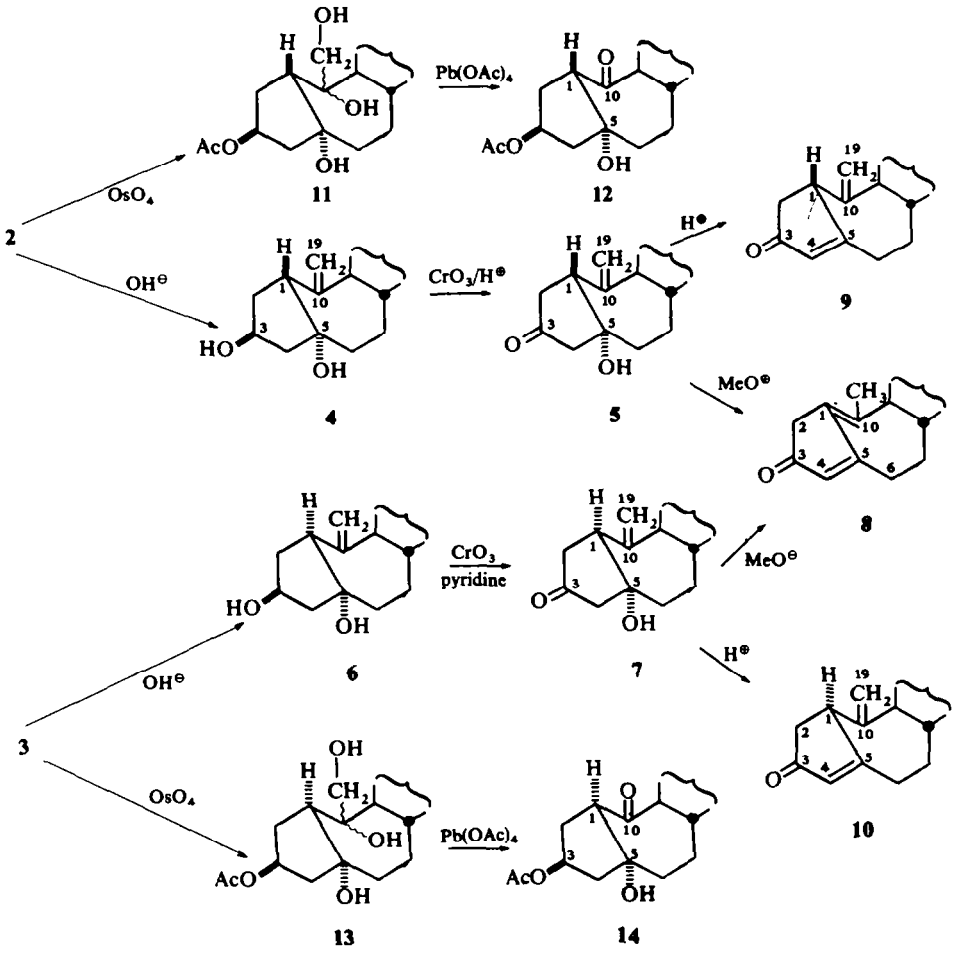
From the reactions of compounds **2** and **3** shown on Scheme 2,* and particularly from conversions **5** → **8** and **7** → **8**, as well as **5** → **9** and **7** → **10**, it can be concluded, on the reasonable assumption that these transformations do not involve isomerization at the junctions of the fused 5- and 7-membered rings A and B, that the starting acetoxy-alcohols **2** and **3**, and their corresponding keto-alcohols **5** and **7**, and **12** and **14**, are respective stereoisomeric pairs which have a different configuration at the junction carbon C-1, and may or may not differ in the stereochemistry of attachment at the C-5 C atom.

For comparison purposes, the ketones **18** and **19**, which are similar to the pairs **5**/**7** and **12**/**14**, respectively, but contain at position C-5 an H atom instead of an OH group, were also prepared (Scheme 3). These ketones were obtained from 5(10 → 1βH)*abeo*-5β-cholest-10(19)-en-3β-ol acetate (**17**), which is a solvolysis product of both the (Z)- and (E)- 5,10-seco-5ξ-cholest-1(10)-en-3β,5-diol 3-acetates (**15** and **16**), by reactions analogous to those used for the synthesis of the 5-OH ketones **5**/**7** and **12**/**14**, respectively (Scheme 2).†

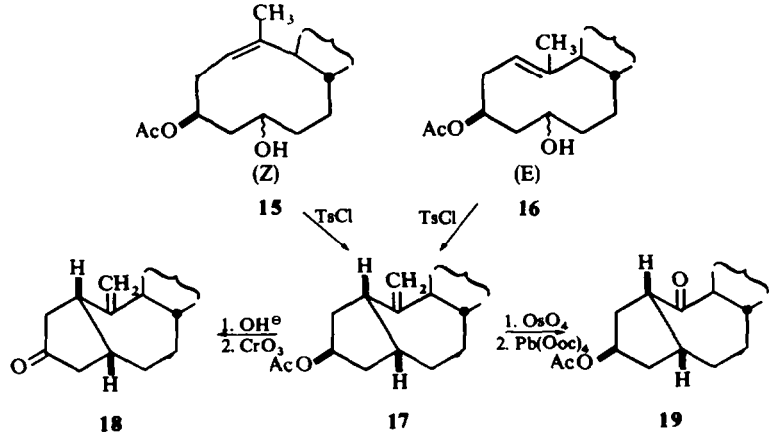
A 5-membered and 7-membered ring can be *cis*- or *trans*-fused, so that 5(10 → 1)*abeo*-steroid derivatives can exist in four stereoisomeric forms (Scheme 4), two with the B-homo/A-nor *cis*-configuration (**A** and **D**) and two with the B-homo/A-nor *trans*-configuration (**B** and **C**). That the above described compounds have the *trans* 1β,5α-configuration **B** (**2**, **4**, **5**, **11**, **12**), the *cis* 1α,5α-configuration **A** (**3**, **6**, **7**, **13**, **14**) and (probably) the *cis* 1β,5β-configuration **D** (**17**, **18**, **19**), respectively, was determined by analysis of data obtained from physical measurements.

*The constitutions of the products were determined on the basis of their mode of formation, analytical data and spectral evidence (IR, UV, NMR spectra; see Experimental).

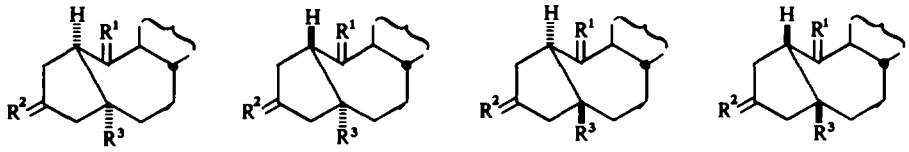
†Details of the stereochemical course of these solvolytic reactions and experimental data will be described in a separate publication.



SCHEME 2



SCHEME 3



cis 1α,5α **A** *trans* 1β,5α **B** *trans* 1α,5β **C** *cis* 1β,5β **D**

Ketones type (I): $R^1 = CH_2$, $R^2 = O$, R^3 = OH (**5**, **7**) or H (**18**)

Ketones type (II): $R^1 = O$, $R^2 =$  , R^3 = OH (**12**, **14**) or H (**19**)

SCHEME 4

CD MEASUREMENTS

The 7-membered ring B in these 5(10 → 1)*abeo*-steroid compounds can adopt several conformations and for all four possible isomers (**A–D**, Scheme 4) of general structures I (5-membered ring ketones) and II (7-membered ring ketones) we estimated their relative stabilities. For the skeleton this was done according to Hendrickson,[7] and in case of the methylene compounds of type I the repulsion energy of the olefinic hydrogens was calculated (from Dreiding models assuming in each conformation ideal twist chairs or twist boats) according to Hill.[8] These data are summarized in Table 1. From known CD data (latest collection in Ref. 9, and own results) we tried to predict $\Delta\varepsilon_{max}$-values for all these conformations, and by comparing them with the measured data (Table 2) we were able to sort out those isomers which give consistent results.

CD of saturated ketones

1α,5α-I (system **A**, *cis*): The most stable conformation of ring B is TC-5; with

TABLE 1. CONFORMATIONAL ENERGIES OF THE FOUR POSSIBLE STEREOISOMERIC 5(10 → 1)*abeo*-STEROID SYSTEMS **A**, **B**, **C** AND **D** OF TYPE I AND II (SCHEME 4)

Isomer (Scheme 4)	Conformation	ΔE (Hendrickson)[a] R^3 = OH	ΔE (Hendrickson)[a] R^3 = H	ΔE (Prelog)[b]
1α,5α (**A**, *cis*)	TC-5	0	0	0·4
	TC-1	2·15	0	0·2
1β,5α (**B**, *trans*)	TC-9	0	0	0·1
	TC-10	1·75	0	0·5
1α,5β (**C**, *trans*)	TC-6	0	0	1·6
	TC-7	0·3	0	0·4
1β,5β (**D**, *cis*)	TC-1	0	0	0·1
	TC-5	0	0	0·8
	TC-8	1·2	0·5	0
	TB-5	0	0	11·0
	TB-7	0·7	0	3·0
	TB-9	2·8	0	3·0

[a] Conformational energies of the skeleton, calculated after ref. 7. Energy for the most stable conformer in each column is taken as 0.

[b] Additional conformational energies of steric repulsion of olefinic hydrogens in ketones of type I (Scheme 4), calculated according to Hill.[8]

R^3 = H, TC-1 is of comparable energy (0·2 kcal/mole less stable), whereas in the hydroxylated compound (R^3 = OH) this conformation is about 1·9 kcal/mole richer in energy than TC-5. The octant projections[10] of these conformations are given in Fig. 1. The 5-membered ring A of TC-5 is twisted and this will lead to a contribution of the second sphere[11,12] of about +3 (in 2-indanones up to about 6). If the contributions of higher spheres are not very large, the dissymmetry of the second sphere will

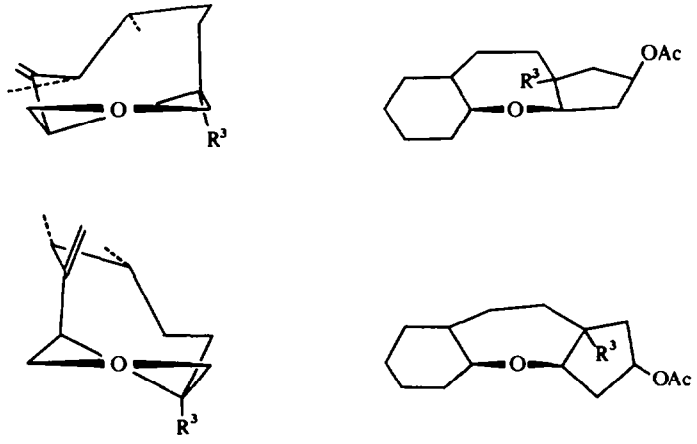


FIG. 1 Octant projections of 1α,5α-isomer (A,*cis*). Left: Ketone type I. Right: Ketone type II. Upper row: Conformation TC-1. Lower row: Conformation TC-5.

govern mainly the Cotton effect. The OH group in the 5α-position (1α,5α-I, R^3 = OH) should give a small positive contribution, because it resembles a β-axial OH in a cyclohexanone, for which we have found a value of about +0·2.[13] The contribution of the double bond 10 : 19 is difficult to estimate, because whether it will give a positive or negative value depends not only on its position but also on the orientation. We have, therefore, not evaluated this contribution explicitly. The third sphere effects are estimated from the octant rule to be positive (about +1). Conformation CT-5 should thus give a CD of about +4·2 ±1 for R^3 = OH, and a slightly smaller value for R^3 = H (4·0 ±1).

TABLE 2. CD-VALUES OF 5(10 → 1)*abeo*-STEROIDAL KETONES

Compound	Solvent	λ (nm) ($\Delta\varepsilon_{max}$)
5	dioxan	317*i*(+1·49), 305(+3·13), 295(+3·34), 285*i*(+2·49)
9	dioxan	352*i*(+0·24), 333(+0·51), 321(+0·56), 310*i*(+0·45), 237(−4·3)
12	dioxan	305*i*(+2·86), 295(+3·52), 287(+3·18)
7	dioxan	318(+1·17), 307(+2·45), 297(+2·69), 287*i*(+2·12), 238(+0·74)
10	dioxan	348*i*(−0·50), 333(−1·10), 320(−1·08), 305*i*(−0·49), 237(+21·61)
	acetonitrile	343*i*(−0·63), 327(−1·40), 317(−1·30), 302*i*(−0·69), 239(+25·16), 197(−18·7)
14	dioxan	322(+0·02), 312(−0·06), 301(−0·09), 291(−0·06)
	ethanol	318(+0·02), 311*i*(−0·03), 301*i*(−0·10), 291(−0·13), 221(−0·07), 199(+0·6)
18	dioxan	319(−0·84), 308(−1·74), 298(−1·92), 288*i*(−1·54), 278*i*(−0·91)
19	dioxan	314*i*(+1·14), 302*i*(+3·18), 292(+3·81), 212(+0·19)

Conformation TC-1, which is important only in case of R^3 = H gives the opposite chirality of ring A ($\Delta\varepsilon_{max} = -3$), and a slight negative contribution (about −0·2) from the third sphere effects, giving $-3{\cdot}2 \pm 1$ as the sum. Assuming equal populations of TC-5 and TC-1 for R^3 = H, we finally get about $+0{\cdot}4 \pm 1$ for the CD.

1β,5α-I (system **B**, *trans*): Conformation TC-9 is about 2·15 kcal/mole more stable than TC-10 in case of R^3 = OH. Octant projection (Fig. 2) leads to an estimation (done in the same way as above) for the CD of about $+2{\cdot}7 \pm 1$ (R^3 = OH) and $+2{\cdot}5 \pm 1$ (R^3 = H).

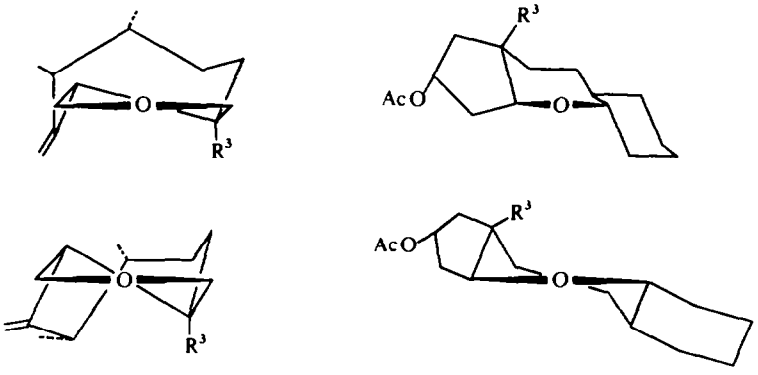


FIG. 2 Octant projections of 1β,5α-isomer (**B**,*trans*). Left: Ketone type I. Right: Ketone type II. Upper row: Conformation TC-9. Lower row: Conformation TC-10.

1α,5β-I (system **C**, *trans*): Conformation TC-7 is more stable than TC-6 by about 0·9 kcal/mole for R^3 = OH, and by about 1·2 kcal/mole for R^3 = H. Conformation TC-7 seems, however, from Dreiding models, to have greater angle (Baeyer) strain. The octant projection (Fig. 3) leads to about −1·7 for TC-6 and −1·2 for TC-7 (R^3 = OH); the corresponding values are less negative for R^3 = H (−1·5 and −1·0, respectively). We estimate, therefore, from these values the CD of 1α,5β-I (system **C**, *trans*) for R^3 = OH to about $-1{\cdot}3 \pm 1$, and for R^3 = H to about $-1{\cdot}1 \pm 1$.

1β,5β-I (system **D**, *cis*) (Figs. 4 and 5): Conformation TC-1 is more stable by 0·7 kcal/mole than TC-5 (R^3 = OH or H), and by about 1·6 kcal/mole (R^3 = OH) or 0·9 kcal/mole (R^3 = H) than TC-8. Twist-boat conformations, which according to the Hendrickson treatment should be of equal energy content, are highly destabilized (3 to 11 kcal/mole) by Prelog strain and must not be considered for the 3-ketones of type I. For R^3 = OH we obtain −0·4, and for R^3 = H about zero as the estimated CD. These data are summarized in Table 3.

Analogously one can estimate the contributions to the Cotton effect of the cycloheptanones of type II and again the dissymmetry of the second sphere has to be taken into account for this 7-membered ring as was done for the 5- and 6-membered rings.[10,11]

1α,5α-II (system **A**, *cis*): Conformation TC-5 leads to a contribution of about zero from the nearly achiral ring B (Fig. 1), the 5-OH gives about −0·2, and the rests of the third and higher sphere contributions will roughly cancel each other, so that we are left with about $-0{\cdot}2 \pm 1$ for R^3 = OH. R^3 = H will give about zero for the same

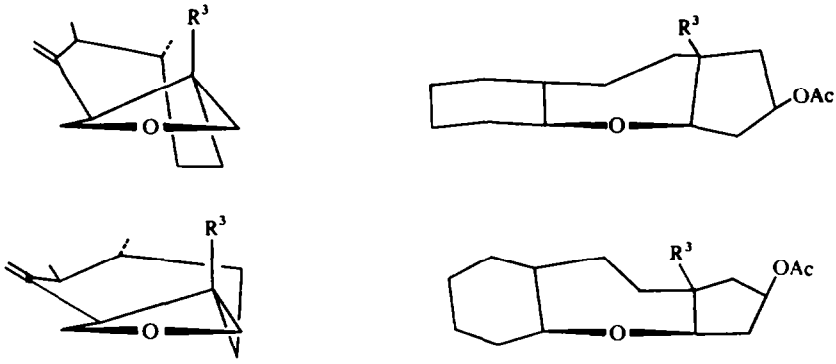


FIG. 3 Octant projections of 1α,5β-isomer (C,*trans*). Left: Ketone type I. Right: Ketone type II. Upper row: Conformation TC-6. Lower row: Conformation TC-7.

conformation; TC-1 should be equally populated, but as this also gives zero as the estimated CD, the resulting Cotton effect will be very weak.

1β,5α-II (system **B**, *trans*) (Fig. 2): In TC-9 the 7-membered ring is twisted and we can estimate about +2·5 for its contribution. In case of R^3 = OH we get then about +4·2 ±1 for the CD. With R^3 = H, TC-9 leads to about +4·0, but here TC-10 has also to be considered, and for it one obtains about +8·0. Taken together we expect a CD of about +6 ±1 for the compound with R^3 = H.

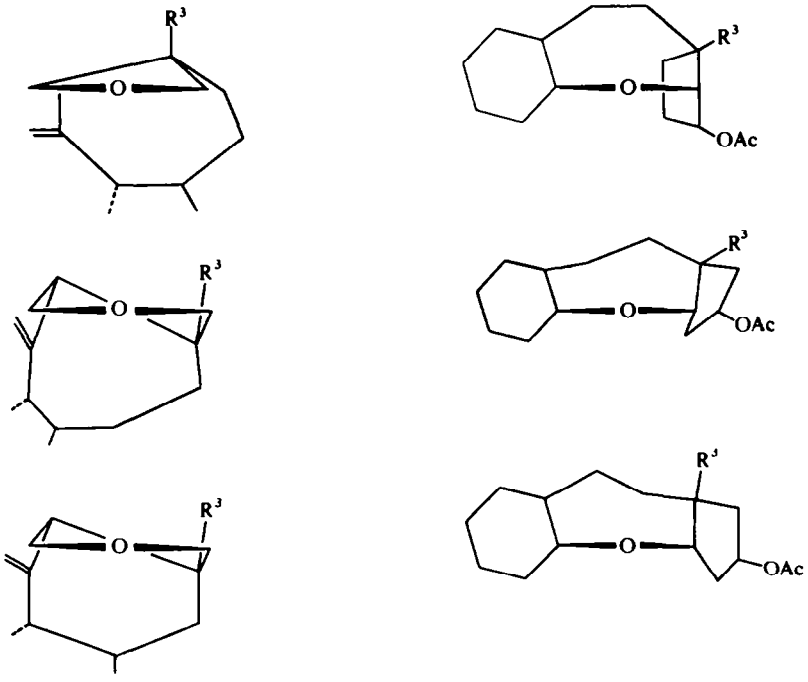


FIG. 4 Octant projections of 1β,5β-isomer (D,*cis*), TC-forms. Left: Ketone type I. Right: Ketone type II. First row: Conformation TC-1. Second row: Conformation TC-5. Third row: Conformation TC-8.

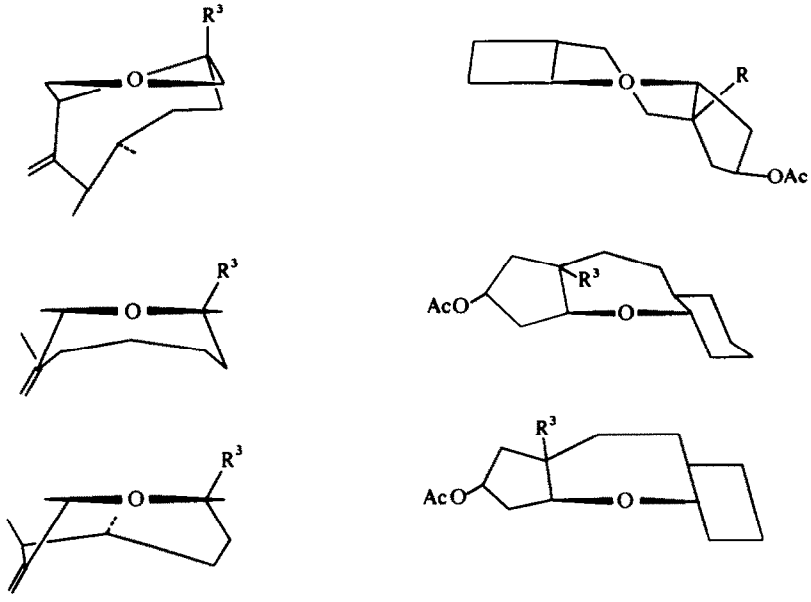


FIG. 5 Octant projections of 1β,5β-isomer (**D**,*cis*), TB-forms. Left: Ketone type I. Right: Ketone type II. First row: Conformation TB-5. Second row: Conformation TB-7. Third row: Conformation TB-9.

1α,5β-II (system **C**, *trans*) (Fig. 3): An estimation of the CD for TC-6 gives a value of about $-1{\cdot}8$ for R^3 = OH and $-1{\cdot}7$ for R^3 = H. For TC-7 the respective values are $+2{\cdot}2$ and $+2{\cdot}3$. Taking into account the conformational equilibrium we obtain thus $-0{\cdot}5 \pm 1$ for R^3 = OH and $+0{\cdot}3 \pm 1$ for R^3 = H.

1β,5β-II (system **D**, *cis*) (Fig. 4): In this isomer twist-boat conformations have to be taken into account. For R^3 = H the energy content is the same for TC-1 ($\Delta\varepsilon_{max}$ about $+0{\cdot}5$), TC-5 ($-1{\cdot}5$), TB-5 ($+7{\cdot}0$), TB-7 ($+4{\cdot}0$) and TB-9 ($+0{\cdot}5$), whereas for R^3 = OH only TC-1 (0), TC-5 ($-1{\cdot}7$) and TB-5 ($+7{\cdot}0$) are of the same energy, TB-7 being higher by 0·7 kcal/mole ($\Delta\varepsilon_{max}$ about $+4{\cdot}2$) and TB-9 by 2·8 kcal/mole. This leads to estimated values for the CD of $+1{\cdot}8 \pm 1$ (R^3 = OH) and $+2{\cdot}1 \pm 1$ (R^3 = H).

TABLE 3. ESTIMATED $\Delta\varepsilon_{max}$-VALUES FOR THE KETONE R-BAND CD IN KETONES OF TYPE I AND II (SCHEME 4). UNCERTAINTY, ABOUT ±1.

Stereochemistry (see Scheme 4)	Substituent (R^3) at C-5	Ketones of type I	Ketones of type II
1α,5α (**A**, *cis*)	OH	+4·2	−0·2
	H	+0·4	0
1β,5α (**B**, *trans*)	OH	+2·7	+4·2
	H	+2·5	+6·0
1α,5β (**C**, *trans*)	OH	−1·3	−0·5
	H	−1·1	+0·3
1β,5β (**D**, *cis*)	OH	−0·4	+1·8
	H	0	+2·1

If no isomerization takes place during oxidation (Schemes 2 and 3), the pairs **5/12**, **7/14** and **18/19** should have the same configurations at C-1 and C-5, respectively. The strong positive CD values for the corresponding pair **5/12** suggests that these compounds must have the *trans* 1β.5α-configuration (**B**), in agreement with assignment from IR spectra.[6] The pair **7/14** fits only the *cis* 1α,5α-configuration (**A**). Deviation for the C-5 nonhydroxylated pair **18/19** is larger, but the *cis* 1β,5β-configuration (**D**) is the most probable from the CD-values.

CD of α,β-unsaturated ketones

Ketone **9** gives a positive R-band and a negative K-band CD of medium intensity, whereas in ketone **10** the signs are inverted and the 237 nm band is unusually big. As from models one cannot unequivocally derive the preferred conformations of the 5-membered ring, the R-band CD of the conjugated ketones **9** and **10** could not be used for the determination of the configuration at C-1.

The most preferred conformation of the 7-membered ring B is such that in the 1β-compound (**9**) the exocyclic methylene double bond is far away from the conjugated enone grouping (Fig. 5), thus leading to no special interaction. In the 1α-isomer (**10**), however, in the most preferred conformation (Fig. 5), the exocyclic methylene double bond comes closer to the enone system and exciton splitting will be expected,[14] which must lead to a very intense K-band CD, whose sign, however, cannot be predicted at the moment because of lack of appropriate model compounds. The high $\Delta\varepsilon_{max}$-value of **10** in the K-band region proves then the 1α-configuration of this isomer, which is in agreement with the results obtained for the corresponding saturated ketone **7** (and other saturated ketones discussed above). In that case, therefore, the conjugated enone **9** should have the opposite, i.e. 1β-configuration.

FIG. 6 Octant projections of **9** (right) and **10** (left). The shaded areas symbolize the π-orbitals of the two C=C double bonds.

Data obtained from ORD-measurements are less conclusive, but in general lines confirm the results derived from CD-measurements.

NMR MEASUREMENTS

In our NMR studies we did not try to predict absolute values, but we found it possible to estimate chemical shift differences from models. These results corroborate the conclusions from the CD-data, but taken alone they are not as conclusive.

NMR of ketones of type **I**

In a 1,5-*cis*-fused 3-ketone of type I (Scheme 4) the chemical shift of the proton at C-1 is scarcely influenced by the 3-keto-CO group, whereas in a 1,5-*trans*-fused stereoisomer this proton comes into the deshielding range of the 3-CO group.[15]

Furthermore, in the *cis*-isomer the 5-OH group shields the eclipsed hydrogen at C-1.[16] Both effects should thus lead to a signal at higher field in the 1,5-*cis*-fused 3-ketone than in the corresponding 1,5-*trans*-fused analogue. The signal of the proton at C-1 is easily seen for **5** (at τ 6·85), but merges together with other signals for **7** in a τ range of 7·09 to 7·80. Ketone **7** must, therefore, be a *cis*-isomer, as was also assumed from CD measurements.

The methylene group attached to C-10 is closer to the 3-keto-CO group in a *cis*-fused compound than in the corresponding *trans*-isomer, and it is always situated in the shielding part of that keto-CO group. The midpoint of the methylene CH_2 signal should then be at a higher field for the *cis*- than for the *trans*-fused compound. For ketone **7** a τ-value of 5·30 is observed, and for **5** this τ-value is 4·90. These results, then, also lead to the *cis* 1,5-stereochemistry for **7** and the *trans* 1,5-stereochemistry for **5**.

Finally, for the same reason (i.e. relative positions with respect to the 3-keto-CO group) the difference of chemical shifts between the signals of the two methylene protons (of C-19) must be greater in the *cis*- than in the *trans*-fused compound. For **7** we observe a difference of 0·31 ppm, for **5** 0·19 ppm, which again confirms the assignment made on the basis of CD-measurements.

NMR of ketones of type **II**

The proton at C-1 is in all four possible stereoisomers **A**, **B**, **C** and **D** of ketones of type II (Scheme 4) in the deshielding part of the 10-keto-CO group (if one assumes the conformations used in the CD-treatment given above). By the same argument as for compounds of type I, the 1-proton signal in the *cis*-fused 10-ketone of type II should be at a higher field than in the corresponding *trans*-isomer. Since this signal is at τ 6·55 for the 10-ketone **12** and at τ 6·97 for the 10-ketone **14**, the latter should have the *cis*-fused 1,5-stereochemistry.

NMR of α,β-*unsaturated ketones*

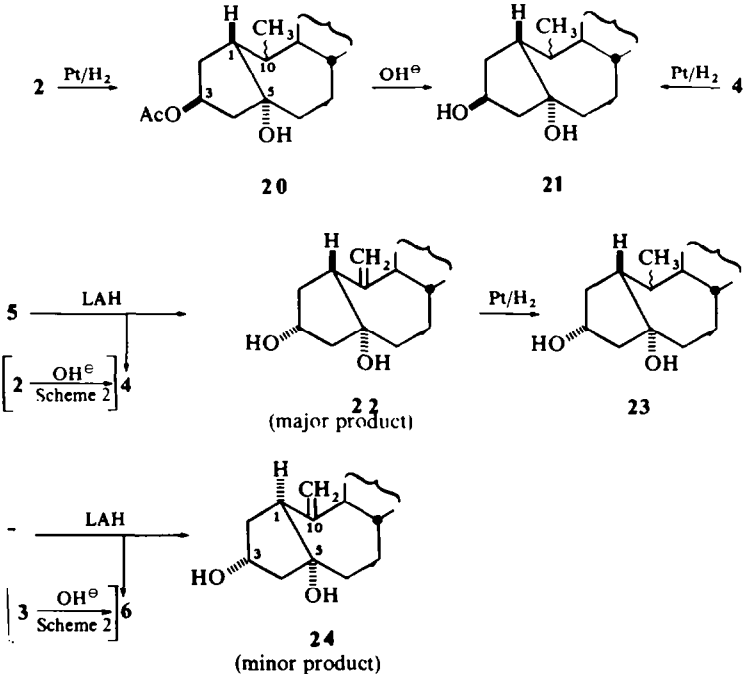
Because of the smaller distance of the unsaturated methylene group attached to C—10 from the enone system in the 1α-isomer, the difference of chemical shifts for the two C—19 methylene protons signals is expected to be greater in this ketone than in the corresponding 1β-stereoisomer. Furthermore, the CH_2—19 comes into the shielding range of the enone grouping in the 1α-form, and this should hence have a higher τ-value for the midpoint of the CH_2-doublet. The shift differences observed are 0·05 ppm for **9**, and 0·17 ppm for **10**, and the midpoint is at τ 4·97 for **9** and at τ 5·15 for **10**. From both arguments one is lead to ascribe the 1β-configuration to **9**, and the 1α-stereochemistry to **10**, again in full agreement with the CD-assignment.

The proton at C—4 is far away from the 19-methylene group in the enone with the 1β-configuration, but is in the shielding range in the 1α-stereoisomer, where the distance between the two double bonds is smaller. In agreement with this argument, the chemical shift for the signal of the C—4 proton is τ 4·08 for **9**, and τ 4·31 for **10**.

For the saturated ketones with a 5-OH group (**5**, **7**, **12**, **14**) and the conjugated enones **9** and **10** all NMR assignments are, therefore, in best agreement with the results derived from CD-data. As we have no corresponding pairs of stereoisomers in the non-hydroxylated series (R^3 = H) available, we cannot correlate stereochemistry with NMR-data of the ketones **18** and **19**.

IR MEASUREMENTS

Analysis of the IR spectra leads to the same conclusion about the 1,5-stereochemistry of the cyclization products **2** and **3** (Scheme 1) and their derivatives (Schemes 2 and 3). For the correct interpretation of the IR data, the additional compounds **20–24** were prepared, according to reactions shown on Scheme 5.



SCHEME 5

IR spectra were determined in CCl_4-solution, by molar concentrations of about 8×10^{-3}, in order to differentiate between the free and the intramolecularly H-bonded OH groups. The IR stretching frequencies of these groups in various compounds are given in Table 4.

The *trans* 1β,5α-configuration of product **2** was deduced by Akhtar and Marsh[6] from the facts (a) that the 5-alcohols containing a 19-methylene group **2**, **4**, **5** and **22** have a band corresponding to a H-bonded 5-OH group (this intramolecular H-bond being formed with the π-electrons of the exocyclic methylene 10(19)-double bond), which disappears (in **20** and **21**) when the 10-methylene group is reduced to a Me group, (b) that the 10-methylene-3β,5α-diol **4** shows a free OH group, and (c) that the stereoisomeric 10-methylene-3α,5α-diol **22** has no band corresponding to a free OH group. Moreover, according to our own finding, the saturated 10-methyl-3α,5α-diol **23** also forms an intramolecular hydrogen bond between the two (therefore *cis*) OH groups.

On the other hand, the 5-alcohols **3**, **6** and **7**, which also contain a 19-methylene group, do not show intramolecular H-bonding of the OH group (Table 4). This fact

Table 4. IR OH-stretching frequencies of the stereoisomeric 5α-hydroxy-5(10 → 1)*abeo*-steroid compounds **2** and **3**, and their derivatives.

Compound	Free OH group (cm^{-1})	Intramolecularly H-bonded OH group (cm^{-1})
1β-*series*		
2	—	3535
20	3620	—
4	3628	3535
21	3620	—
5	—	3535
22	—	3520
23	3610	3535
1α-*series*		
3	3600	—
6	3630, 3600	—
7	3610	—
24	3610	3540

suggests a *cis* 1,5-fusion for these compounds, in which the 5-OH group cannot form an H-bond with the exocyclic 10(19)-double bond. LAH reduction of ketone **7** affords as major product the known 3β,5α-diol **6** (obtained also by hydrolysis of **3**; see Scheme 2), and as minor product (in about 10% yield) another 3,5-diol (**24**, Scheme 5), which shows two OH bands, one for the free and one for the H-bonded OH group. Therefore, these two OH groups on C—3 and C—5 are on the same side of the ring. Since the 3-OH must have the α-orientation (i.e. the opposite orientation to that of the diol **6**), the orientation of the 5-OH group in **24** must also be α. From these facts and the already assigned *trans* 1β,5α-configuration to product **2** and its derivatives, it is evident that compounds **3**, **6**, **7** and **24** must have the *cis* 1α,5α-stereochemistry, which is in agreement with other (above-described) chemical and physical evidence.

CONCLUSION

The stereochemical course of the cyclization of (E)-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (**1**, Scheme 1), i.e. the predominant formation of the *trans* 1β,5α-5(10 → 1)*abeo*-steroid product **2** in the proton-catalyzed reaction, and the exclusive formation of this compound (**2**) under thermal reaction conditions, may be rationalized by assuming that the conformation in the transition states for both cyclization processes of the (E)-5,10-seco-enone **1** (and probably the ground state conformation of **1**) have the geometry (**E** and **F**) shown in Fig. 7, which resembles the recently determined ground state conformation of *trans*-cyclodecene (in its complex with silver nitrate).[17]

However, the fact that in the acid-catalyzed cyclization of **1** the *cis* 1α,5α-isomer **3** is also formed, though in considerably lower yield (Scheme 1), indicates that the transition state for this reaction can adopt other, less favourable conformations as well, for example the CCC-conformation **G** (Fig. 8). Because of the large distance between the 5-keto-CO group and the Me group C—19, such a conformation (of type **G**) does

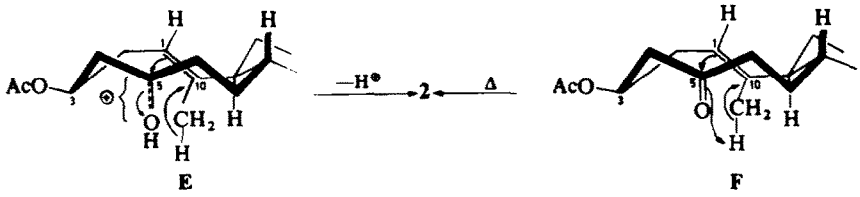


FIG. 7 Transition state conformation for the acid-catalyzed cyclization (E) and thermal cyclization (F) of the (E)-5,10-seco-enone 1 to the *trans* 1β,5α-5(10 → 1)-*abeo*-steroid product 2.

not allow the formation of a 6-membered cyclic transition state which controls the thermal cyclization of 1 (see transition state F in Fig. 7), and this would explain why the *cis*-isomer 3 is not produced in the thermal reaction.

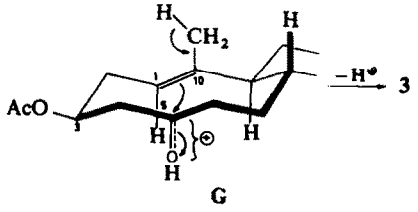


FIG. 8 Transition state conformation for the acid-catalyzed cyclization (G) of the (E)-5,10-seco-enone 1 to the *cis* 1α,5α-5(10 → 1)*abeo*-steroid product 3.

EXPERIMENTAL*

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ unless mentioned otherwise. The CD measurements were done with a Roussel–Jouan dichrographe Model 185 in cells of pathlengths of 2, 1, 0·5, 0·1 and 0·01 cm at room temp and a concentration of 0·1–1 mg/ml. NMR spectra were obtained at 100 MHz with a Varian HA-100 spectrometer and at 90 MHz with a Spectrospin KIS-HX, in $CDCl_3$ soln at room temp using TMS as internal standard (chemical shifts are reported in τ-values (TMS: τ = 10·00). IR spectra were determined on a Perkin–Elmer double-beam instrument, Model 221 or on a Perkin–Elmer grating infrared spectrophotometer, Model 337, in KBr, CH_2Cl_2 and CCl_4. UV absorption spectra were recorded in 95% EtOH with a Perkin–Elmer 137 UV spectrophotometer. Light petroleum refers to the fraction b.p. 40–60°. The separation of products was controlled by TLC, which was carried out on silica gel G (Stahl) with benzene-AcOEt (9 : 1 or 1 : 1); the detection was effected with 50% H_2SO_4.

Cyclization of (E)-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (1)

A. *Acid-catalyzed cyclization.* According to the previously described procedure,[4] two cyclization products were obtained from 1. Compound 2, m.p. 109° (from MeOH), $[\alpha]_D^{20} = +46°$ (c = 0·67), in 67% yield (lit. m.p. 109°,[4] and 108–109°[6]); IR ($c = 8 \times 10^{-2}$ M, CH_2Cl_2): ν_{max} = 3535, 1735, 1630, 1238 cm^{-1}; IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3535, 1740, 1624, 1238 cm^{-1}.† The other stereoisomer, i.e. 3, m.p. 135–136° (from MeOH), $[\alpha]_D^{20} = -6°$ (c = 0·42), was obtained in 8% yield;[4] IR ($c = 5 \times 10^{-2}$ M, CH_2Cl_2): ν_{max} = 3600, 1738, 1640, 1240 cm^{-1}; IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3600, 1740, 1640, 1238 cm^{-1}.†

B. *Thermal cyclization.* (1) *In ethanol solution.* A soln of 100 mg 1 in 10 ml EtOH was refluxed for 36 hr and then evaporated to dryness. The resulting product was chromatographed on silica gel (5 g; 0·20–0·05) giving (by elution with benzene-ether, 98 : 2) 62 mg of starting 1 (m.p. undepressed upon admixture with authentic sample, IR and NMR spectra) and (by elution with benzene-ether, 90 : 10) 31 mg (31%) of

*We thank Mrs. R. Tasovac (Belgrade) for elemental microanalyses, and Miss L. Penzien and Mr. E. Kirmayr (Bonn) for technical assistance.

†For additional analytical and physical data see Ref. 4.

cyclization product **2** (identified by m.p. and mixed m.p. determinations, by its IR and NMR spectra). (2) *In toluene solution.* Heating 100 mg **1** in 10 ml toluene at reflux for 16 hr gave upon chromatography on silica gel (as described above) 41 mg of starting **1** and 44 mg (44%) of cyclization product **2**.

Hydrolysis of 5(10 → 1βH)abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* 3-acetate (**2**)

A soln of **2** (1·0 g) in 100 ml 5% methanolic KOH was left overnight at room temp, poured into water and extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4 and evaporated under reduced press, to give 750 mg (82%) of **4**, m.p. 163° (from MeOH), $[\alpha]_D^{20} = +52°$ ($c = 1·02$) (lit.[6] m.p. 148–149°); IR (KBr): $\nu_{max} = 3490, 3340, 1620\ cm^{-1}$; IR ($c = 8 \times 10^{-3}$ M, CCl_4): $\nu_{max} = 3628, 3535, 1620\ cm^{-1}$. (Found: C, 80·4; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%).

Hydrolysis of 5(10 → 1αH)abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* 3-*acetate* (**3**)

Hydrolysis of **3** (500 mg) as above gave 400 mg (88%) of 5(10 → 1αH)aleo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* (**6**), m.p. 182–183° (from MeOH), $[\alpha]_D^{20} = -9°$ ($c = 1·2$); IR (KBr): $\nu_{max} = 3400, 1640\ cm^{-1}$; IR ($c = 8 \times 10^{-3}$ M, CCl_4): $\nu_{max} = 3630, 3600, 1638\ cm^{-1}$. (Found: C, 80·4; H, 11·6. $C_{27}H_{46}O_2$ requires: C, 80·5; H, 11·5%).

Oxidation of 5(10 → 1βH)abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* (**4**)

To a cooled soln (0–5°) of **4** (1·0 g) in acetone (150 ml) a slight excess of Jones reagent[18,19] was added with constant swirling. After 5 min ice-cold water was added, the white solid filtered off, washed thoroughly with water and crystallized from MeOH, to give 850 mg (85%) of **5**, m.p. 121° (lit.[6] m.p. 105–107°), $[\alpha]_D^{20} = +60$ ($c = 0·04$, dioxan); IR (KBr): $\nu_{max} = 3530, 3500, 1736, 1618, 1626\ cm^{-1}$; IR ($c = 8 \times 10^{-3}$ M, CCl_4): $\nu_{max} = 3535, 1748, 1626\ cm^{-1}$. NMR: $\tau = 9·28$ (CH_3—18, *s*), 9·16 (CH_3—26 and CH_3—27, *d*), 9·12 (CH_3—21, *d*), 6·88 (proton at C—1), 4·96 and 4·78 (exocyclic $\overset{10}{\diagdown}\!\!\!\diagup\overset{19}{}C{=}CH_2$ protons). (Found: C, 80·7; H, 11·0. Calc. for $C_{27}H_{44}O_2$: C, 80·9; H, 11·1%).

Oxidation of 5(10 → 1αH)abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* (**6**)

A soln of **6** (200 mg) in pyridine (2·5 ml) was added to a slurry of CrO_3 (200 mg) in pyridine (2 ml).[20] The mixture was left overnight at room temp, diluted with ether and filtered. The ethereal filtrate was washed with dilute AcOH, $NaHCO_3$aq, and water. Removal of the solvent afforded 160 mg (80%) of 5-hydroxy-5(10 → 1αH)*abeo*-5α-cholest-10(19)-en-3-one (**7**), m.p. 152–153° (from MeOH), $[\alpha]_D^{20} = +73°$ ($c = 0·04$, dioxan); IR (KBr): $\nu_{max} = 3600, 3550, 1750, 1640\ cm^{-1}$; IR ($c = 8 \times 10^{-3}$ M, CCl_4): $\nu_{max} = 3610, 1747, 1638\ cm^{-1}$; NMR: $\tau = 9·28$ (CH_3—18, *s*), 9·16 (CH_3—26 and CH_3—27, *d*), 7·18 (*m* for two protons), 5·44 and 5·14 (exocyclic $\overset{10}{\diagdown}\!\!\!\diagup\overset{19}{}C{=}CH_2$ protons). (Found: C, 80·7; H, 11·1. $C_{27}H_{44}O_2$ requires: C, 80·9; H, 11·1%).

Dehydration of 5-*hydroxy*-5(10 → 1βH)abeo-5α-*cholest*-10(19)-*en*-3-*one* (**5**)

A. *With sodium methoxide.* Ketone **5** (200 mg) was dissolved in MeOH (40 ml, dried over Mg). A soln of NaOMe in MeOH (40 ml of 1 N) was added at once and the mixture stirred for 2 hr at room temp. The soln was slightly acidified with glacial AcOH and most of the solvent removed under reduced press. The remainder was treated with water and extracted with ether. The organic layer was washed with $NaHCO_3$aq and water, and evaporated to dryness, leaving 130 mg (68%) of 5(10 → 1)abeo-*cholesta*-1(10),4-*dien*-3-*one* (**8**), m.p. 82° (after 2 crystallizations from MeOH); UV: $\lambda_{max} = 308$ nm ($\varepsilon = 16·550$). IR (KBr): $\nu_{max} = 1692, 1568\ cm^{-1}$; NMR: $\tau = 9·29$ (CH_3—18, *s*), 9·15 (CH_3—26 and CH_3—27, *d*), 9·11 (CH_3—21, *d*), 8·21 (CH_3—19, *s*), about 7·36 (two protons at C—6, *m*), 7·08 (two protons at C—2, *s*), 4·12 (vinylic proton, *s*). (Found: C, 84·5; H, 11·2. $C_{27}H_{42}O$ requires: C, 84·75; H, 11·1%).

B. *Acid-catalyzed dehydration.* To a soln of **5** (1·3 g) in glacial AcOH (100 ml) a soln of 60% $HClO_4$ (32 ml) in glacial AcOH (300 ml) was added and left overnight at room temp. The mixture was then poured into ice-cold water and extracted with ether. The organic layer was washed with $NaHCO_3$aq and water, dried over Na_2SO_4 and evaporated to dryness, leaving an oily product, which was chromatographed on 65 g silica gel (0·20–0·05). The first benzene-ether (95:5) fractions afforded 611 mg (49%) of 5(10 → 1βH) abeo-*cholesta*-4,10(19)-*dien*-3-*one* (**9**) as an oil, though on TLC it showed only one spot. $[\alpha]_D^{20} = 0° \pm 5°$ ($c = 0·2$); UV: $\lambda_{max} = 232$ nm ($\varepsilon = 15·800$). IR (KBr): $\nu_{max} = 1704, 1636, 1610\ cm^{-1}$; NMR: $\tau = 9·28$ (CH_3—18, *s*), 9·14 (CH_3—26 and CH_3—27, *d*), 9·11 (CH_3—21, *d*), about 7·30 (two protons at C—2, *m*),

about 6·45 (proton at C—1, *m*), 4·99 and 4·94 (exocyclic $\rangle C^{10}{=}C^{19}H_2$ protons), 4·06 (vinylic proton at C—4, *d*).

Reduction of ketone **9** *with lithium aluminium hydride*

A mixture of **9** (300 mg) and LAH (75 mg) in dry ether (100 ml) was heated under reflux for 1 hr, and then worked up as usual. The crude product was chromatographed on 15 g silica gel (0·20–0·05). The first benzene-ether (95:5) fractions gave 5(10 → 1βH)abeo-*cholesta*-4,10(19)-*dien*-3ξ-*ol* (196 mg), which after 2 crystallizations from acetone melted at 86°; $[\alpha]_D^{20}$ = +7° ±3° (*c* = 0·31); IR (KBr): ν_{max} = 3300, 1630 cm^{-1}; NMR: τ = 9·28 (CH_3—18, *s*), 9·15 (CH_3—26 and CH_3—27, *d*), 9·12 (CH_3—21, *d*), 6·78 (proton at C—3), 5·10 and 5·05 (exocyclic $\rangle C^{10}{=}C^{19}H_2$ protons), 4·55 (vinylic proton at C—4, *m*). (Found: C, 84·0; H, 11·6. $C_{27}H_{44}O$ requires: C, 84·3; H, 11·5%).

Oxidation of this alcohol (60 mg) in acetone soln with a slight excess of Jones reagent[18, 19] in the usual way afforded 52 mg of **9**, again as an oil and which was identical in every respect (UV, IR, NMR) with the above described product.

Dehydration of 5-*hydroxy*-5(10 → 1αH)abeo-5α-*cholest*-10(19)-*en*-3-*one* (**7**)

A. *With sodium methoxide.* A soln of **7** (50 mg) in dry MeOH (10 ml) was treated with methanolic NaOMe (10 ml of 1 N) as described above, whereby 32 mg (66%) of the conjugated **8** was obtained. It was identified by comparison of UV, IR and NMR spectra.

B. *Acid-catalyzed dehydration.* Ketone **7** (120 mg) in 10 ml glacial AcOH was dehydrated with a soln of 60% $HClO_4$ (3·2 ml) in glacial AcOH (30 ml) as described above, giving 68 mg (59%) 5(10 → 1αH)abeo-*cholesta*-4,10(19)-*dien*-3-*one* (**10**), m.p. 121–122° (after 3 crystallizations from MeOH-acetone), $[\alpha]_D^{20}$ = +198° (*c* = 0·1, dioxan); IR (KBr): ν_{max} = 1710, 1640, 1618 cm^{-1}; NMR: τ = 9·28 (CH_3—18, *s*), 9·14 (CH_3—26 and CH_3—27, *d*), 9·09 (CH_3—21, *d*), about 7·10 (two protons at C—2, *m*), about 6·54 (proton at C—1, *m*), 5·22 and 5·06 (exocyclic $\rangle C^{10}{=}C^{19}H_2$ protons), 4·31 (vinylic proton at C—4, *m*). (Found: C, 84·5; H, 11·2. $C_{27}H_{42}O$ requires: C, 84·75; H, 11·1%).

Hydroxylation of 5(10 → 1βH) abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* 3-*acetate* (**2**)

Osmium tetroxide (310 mg) was added to a soln of **2** (450 mg) in benzene (15 ml) containing pyridine (1 ml). After standing at room temp for 24 hr the mixture was diluted with AcOEt (50 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 380 mg (78%) 5(10 → 1βH)abeo-5α-*cholestane*-3β,5,10ξ,19-*tetraol* 3-*acetate* (**11**), m.p. 205–206 (from MeOH). $[\alpha]_D^{20}$ = +2 (*c* = 0·4); IR (Nujol): ε_{max} = 3540, 3280, 1718, 1272 cm^{-1}. (Found: C, 72·9; H, 10·5. $C_{29}H_{50}O_5$ requires: C, 72·8; H, 10·5%).

Hydroxylation of 5(10 → 1αH) abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* 3-*acetate* (**3**)

Treatment of **3** (450 mg) with osmium tetroxide (310 mg) as described above, afforded 340 mg (70%) of 5(10 → 1αH)abeo-5α-*cholestane*-3β,5,10ξ,19-*tetraol* 3-*acetate* (**13**), m.p. 212–213° (after 2 crystallizations, from MeOH); $[\alpha]_D^{20}$ = +18° (*c* = 1·0); IR (KBr); ν_{max} = 3520, 3430, 3320, 1720, 1278 cm^{-1}; IR (CH_2Cl_2): ν_{max} = 3600, 3550, 3450, 1735, 1238 cm^{-1}. (Found: C, 72·5; H, 10·5. $C_{29}H_{50}O_5$ requires: C, 72·8; H, 10·5%).

Glycol cleavage of 5(10 → 1βH)abeo-5α-*cholestane*-3β,5,10ξ,19-*tetraol* 3-*acetate* (**11**)

Lead tetraacetate (220 mg) and **11** (200 mg) in dry benzene (20 ml) were heated under reflux for 0·5 hr. The mixture was then diluted with ether, filtered through a Celite mat, and the insoluble ppt was washed with ether (and benzene). The organic soln was washed with $NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated to dryness. Two crystallizations of the residue from MeOH afforded 153 mg (82%) of 3β,5-*dihydroxy*-5(10 → 1βH)abeo-19-*nor*-5α-*cholestan*-10-*one* 3-*acetate* (**12**), m.p. 177–179°. $[\alpha]_D^{20}$ = +59° (*c* = 0·2, dioxan); IR (CH_2Cl_2): ν_{max} = 3610, 3500, 1735, 1692, 1234 cm^{-1}; NMR: τ = 9·27 (CH_3—18, *s*), 9·15 (CH_3—26 and CH_3—27, *d*), 9·11 (CH_3—21, *d*), 8·01 (CH_3COO, *s*), 6·56 (proton at C-1, *qu*), 4·78 (proton at C-3, *m*). (Found: C, 75·6; H, 10·4. $C_{28}H_{46}O_4$ requires: C, 75·3, H, 10·4%).

Glycol cleavage of 5(10 → 1αH)abeo-5α-*cholestane*-3β,5,10ξ,19-*tetraol* 3-*acetate* (**13**)

Compound **13** (200 mg) was oxidized with lead tetraacetate (220 mg) as described above. Removal of the

solvents and 2 crystallizations of the residue from MeOH afforded 160 mg (86%) of 3β,5-*dihydroxy*-5(10 → 1αH)abeo-19-*nor*-5α-*cholestan*-10-*one* 3-*acetate* (**14**), m.p. 142–144°. $[\alpha]_D^{20} = -11°$ (c = 0·2, dioxan); IR (CH_2Cl_2): ν_{max} = 3600, 3480, 1735, 1705, 1235 cm^{-1}; NMR: τ = 9·29 (CH_3—18, *s*), 9·15 (CH_3—26 and CH_3—27, *d*), 8·11 (CH_3—21, *d*), 8·01 (CH_3COO, *s*), 6·96 (proton at C-1, *t*), 4·82 (proton at C-3, *m*). (Found: C, 75·1; H, 10·6. $C_{28}H_{46}O_4$ requires: C, 75·3; H, 10·4%).

Hydrogenation of 5(10 → 1βH(abeo-5α-*cholest*-10(19)-*ene*-3β,5-*diol* (**4**)

A soln of **4** (250 mg) in AcOEt (25 ml) containing one drop of $HClO_4$ was hydrogenated in the presence of Adams catalyst (100 mg) until no more H_2 was absorbed. The resulting mixture was filtered through a Celite mat and the filtrate worked up as usual. The residue was recrystallized from MeOH to give a mixture (95 mg) of diols **21**, m.p. 162–164° (lit.[6] m.p. 145–146°); IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3620 cm^{-1}. (Found: C, 80·4; H, 12·0. Calc. for $C_{27}H_{48}O_2$: C, 80·2; H, 12·0%).

Lithium aluminium hydride reduction of 5-*hydroxy*-5(10 → 1βH)abeo-5α-*cholest*-10(19)-*en*-3-*one* (**5**)

A soln of **5** (500 mg) in dry ether (100 ml) was reduced with LAH (100 mg) at room temp for 1 hr and then worked up as usual. The crude product (for which TLC showed that it contained mainly the 3α-OH isomer **22** and only small amounts of the 3β-OH isomer **4**) was recrystallized several times from MeOH to give 350 mg (69%) of pure **22**, m.p. 136° (lit.[6] m.p. 129°); $[\alpha]_D^{20} = +45°$ (c, = 0·8). IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3520 cm^{-1}. (Found: C, 80·4; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%).

Hydrogenation of 5(10 → 1βH)abeo-5α-*cholest*-10(19)-*ene*-3α,5-*diol* (**22**)

Diol **22** (100 mg) was hydrogenated under the same experimental conditions used for **4**, giving quantitatively a mixture of the 5(10 → 1βH)abeo-5α,10ξ-*cholestane*-3α,5-*diols* (**23**), m.p. 120° (from ether); IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3610, 3535 cm^{-1}. (Found: C, 80·4; H, 12·1. $C_{27}H_{48}O_2$ requires: C, 80·2; H, 12·0%).

Lithium aluminium hydride reduction of 5-*hydroxy*-5(10 → 1αH)abeo-5α-*cholest*-10(19)-*en*-3-*one* (**7**)

Ketone **7** (250 mg) in dry ether (45 ml) and THF (5 ml) was reduced with LAH (50 mg) as described above. TLC showed that the 3β-OH isomer **6** was the chief reaction product. In order to isolate the 3α-OH-isomer **24**, the reaction mixture was chromatographed on Al_2O_3 II (9 g). The first ether-AcOEt (4 : 1) fractions afforded 25 mg (10%) of 5(10 → 1αH)abeo-5α-*cholest*-10(19)-*ene*-3α,5-*diol* (**24**), m.p. 145–146° (from MeOH). $[\alpha]_D^{20} = +70°$ (c = 0·73); IR ($c = 8 \times 10^{-3}$ M, CCl_4): ν_{max} = 3610, 3540 cm^{-1}. (Found: C, 80·3; H, 11·4. $C_{27}H_{46}O_2$ requires: C, 80·5; H, 11·5%).

Further elution with ether-AcOEt (1 : 1) afforded 200 mg (80%) of the 3β-hydroxy isomer **6**, which was identified by m.p. and mixed m.p. determinations, and by comparison of IR spectra.

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