REACTION OF 3,4a-DISUBSTITUTED 4,4-DIMETHYL-5,6β-EPOXY-A-HOMO-5β-CHOLESTANE DERIVATIVES WITH REDUCING AGENTS

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Reaction of all stereoisomeric 3-acetoxy-4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestan-4a-ols *I*—*IV* with lithium aluminum hydride and reduction of 3-acetoxy-4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestan-4a-ones *XXII* and *XXIII* with sodium borohydride were studied. It was found that reductive opening of the 5β,6β-epoxide ring occurred only in the case of the derivatives *III* and *IV* due to $5(O)^n$ participation of the 3α-oxygen-containing substituent under formation of the transannular 3α,5α-epoxides *VIII* and *IX*, resp. On reduction of the 4a-keto epoxides *XXII* and *XXIII* with sodium borohydride the *trans*-epoxy alcohols *III* and *I* were formed. On the basis of ^{1}H NMR data the conformation of the A-ring in the epoxides *I*—*IV*, *XXII*, and *XXIII* is also discussed.

In our preceding papers[1-3] we have found that an oxygen-containing substituent in the position 3 can participate through the $5(O)^n$ process (for the notation see ref.[4]) both in the acid catalyzed and in the reductive opening of the 4a,5- and 5β,6β-epoxide rings of some 3-substituted 4,4-dimethyl-A-homocholestane derivatives. In connection with these investigations it was of interest to examine the course of analogous reactions of some 3,4a-disubstituted 4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestane derivatives. This paper concerns both reductive opening of the 5β,6β-epoxide ring in all stereoisomeric 3-acetoxy-4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestan-4a-ols *I*—*IV* with lithium aluminum hydride and reduction of the 4a-carbonyl group in epimeric 3-acetoxy-4,4-dimethyl-5,6β-epoxy-A-homo-5β-cholestan-4a-ones *XXII* and *XXIII* with sodium borohydride.

The already known[5] epoxides *I*—*IV* were treated with lithium aluminum hydride in ether at room temperature (the yields of the main products of the reaction are given in Table I). As evident from Table I under these conditions the 5β,6β-epoxide ring in the 3β-acetoxy derivatives *I* and *II* was resistent to cleavage and the known[5] 3β,4a-dihydroxy derivatives *V* and *VI*, resp., were formed as the main products of the reaction. The 5β,6β-epoxide ring in the 3α-acetoxy-4aβ-hydroxy derivative *III* was also relatively stable and the known[5] 3α,4aβ-dihydroxy derivative *VII* was

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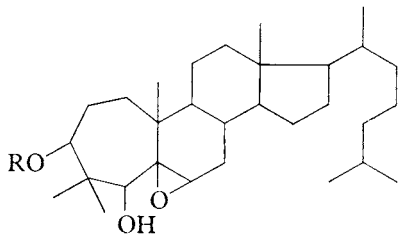
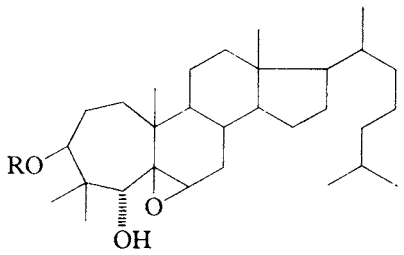
obtained as the main product of the reaction (82% yield), whereas a product of the 5(O)^n participation of the 3α-substituent, *i.e.* the transannular epoxide *VIII*, was formed in only 10% yield (according to the preparative TLC). However, already by a column chromatography on silica gel the epoxide *VII* could be almost quantita-



I, R = Ac
V, R = H



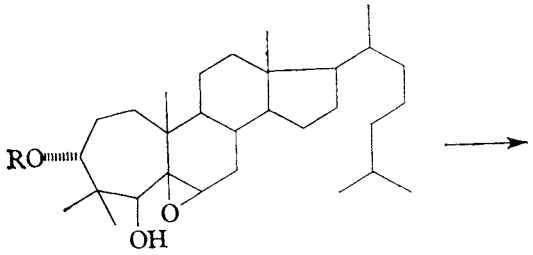
II, R = Ac
VI, R = H

tively converted into the transannular 3α,5α-epoxide *VIII*, which was also the main product of the acid catalyzed cleavage of the 5β,6β-epoxide *VII* with perchloric acid in dioxane (Table I). On the contrary, the 5β,6β-epoxide ring in the 3α-acetoxy-4aα-hydroxy derivative *IV* was readily opened with lithium aluminum hydride in ether to give a product of the 5(O)^n participation of the 3α-substituent, *i.e.* the transannular 3α,5α-epoxide *IX*, in 82% yield. In accord with the suggested structures, the ^{1}H NMR spectra of the compounds *VIII* and *IX* exhibit signals of two CH—OH protons, which appear as a singlet (δ = 3·83 in *VIII* and δ = 4·13 in *IX*) and a multiplet (δ = 3·57 in *VIII* and δ = 3·64 in *IX*), and of one CH—O proton, which appears as a multiplet (δ = 3·57 in *VIII* and δ = 3·87 in *IX*). The structures of the transannular epoxides *VIII* and *IX* were also confirmed by the following correla-

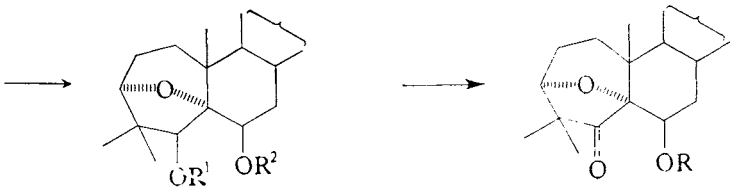
TABLE I
Yields (in % of the total yield) of the products of the cleavage of the epoxides *I*–*IV* and *VII*

Compound	Reagent	3α,5α-Epoxide	5β,6β-Epoxide	Total yield	Ref.
I	$LiAlH_4$	—	95 (*V*)	98	5
II	$LiAlH_4$	—	98 (*VI*)	100	5
III	$LiAlH_4$	10 (*VIII*)	82 (*VII*)	95	5
IV	$LiAlH_4$	82 (*IX*)	—	95	—
VII	$HClO_4$	89 (*VIII*)	—	95	—

tion with the known[1] 4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4a-one (*XIII*). On acetylation the diol *IX* afforded the 4aα-acetoxy derivative *X* (82% yield), the ^{1}H NMR spectrum of which displays signals of one CH—OH proton (a multiplet at $\delta = 3{\cdot}96$) and of one CH—$OCOCH_3$ proton (a singlet at $\delta = 5{\cdot}25$) in agreement with the proposed structure. The keton *XI*, obtained by oxidation of the alcohol *X*, was transformed into the 4aα-hydroxy derivative *XII* by the Huang–Minlon reduction. On oxidation the alcohol *XII* then gave the known[1] ketone *XIII*. Since both the diols *VIII* and *IX* afforded on oxidation the same diketone *XIV*, the structure of the transannular 3α,5α-epoxides could be assigned to the compounds *VIII* and *IX*.

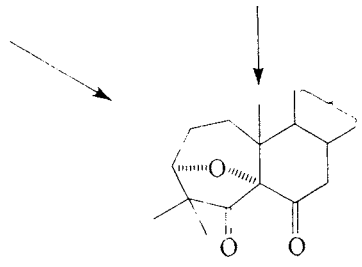


III, R = Ac
VI, R = H



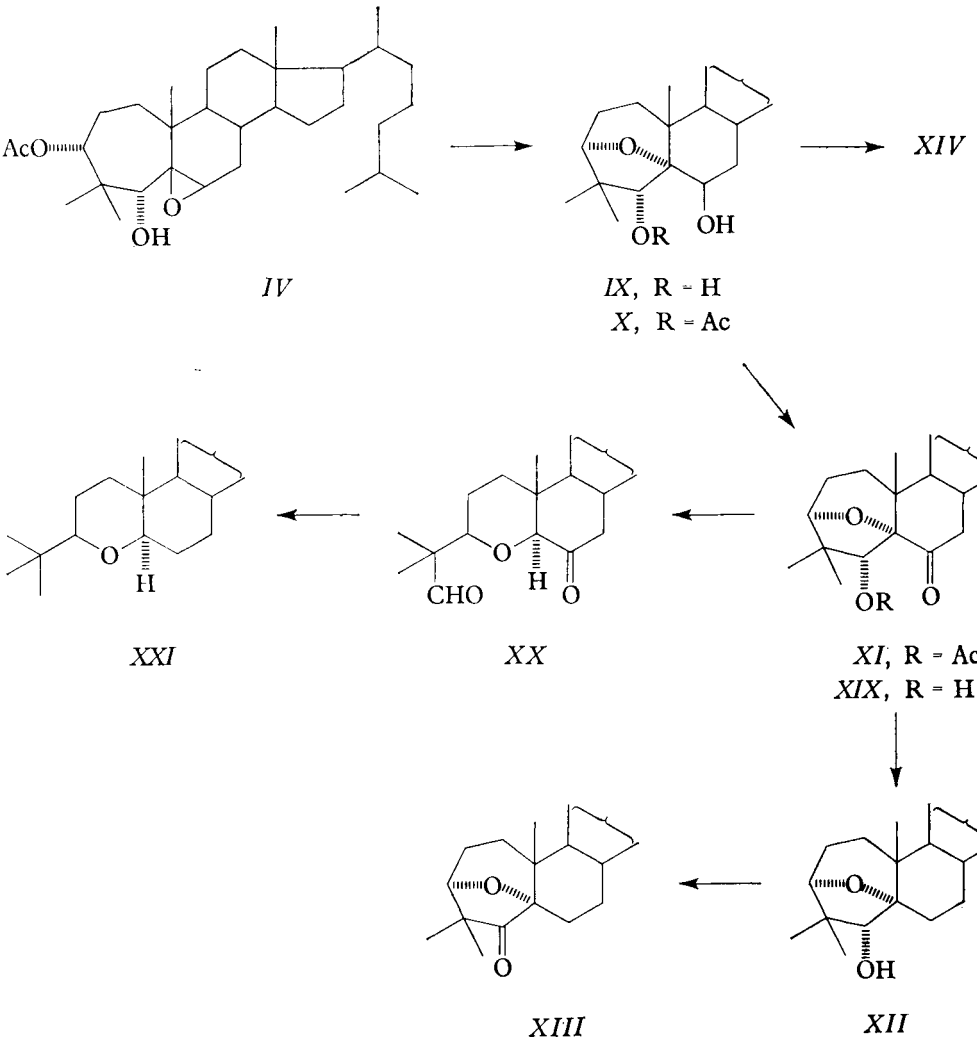
VIII, $R^1 = R^2 = H$
XV, $R^1 = R^2 = Ac$
XVI, $R^1 = H$, $R^2 = Ac$

XVII, R = Ac
XVIII, R = H



XIV

Hence, it may be concluded that even in the case of the 3α,4-disubstituted 4,4-dimethyl-A-homocholestane derivatives the 3α-substituent participates through the $5(O)^n$ process in the reductive opening of the 5β,6β-epoxide ring. The decrease in ability of the 3α-substituent to participate in the reductive cleavage of the 5β,6β-epoxide ring in the 4aβ-hydroxy derivative *III* in comparison with the 4aα-hydroxy derivative *IV* could be probably explained by a strong steric interaction between the relatively bulky solvated 4aβ-alkoxyaluminum group and 1β-hydrogen atom in the transition state of the transformation to the transannular 3α,5α-epoxide *VIII*.



IV

IX, R = H
X, R = Ac

XXI

XX

XI, R = Ac
XIX, R = H

XIII

XII

On acetylation the diol *VIII* gave, in addition to the diacetate *XV* (23% yield), the 6β-acetoxy derivative *XVI* (53% yield), the ^{1}H NMR spectrum of which displays signals of one CH—$OCOCH_3$ proton (a multiplet at δ = 4·74) and of one CH—OH proton (a singlet at δ = 3·74) in accordance with the proposed structure. On oxidation the 6β-acetoxy derivative *XVI* afforded the 4a-ketone *XVII* which was subjected to alkaline saponification with potassium hydroxide in refluxing methanol to yield the 6β-hydroxy derivative *XVIII*. On the contrary, an analogous alkaline saponification of the 4aα-acetoxy-6-keto derivative *XI* gave, along with the expected 4aα--hydroxy derivative *XIX*, also a product of the retroaldolization cleavage, *i.e.* the keto aldehyde *XX*, in 52% yield. The keto aldehyde *XX* was submitted to the Huang--Minlon reduction to yield the deoxo derivative *XXI*, the structure of which was confirmed by its mass and ^{1}H NMR spectra. Mass spectrometry demonstrated the molecular weight 430 and the molecular formula $C_{30}H_{54}O$. Apart from signals of both angular methyls (δ = 0·65 and δ = 1·25), the ^{1}H NMR spectrum of this compound displays a signal of one tert-butyl group (a singlet at δ = 0·89) and signals of two CH—O protons which appear as doublets of doublets at δ = 2·88 (J = 4·1 and 11·4 Hz) and at δ = 2·91 (J = 3·3 and 10·8 Hz). The large value of the vicinal coupling constants can only be reconciled with location of these protons in the 3α- and 5α-positions and, therefore, the structure of 3β-tert-butyl-4-oxa-5α-cholestane can be assigned to the compound *XXI*.

Reduction of the epimeric 3-acetoxy-4a-keto-5β,6β-epoxides *XXII* and *XXIII*, prepared already earlier[5], was carried out with sodium borohydride in methanol at room temperature and the yields of the main products of the reduction are given in Table II. The 3α-acetoxy derivative *XXII* afforded smoothly the 4aβ-hydroxy derivative *III* as the main product, whereas the 4a-carbonyl group in the 3β-acetoxy-derivative *XXIII* was reduced to the 4aβ-hydroxy derivative *I* less easily and, along with a small amount of the known[5] 3β-hydroxy-4,4-dimethyl-5,6β-epoxy-A-homo--5β-cholestan-4a-one (*XXIV*), the unchanged starting ketone *XXIII* was mainly recovered.

TABLE II

Yields (in % of the total yield) of the products of reduction of the keto epoxides *XXII* and *XXIII* with sodium borohydride

Compound	4aβ-Alcohol	Other products	Total yield	Ref.
XXII	94 (*III*)	—	96	5
XXIII	20 (*I*)	51 (*XXIII*)	98	5
		20 (*XXIV*)		5

In order to explain stereochemistry of the reduction of the epoxy ketones *XXII* and *XXIII*, it was necessary to determine the preferred conformation of the seven-membered ring A in the epoxy alcohols *I*–*IV* and in the epoxy ketones *XXII* and *XXIII*, for which the ^{1}H NMR data were used of. In the spectra of these derivatives a signal of the $C_{(3)}$—H proton can be easily identified. Vicinal coupling constants of this proton with protons attached to the adjacent $C_{(2)}$-carbon atom, *i.e.* $J_{2\alpha,3}$ and $J_{2\beta,3}$, then would permit to determine the preferred conformation of the A-ring by means of the known[6] Karplus relation between the vicinal coupling constants and the dihedral angles. The signal of the $C_{(3)}$—H proton in the derivatives studied represents an X part of an ABX spin system pattern in which the AB part is formed by signals of protons at the $C_{(2)}$-carbon atom. For the character of the X part of the spectrum a degree of interaction $(J_{AB}/(\nu_A - \nu_B))$ is also decisive. In the case of the derivatives *III*, *IV*, *XXII*, and *XXIII* the signal of the $C_{(3)}$—H proton appears as a doublet of doublets and in the case of derivatives *I* and *II* as a triplet. Therefore the knowledge of the AB part of the spectrum is necessary for determination of correct values of the coupling constants J_{AX}, *i.e.* $J_{2\alpha,3}$ and $J_{2\beta,3}$. This part, however, cannot be identified in the spectra of derivatives studied due to an overlap by signals of other protons at the steroid skeleton. Hence, the values of the coupling constants $J_{2\alpha,3}$ and $J_{2\beta,3}$ were determined only approximately by direct extraction from the spectrum as it is common in the case of the first order spectra. The adjustment was carried out under the assumption that values of coupling constants are usually larger for *trans*-oriented hydrogen atoms than for *cis*-oriented ones. The opposite adjustment would lead to structurally impossible conformations.

For calculation of the dihedral angles $\Phi_{2,3}$ we have used the method of Slessor and Tracey[7], which is useful especially with fragments —CH(X)—CH_2—. The method is based on the assumption[7] that the ratio of constants $k_1 : k_2$ in the classical form of the Karplus relation is constant and approximately equal to 0·9. This assumption permits to calculate from the equation (*1*) values

$$J_1 = k_1 \cdot \cos^2 \Phi - 0{\cdot}28 \qquad 0° \leqq \Phi \leqq 90° \qquad (1)$$

$$J_2 = k_2 \cdot \cos^2 \Phi - 0{\cdot}28 \qquad 90° < \Phi \leqq 180°$$

of the dihedral angles as well as of the constants k_1 and k_2. The calculated dihedral angles $\Phi_{2,3}$ for the derivatives *I*–*IV*, *XXII* and *XXIII* together with the experimentally determined coupling constants $J_{2,3}$ are presented in Table III. As follows from Table III the values of dihedral angles $\Phi_{2\alpha,3\beta}$ and $\Phi_{2\beta,3\beta}$ for the epoxy alcohols *III* and *IV* are approximately equal. They are not considerably different from the known[5] values of the corresponding dihedral angles in 3α-acetoxy-4,4-dimethyl--A-homo-5-cholesten-4a-ols ($\Phi_{2\alpha,3\beta} = 160°$ and $\Phi_{2\beta,3\beta} = 45°$) and, therefore, it may be supposed that substitution of the 5,6-double bond for the 5β,6β-epoxide

ring has no substantial effect on the preferred conformation of the A-ring and that also in the case of the epoxy alcohols *III* and *IV* it can be characterized as the $C_{(10)}$-twist chair conformation (Fig. 1). In the case of epoxy alcohols *I* and *II* the values of the coupling constants $J_{2\alpha,3\alpha}$ and $J_{2\beta,3\alpha}$ extracted from the spectra are approximately equal, which indicates that both dihedral angles $\Phi_{2\alpha,3\alpha}$ and $\Phi_{2\beta,3\alpha}$ should be about 60°. However, without knowledge of the spectrum of protons attached to the $C_{(2)}$ atom it is impossible to decide unequivocally whether the observed splitting of signal of the $C_{(3)}$—H proton corresponds to the correct values of $J_{2,3}$ or whether it represents only $(J_{2\alpha,3\alpha} + J_{2\beta,3\alpha})/2$ in a deceptively simple spectrum. In structurally similar 3β-acetoxy-4,4-dimethyl-A-homo-5-cholesten-4a-ols the calculated[5] values of the dihedral angles $\Phi_{2,3}$ ($\Phi_{2\alpha,3\alpha} = 44°$ and $\Phi_{2\beta,3\alpha} = 71°$) satisfy the $C_{(10)}$-twist chair conformation as the preferred conformation of the A-ring. With respect to the

TABLE III

Calculated dihedral angles $\Phi_{2,3}$ of the epoxides *I*—*IV*, *XXII*, and *XXIII*

Compound	Observed $J_{2,3}$ [Hz]		Calculated $\Phi_{2,3}$ [°]	
	$J_{2\alpha,3}$	$J_{2\beta,3}$	$\Phi_{2\alpha,3}$	$\Phi_{\beta 2,3}$
I	3·7	3·7	60	60
II	3·8	3·8	60	60
III	8·5	6·4	154	34
IV	8·7	5·7	157	37
XXII	6·3	2·0	172	52
XXIII	6·0	11·0	42	162

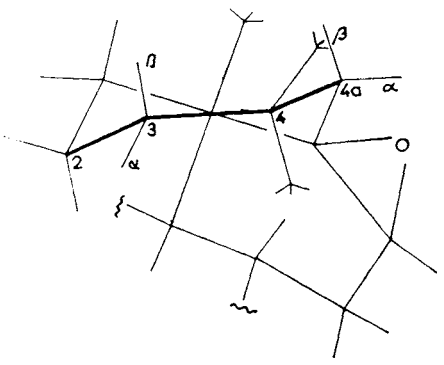
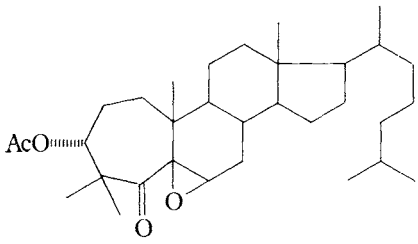


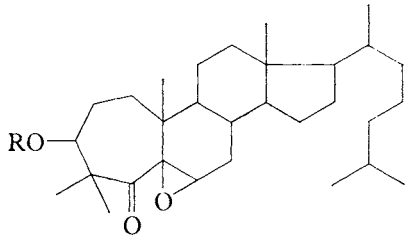
FIG. 1

Conformation of the A-ring in the epoxy alcohols *I*—*IV*

above mentioned fact that in 3α-acetoxy-4,4-dimethyl-A-homocholestane derivatives substitution of the 5,6-double bond for the 5β,6β-epoxide ring does not lead to a substantial change in the preferred conformation of the seven-membered ring A, we suppose that also in the case of epoxy alcohols *I* and *II* the $C_{(10)}$-twist chair conformation is likely to be the preferred conformation of the A-ring (Fig. 1). In line with this assumption is also the fact that the infrared spectra of the epoxy alcohols *I*–*IV* demonstrate the presence of a strong intramolecular hydrogen bonding only in the case of the 4aα-hydroxy-5β,6β-epoxides *II* and *IV* (Table IV). In the conformation $TC_{(10)}$ the approximately equatorial 4aα-hydroxy group and the 5β,6β-epoxide ring are synclinal, which permits hydrogen bonding between these groups, whereas in the case of the 4aβ-hydroxy derivatives *I* and *III* formation of a hydrogen bond between the approximately axial 4aβ-hydroxy group and the 5β,6β-epoxide ring is excluded due to their *trans* orientation.



XXII



XXIII, R = Ac
XXIV, R = H

TABLE IV

Wavenumbers (cm^{-1}) of bands of O—H stretching vibrations of the epoxy alcohols *I*–*IV*

Compound	ν(OH) free	ν(OH) bonded
I[a]	3 613	—
II[b]	3 617[d]	3 502
III[c]	3 625	—
IV[b]	3 617[d]	3 491

[a] IR spectrum was measured on a Zeiss UR 20 instrument in tetrachloromethane, concentration $2{\cdot}5 \cdot 10^{-3}$ mol l^{-1}, cell length 2 cm. [b] IR spectrum was measured on a Perkin–Elmer 580 instrument in tetrachloromethane, concentration $5 \cdot 10^{-3}$ mol l^{-1}, cell length 1 cm. [c] IR spectrum was measured on a Zeiss UR 20 instrument in chloroform, concentration 6%, cell length 0·1 cm. [d] A minute residue.

In the case of epoxy ketones *XXII* and *XXIII* we suppose, after evaluation of steric interactions and steric strain in conformations of the A-ring conforming the calculated dihedral angles (Table III), that the $C_{(10)}$-twist chair conformation (Fig. 2) is likely to be the preferred conformation of the A-ring in the epoxy ketone *XXII*, whereas in the case of the epoxy ketone *XXIII* it is to be the $C_{(3)}$-twist chair conformation (Fig. 3). In both these conformations the 3-acetoxy group assumes the approximately equatorial conformation. With regard to the known[8] antioctant effect of the epoxide ring upon $n \rightarrow \pi^*$ transition, both the conformations $TC_{(10)}$ and $TC_{(3)}$ are consistent with a strong negative Cotton effect observed[5] in the epoxy ketones under discussion ($\Delta\varepsilon_{302} = -3{\cdot}53$ in *XXII* and $\Delta\varepsilon_{300} = -2{\cdot}99$ in *XXIII*).

It may be concluded that on the reduction of the epoxy ketones *XXII* and *XXIII* with sodium borohydride in methanol the *trans*-epoxy alcohols, *i.e.* the 4aβ-hydroxy derivatives *III* and *I*, resp., are predominantly formed, which is in line with the observations[9,10] on the course of this reduction of steroidal tri- and tetrasubstituted α,β-epoxy ketones. However, under the assumption that in the transition state of the reduction the A-ring in ketones *XXII* and *XXIII* assumes preferentially the $TC_{(10)}$ and $TC_{(3)}$ conformation, resp., it would not be possible to explain satisfactorily the decreased reactivity of the 4a-carbonyl group in the ketone *XXIII* in comparison with the ketone *XXII*. In both conformations $TC_{(10)}$ and $TC_{(3)}$ the steric situations in the environment of the 4a-carbonyl group are very similar. It seems to be improbable that the access of the reducing agent from the α-side of the cyclic system would be exposed to a much larger steric hindrance in the $TC_{(3)}$ conformation than in the $TC_{(10)}$ one. On the other hand, the fact that the 3β-acetoxy

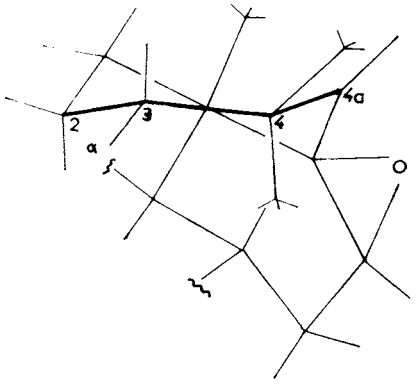


FIG. 2
Conformation of the A-ring in the epoxy ketone *XXII*

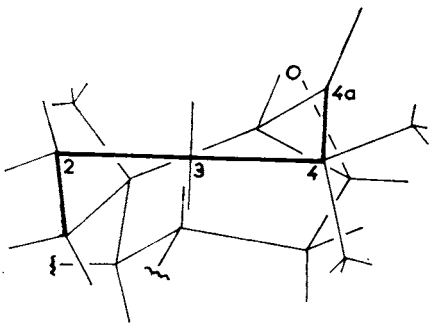


FIG. 3
Conformation of the A-ring in the epoxy ketone *XXIII*

group in the ketone *XXIII* is attacked by the reducing agent could be probably explained by a chelatation both of the ester oxygen and of the 4a-carbonyl group with sodium cation in the $TC_{(3)}$ conformation, which would facilitate the reductive elimination of the ester group.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured in chloroform. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane, unless stated otherwise. The ^{1}H NMR spectra were recorded on spectrometers Tesla B 467 (60 MHz) and Varian XL-200 (200 MHz) in deuteriochloroform with tetramethylsilane as internal standard at 22°C. Chemical shifts are given in δ-scale. The spectra were interpreted only as first order spectra. The CD spectra were measured on Dichrographe II (Jouan--Roussel) in dioxane. The mass spectra were measured on a mass spectrometer AEI MS 902. The identity of samples prepared by different routes was checked by mixture melting points and infrared spectra. The term "usual work-up procedure" means that the solution was washed with 5% hydrochloride acid, 5% aqueous solution of potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent was evaporated *in vacuo*. Preparative thin-layer chromatography of crude products was carried out on silica gel plates (20 × 20 × 0·07 cm) in light petroleum–ether (9 : 1), unless stated otherwise. The corresponding zones were combined, eluted with ether and the solvent was evaporated under reduced pressure.

Reaction of Epoxides *I*—*IV* with Lithium Aluminum Hydride

Lithium aluminum hydride (50 mg) was added to a solution of the epoxide (100 mg) in ether (5 ml) and the mixture was allowed to stand at room temperature for 15 min. The excess of hydride was decomposed with a saturated aqueous sodium sulfate solution and the mixture was filtered through a small column of sodium sulfate. The filtrate was concentrated *in vacuo* and the residue was preparatively chromatographed on two plates of silica gel in light petroleum–ether (8 : 2). The yields of the main products of the reaction are given in Table I.

Reduction of Epoxides *XXII* and *XXIII* with Sodium Borohydride

Sodium borohydride (200 mg) was added to a solution of the keto epoxide (200 mg) in methanol (22 ml) and the mixture was allowed to stand at room temperature for 1 h (in the case of *XXII*) or 3 h (in the case of *XXIII*). The mixture was then poured into an ice – 5% hydrochloric acid mixture and the product was extracted with ether. The extract was washed with 5% aqueous potassium hydrogen carbonate solution, water, dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was preparatively chromatographed on 4 plates of silica gel. The yields of the main products of the reduction are given in Table II.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4aβ,6β-diol (*VIII*)

a) Water (0·3 ml) and perchloric acid (0·4 ml, 72%) were added to a solution of 4,4-dimethyl--5,6β-epoxy-A-homo-5β-cholestane-3α,4aβ-diol (*VII*; ref.[5]; 100 mg) in dioxane (5 ml). The mixture was allowed to stand at room temperature for 3 h, then poured into water and the product was extracted with ether. The extract was washed with 5% aqueous potassium hydrogen carbonate solution, water, dried over sodium sulfate and the solvent was evaporated *in vacuo*.

The residue (98 mg) was preparatively chromatographed on two plates of silica gel in light petroleum–ether (8 : 2) to give 89 mg of the epoxide *VIII*, m.p. 181—182°C (heptane). IR spectrum: 3 627 (hydroxyl), 1 083, 1 017, 1 003, 983 (ether) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·66 (s, 18-H), 0·84 (d, 26 + 27-H, $J = 6$ Hz), 0·99, 1·13, 1·23 (s, 19-H; s, 4,4-dimethyl), 3·57 (mt, 3β-H + 6α-H), 3·83 (s, 4aα-H). For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 78·00% C, 11·22% H.

b) Lithium aluminum hydride (50 mg) was added to a solution of the diketone *XIV* (50 mg) in ether (5 ml) and the mixture was allowed to stand at room temperature for 5 min. The excess of hydride was decomposed with a saturated aqueous sodium sulfate solution and the mixture filtered through a small column of sodium sulfate. The filtrate was concentrated under reduced pressure to give 45 mg of a product which was preparatively chromatographed on one plate of silica gel in light petroleum–ether (8 : 2). The corresponding zone was worked up to yield 40 mg of the diol *VIII* which was crystallized from heptane (26 mg), m.p. 181—182°C.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4aα,6β-diol (*IX*)

Lithium aluminum hydride (40 mg) was added to a solution of the ketone *XI* (80 mg) in ether (6 ml) and the mixture was allowed to stand at room temperature for 15 min. The same work-up as in the preceding experiment (under *b*) gave 75 mg of a product which was preparatively chromatographed on one plate of silica gel in light petroleum–ether (8 : 2). The required zone was worked up affording 70 mg of the diol *IX* which resisted all crystallization attempts, $[\alpha]_D^{20}$ −14° (*c* 0·5). IR spectrum (chloroform): 3 615 (hydroxyl), 1 066, 1 025, 981, 910 (ether) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·67 (s, 18-H), 0·85 (d, 26 + 27-H, $J = 6$ Hz), 1·02, 1·09 (s, 19-H; s, 4,4-dimethyl), 3·64 (mt, 6α-H), 3·87 (mt, 3β-H), 4·13 (s, 4aβ-H). For $C_{30}H_{52}O_3$ (460·7) calculated: 78·20% C, 11·38% H; found: 78·02% C, 11·26% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4aα,6β-diol 4a-Acetate (*X*)

The diol *IX* (170 mg) was acetylated with acetic anhydride (0·6 ml) in pyridine (5 ml) for two days. The usual work-up gave 170 mg of a product which was preparatively chromatographed on 3 plates of silica gel. The corresponding zones were combined and worked up affording 151 mg of the acetate *X*, m.p. 175—177° (methanol), $[\alpha]_D^{20}$ −30° (*c* 0·5). IR spectrum: 3 635 (hydroxyl), 1 747, 1 246, 1 030 (acetate), 1 059, 978 (ether) cm^{-1}. ^1H NMR spectrum (200 MHz): 0·68 (s, 18-H), 1·00, 1·02, 1·15 (s, 19-H; s, 4,4-dimethyl), 2·14 (s, acetate), 3·68 (dd, 3β-H, $J_{3\beta,2} = 3{\cdot}3 + 0{\cdot}8$ Hz), 3·96 (dd, 6α-H, $J_{6\alpha,7\beta} = J_{6\alpha,7\alpha} = J_{6\alpha,OH} = 2{\cdot}9$ Hz), 5·25 (s, 4aβ-H). For $C_{32}H_{54}O_4$ (502·75) calculated: 76·44% C, 10·83% H; found: 76·27% C, 10·68% H.

4aα-Acetoxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-6-one (*XI*)

Chromium trioxide (60 mg) was added to a solution of the alcohol *X* (100 mg) in pyridine (5 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up afforded 95 mg of a product which was preparatively chromatographed on two plates of silica gel. The combined corresponding zones were worked up to give 90 mg of the ketone *XI*, m.p. 155 to 157°C (methanol), $[\alpha]_D^{20}$ +62° (*c* 0·5). IR spectrum: 1 745, 1 240, 1 027 (acetate), 1 724 (ketone), 1 060, 1 012, 905, 898 (ether) cm^{-1}. For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·51% C, 10·26% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4aα-ol (*XII*)

A solution of the ketone *XI* (50 mg) in triethylene glycol (2·75 ml) was treated with hydrazine hydrate (0·4 ml) and solid potassium hydroxide (80 mg) and heated in an open flask to 140°C.

An air condensor was then attached and the mixture was kept at this temperature for 30 min, whereupon the heating was continued without the condensor until the temperature reached 200°C. The mixture was then heated at this temperature for 3 h (again under the air condensor), cooled and poured into water. The product was taken up in ether, the ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (45 mg) was preparatively chromatographed on one plate of silica gel affording 38 mg of the alcohol *XII*, m.p. 161–163°C (methanol), $[\alpha]_D^{20}$ 0° (*c* 0·5). IR spectrum: (chloroform): 3 620 (hydroxyl), 1 054, 1 021 (ether) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·65 (s, 18-H), 0·86 (d, 26 + 27-H, J = 6 Hz), 1·06, 1·08 (s, 19-H; s, 4,4-dimethyl), 3·60 (mt, 3β-H), 3·87 (s, 4aβ-H). For $C_{30}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 80·85% C, 12·02% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4a-one (*XIII*)

Chromium trioxide (10 mg) was added to a solution of the alcohol *XII* (20 mg) in pyridine (1 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up afforded 20 mg of a product which was preparatively chromatographed on one plate of silica gel to yield 17 mg of the ketone *XIII*, m.p. 120–121°C (methanol), $[\alpha]_D^{20}$ −60° (*c* 0·5) in accordance with literature data[1].

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4a,6-dione (*XIV*)

a) Chromium trioxide (40 mg) was added to a solution of the diol *IX* (40 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up gave 40 mg of a product which was preparatively chromatographed on one plate of silica gel. The corresponding zone was worked up affording 35 mg of the diketone *XIV*, m.p. 160–162°C (methanol), $[\alpha]_D^{20}$ −76° (*c* 0·5). IR spectrum (chloroform): 1 764 (ketone), 1 714 (ketone), 1 295, 1 001, 909 (ether) cm^{-1}. For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·73% C, 10·37% H.

b) Chromium trioxide (80 mg) was added to a solution of the diol *VIII* (100 mg) in pyridine (4 ml). Standing overnight followed by the usual work-up gave 97 mg of a product which was crystallized from methanol to yield 70 mg of the diketone *XIV*, m.p. 160–162°C, $[\alpha]_D^{20}$ −76° (*c* 0·5).

c) Chromium trioxide (10 mg) was added to a solution of the alcohol *XVIII* (20 mg) in pyridine (1 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up gave 19 mg of a product which on crystallization from methanol yielded 10 mg of the diketone *XIV*, m.p. 160–162°C, $[\alpha]_D^{20}$ −76° (*c* 0·5).

d) The alcohol *XIX* (20 mg) was treated with chromium trioxide in pyridine as described above. The usual work-up and crystallization of a product (18 mg) from methanol afforded 9 mg of the diketone *XIV*, m.p. 160–162°C, $[\alpha]_D^{20}$ −76° (*c* 0·5).

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4aβ,6β-diol 4a,6-Diacetate (*XV*)

The diol *VIII* (120 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (3 ml) for two days. The usual work-up afforded 120 mg of a product which was purified by preparative TLC on two plates of silica gel. Zones with the lipophilic component gave after working up 30 mg of the diacetate *XV* which was crystallized from methanol (16 mg), m.p. 118–119°C, $[\alpha]_D^{20}$ −18° (*c* 0·5). IR spectrum (chloroform): 1 738, 1 258 (acetate), 1 061, 1 074, (ether) cm^{-1}. For $C_{34}H_{56}O_5$ (544·8) calculated: 74·95% C, 10·36% H; found: 74·79% C, 10·19% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane-4aβ,6β-diol 6-Acetate (*XVI*)

Zones with the polar component from the preparative TLC from the foregoing experiment gave after working up 69 mg of a product which on crystallization from methanol afforded 49 mg of the acetate *XVI*, m.p. 166–167°C, $[\alpha]_D^{20}$ −9° (*c* 0·5). IR spectrum (chloroform): 3 630 (hydroxyl), 1 730, 1 260 (acetate), 1 081, 1 070, 1 061, 950 (ether) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·66 (s, 18-H), 0·85 (d, 26 + 27-H, J = 6 Hz), 0·95, 1·12, 1·21 (s, 19-H s, 4,4-dimethyl), 2·08 (s, acetate), 3·58 (mt, 3β-H), 3·74 (s, 4aα-H), 4·74 (mt, 6α-H). For $C_{32}H_{54}O_4$ (502·75) calculated: 76·44% C, 10·83% H; found: 76·32% C, 10·78% H.

6β-Acetoxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4a-one (*XVII*)

Chromium trioxide (70 mg) was added to a solution of the alcohol *XVI* (100 mg) in pyridine (6 ml) and the mixture was allowed to stand at room temperature overnight. The usual work-up afforded 98 mg of a product which was preparatively chromatographed on two plates of silica gel. The combined corresponding zones were worked up to give 93 mg of the ketone *XVII* which could not be induced to crystallization, $[\alpha]_D^{20}$ −48° (*c* 0·5). IR spectrum: 1 750, 1 235, 1 023 (acetate), 1 750 (ketone), 1 047, 1 038, 1 023, 910 (ether) cm^{-1}. For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·54% C, 10·32% H.

6β-Hydroxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4a-one (*XVIII*)

Solid potassium hydroxide (200 mg) was added to a solution of the acetate *XVII* (100 mg) in methanol (10 ml). The mixture was refluxed for 5 h, then poured into water and the product was taken up in ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue (93 mg) was preparatively chromatographed on two plates of silica gel to give 70 mg of the alcohol *XVIII* which was crystallized from methanol (46 mg), m.p. 171–173°C, $[\alpha]_D^{20}$ −40° (*c* 0·5). IR spectrum (chloroform): 1 734 (ketone), 3 550 (hydroxyl), 1 082, 1 016 (ether) cm^{-1}. ^1H NMR spectrum (60 MHz): 0·67 (s, 18-H), 0·85 (d, 26 + 27-H, J = 6 Hz), 1·02, 1·06, 1·20 (s, 19-H s, 4,4-dimethyl), 3·76 (mt, 6α-H), 4·06 (mt, 3β-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·24% C, 10·68% H.

4aα-Hydroxy-4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-6-one (*XIX*)

Solid potassium hydroxide (200 mg) was added to a solution of the acetate *XI* (100 mg) in methanol (10 ml) and the mixture was refluxed for 2 h. The similar working up as in the foregoing experiment afforded 95 mg of a product which was purified by preparative TLC on two plates of silica gel. Zones with the lipophilic component gave after working up 38 mg of the alcohol *XIX* which was crystallized from methanol (21 mg), m.p. 130–131° C, $[\alpha]_D^{20}$ −38° (*c* 0·5). IR spectrum: 3 480 (hydroxyl), 1 736 (ketone), 1 027, 1 012 (ether) cm^{-1}. For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·30% C, 11·14% H.

3β-(2′-Formyl)isopropyl-4-oxa-5α-cholestan-6-one (*XX*)

Zones with the polar component from the preparative TLC from the foregoing experiment gave after working up 48 mg of the keto aldehyde *XX* which was crystallized from methanol (27 mg), m.p. 179–181°C, $[\alpha]_D^{20}$ +11° (*c* 0·5). IR spectrum (chloroform): 1 728 (ketone), 1 137, 1 076, 1 046 (ether) cm^{-1}. ^1H NMR spectrum (200 MHz): 0·66 (s, 18-H), 0·81 (s, 19-H), 1·10, 1·15 (s, 2′,2′-dimethyl), 2·33 (dd, 7β-H, $J_{7\beta,8\alpha}$ = 4·0 Hz, $J_{7\beta,7\alpha}$ = −12·4 Hz), 3·41 (dd, 3α-H, $J_{3\alpha,2\beta}$ = = 10·6 Hz, $J_{3\alpha,2\alpha}$ = 3·1 Hz), 3·78 (s, 5α-H), 9·06 (s, CH=O). CD spectrum: $\Delta\varepsilon_{303}$ = −0·84. For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·37% C, 10·89% H.

3β-Tert-butyl-4-oxa-5α-cholestane (*XXI*)

A solution of the keto aldehyde *XX* (50 mg) in triethylene glycol (3 ml) was treated with hydrazide hydrate (0·35 ml) and solid potassium hydroxide (80 mg) and the mixture was heated and worked up in the same manner as it was described for *XII*. The product thus obtained was purified by preparative TLC on one plate of silica gel. The corresponding zone was worked up affording 38 mg of the derivative *XXI* which was crystallized from methanol (24 mg), m.p. 141—143°C, $[\alpha]$ +41° (*c* 0·5). IR spectrum: 1 395, 1 363 (tert-butyl), 1 104 (ether) cm^{-1}. ^1H NMR spectrum (200 MHz): 0·65 (s, 18-H), 1·26 (s, 19-H), 0·89 (s, tert-butyl), 2·88 (dd, 3α-H, $J_{3\alpha,2\alpha} = 4{\cdot}1$ Hz, $J_{3\alpha,2\beta} = 11{\cdot}4$ Hz), 2·91 (dd, 5α-H, $J_{5\alpha,6\alpha} = 3{\cdot}3$ Hz, $J_{5\alpha,6\beta} = 10{\cdot}7$ Hz). For $C_{30}H_{54}O$ (430·7) calculated: 83·65% C, 12·64% H; found: 83·38% C, 12·45% H. Mass spectrum: *m/z* 430 (M^+).

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