SOLVOLYTIC REARRANGEMENTS IN 4β,5-CYCLOPROPANO--5β-CHOLESTANE-3β,19-DIOL 3-ACETATE 19-*p*-TOLUENESULPHONATE*

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Received April 9th, 1987

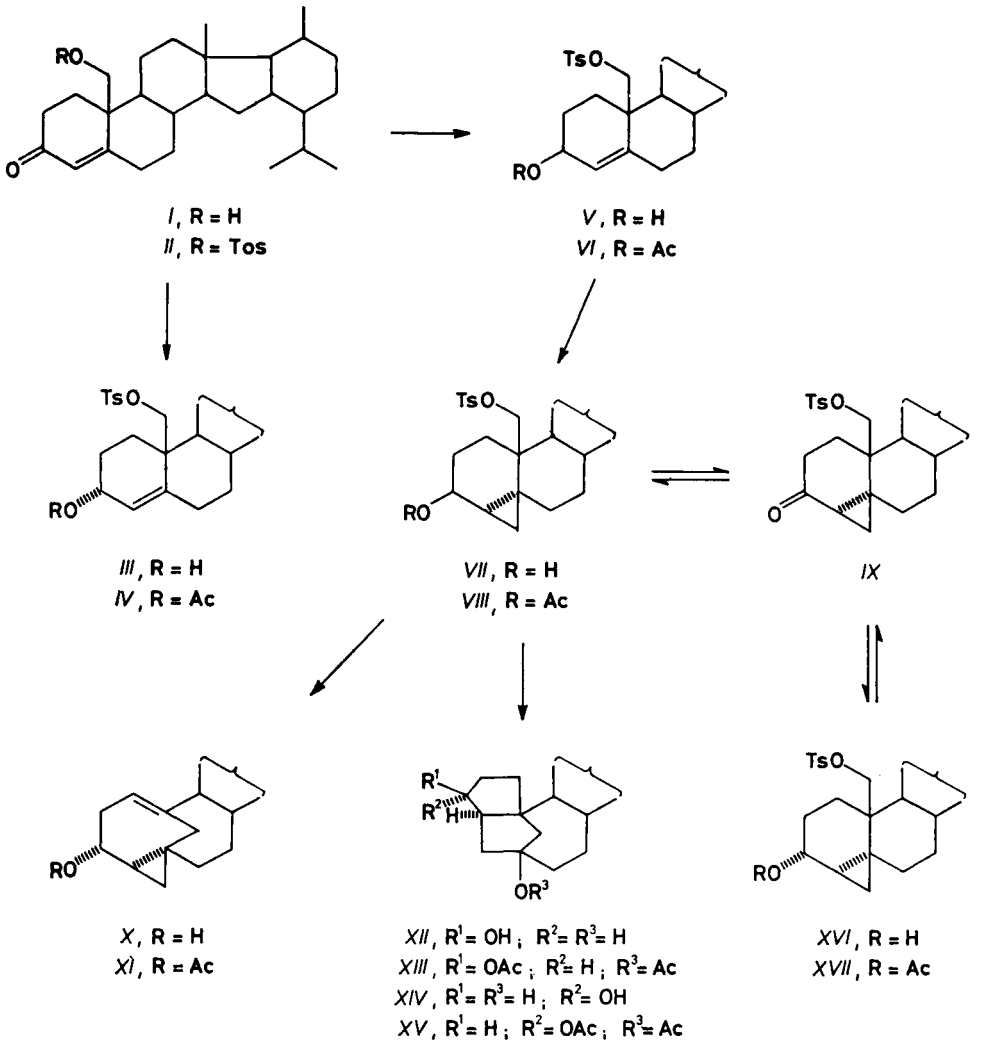
Acetolysis of the tosylate *VIII* proceeded under participation of the cyclopropane ring at the electron-deficient center formed during the reaction to yield three products all having modified steroid skeletons. They were the diene *XXIII*, the unsaturated acetate *XI*, and the saturated 4β,10β-cycloderivative *XIII* carrying two acetoxy groups in the molecule. For the purpose of spectral studies and structure elucidation the acetolysis has been carried out with the labelled tosylate *XXXII* the synthesis of which is described and analogous three labelled products were isolated. The structures of these products were established on the basis of spectral and chemical evidence and a mechanism of the rearrangements is proposed.

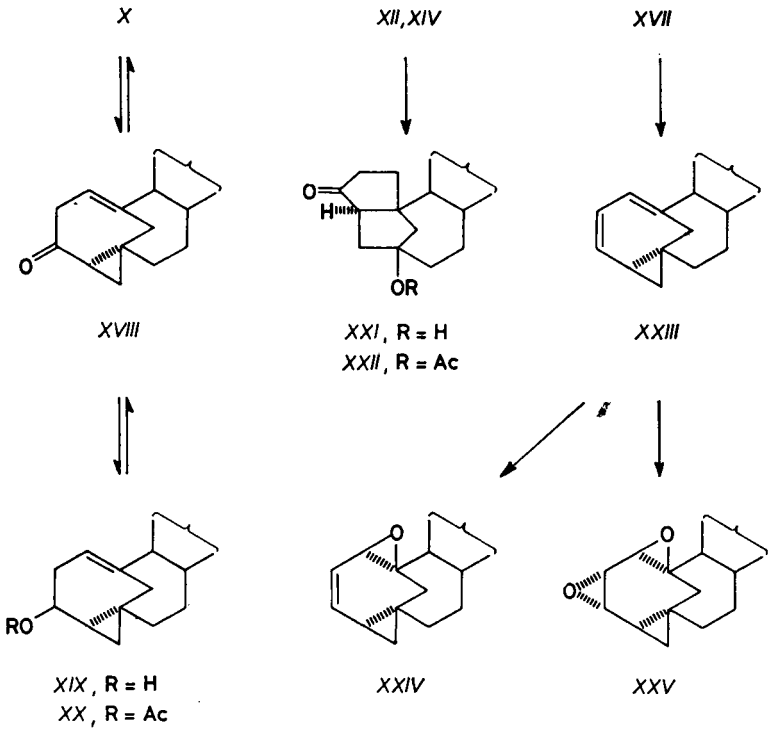
In our previous papers[1-3] we dealt with the Simmons–Smith methylenation of steroidal olefins. Of our main interest were reactions of the cyclopropane ring attached to the steroid skeleton, especially those in which the cyclopropane ring participated in the solvolytic displacement of a sulphonate group under formation of steroids with modified skeletons. In this paper we describe Simmons–Smith methylenation of the 4,5-unsaturated alcohol *V* and solvolysis of the corresponding cyclopropane derivative.

The starting compound, the 19-hydroxy derivative *I* was prepared as described in the literature[4]. Tosylation of the 19-hydroxy group afforded the tosyloxy derivative *II* which on sodium borohydride reduction in ethyl acetate–methanol solution gave the allylic alcohol *V*, characterized also as the acetate *VI*. Simmons–Smith methylenation of the alcohol *V* yielded the cyclopropano derivative *VII*. The structure of this compound and, especially, the β-configuration of the cyclopropane ring follows from spectral evidence and is in agreement with the well-known observations that the steric course of the Simmons–Smith methylenation is directed by the configuration of the hydroxy group situated close to the reacting center[5]. The alcohol *VII* was oxidized with Jones' reagent to the ketone *IX* which on metal hydride

* Part CCCXXXVI in the series On Steroids; Part CCCXXXV: Steroids, in press.

reduction afforded a mixture of the epimeric alcohols *VII* and *XVI*, the latter being the main component. The alcohols were transformed to the corresponding acetates *VIII* and *XVII* and the latters submitted to acetolysis (1 h reflux in acetic acid–acetic anhydride–potassium acetate). The reaction mixture, which according to TLC consisted in both cases of three main components, was separated by column chromatography over silica gel. The most lipophilic component which contained a conjugated diene system was isolated from both reactions. Similarly, both reactions gave rise to the same unsaturated acetoxy deriative, but two different saturated diacetates were isolated as the most polar components. For physicochemical studies and structure

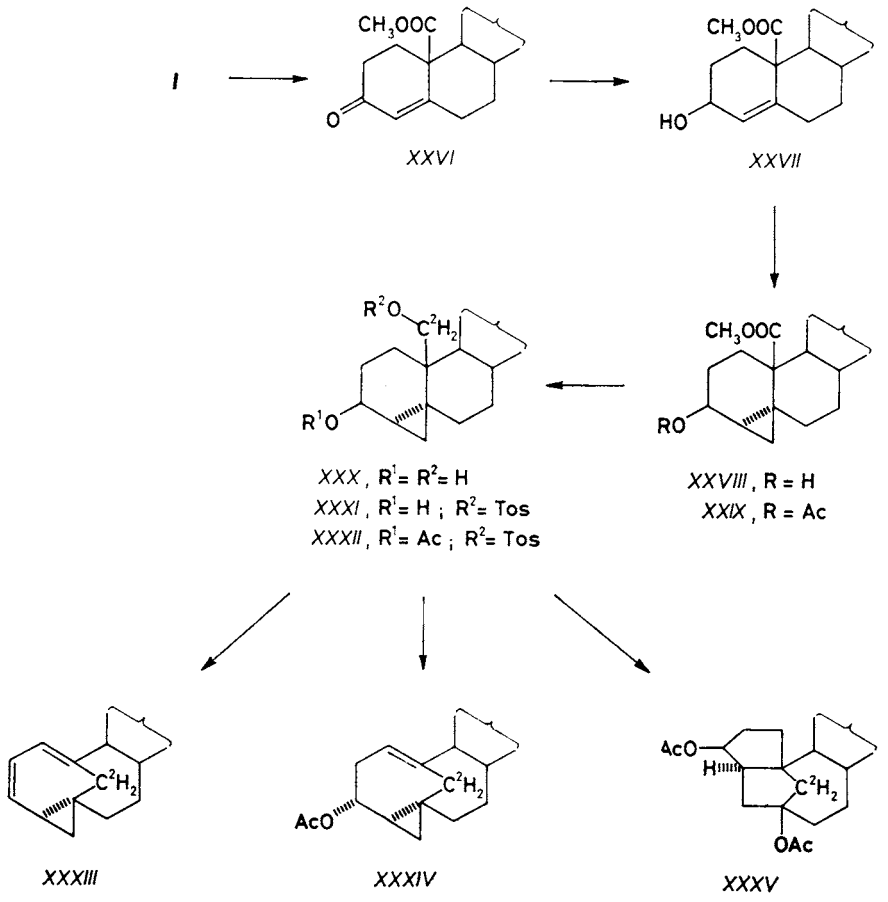




elucidation we carried out the solvolysis with the labelled tosylate *XXXII* which contained two deuterium atoms at $C_{(19)}$. This compound was prepared from the 19-hydroxy derivative *I* by oxidation to the acid and esterification to the ester *XXVI*. Sodium borohydride reduction led to the allylic alcohol *XXVII* which was submitted to the Simmons–Smith methylenation to yield the cyclopropano derivative *XXVIII*. Acetylation of the 3-hydroxy group and reduction with lithium aluminium deuteride afforded the diol *XXX* which was selectively tosyltaed at $C_{(19)}$ to yield after acetylation the labelled tosylate *XXXII* for acetolysis. No unlabelled material was detected by spectral evidence in this compound. The acetolysis afforded the three expected products each containing two deuterium atoms incorporated in a methylene group. Structures of these compounds were established by spectral and chemical means.

The high resolution mass spectrum of the diene *XXIII* exhibits molecular ions $C_{28}H_{44}^{+\cdot}$ at m/z 380 indicating that the product was formed from the tosylate *VIII* by formal loss of *p*-toluenesulphonic acid and acetic acid. The presence of a conjugated diene system consisting of three methine groups and one quaternary sp^2 carbon atom is apparent from the UV as well as from the NMR spectra. From the latter it follows that the diene further contains a trisubstituted cyclopropane ring (δ(C) 9·84 t, 22·69 d, 34·19 s; δ(H) 0·05, 0·12, 0·85) and the original C and D rings

with the cholestane side chain. The presence of the latter structural moiety is also consistent with the mass spectrum of this diene which displays fragment ions due to typical losses of C_8H_{17} and $C_{11}H_{23}$ neutral fragments from the molecular ions.



The bond connectivity in the A ring was established from double resonance experiments in the ^{1}H NMR spectrum and confirmed by secondary and tertiary deuterium isotope effects on the ^{13}C chemical shifts in the ^{13}C NMR spectrum of the labelled derivative *XXXIII*. The cyclopropane protons form an ABX subsystem whose X-part ($H_{(4)}$) has a vicinal coupling with $H_{(3)}$ ($J(3, 4b = 2{\cdot}1)$ and allylic one with $H_{(2)}$ ($J(2, 4) = 2$). The coupling between $H_{(2)}$ and $H_{(3)}$ ($J(2, 3) = 10{\cdot}6$) is typical of a double bond in a six membered or larger rings, while $J(1, 2)$ is small (3·9 Hz) The protons of the 10a-methylene group form an isolated AB system (δ 1·78, 2·33, $J(10, 10a) = 12{\cdot}1$) whose A-part has a small long-range coupling with $H_{(1)}$

($J(1, 10a) = 0{\cdot}9$). The signals of the 10a-methylene protons are absent in the ^{1}H NMR spectrum of the labelled diene *XXXIII*.

Because of the absence of vicinal couplings, the 10a-methylene group must be isolated from the proton bearing rest of the molecule by quaternary carbon atoms at each side. This was confirmed through the ^{13}C NMR spectrum of the labelled diene *XXXIII* (Table I). While the quintet of $C_{(10a)}$ (δ(C) 35·25 for *XXIII*) was lost in the noise, the singlets of the quaternary carbon atoms $C_{(10)}$ (δ(C) 153·51) and $C_{(5)}$ (δ(C) 34·19) were broadened by two bond couplings with 10a-^{2}H and shifted upfield by 0·10 and 0·15 ppm, respectively, because of the secondary isotope effect of the 10a-deuterons. Four tertiary (γ) isotope effects can be further discerned affecting $C_{(9)}$ ($\Delta\delta$(C) = −0·03), $C_{(4a)}$ (δ(C) = −0·05), $C_{(4)}$ (δ(C) = −0·04), and $C_{(6)}$ (δ(C) = −0·04). The other ^{13}C chemical shifts in the spectrum of the labelled diene were reproducible within 0·01 ppm. On the basis of these data we assign structure *XXIII* to the diene and the ensuing bond connectivity (Fig. 1) is fully compatible with this structure. This diene contains a double bond sticking out of one of the bridgehead carbon atoms which formally violates Bredt's rule. However, as follows from molecular mechanics calculations[6,7], the "anti-Bredt" bicyclo[4.4.1]undec-1--ene system is free of strain, which indicates that the ten-membered perimeter ring can well accomodate a bridgehead doule bond.

On peracid epoxidation under mild conditions the diene *XXIII* afforded a monoepoxide (*XXIV*) which under more vigorous conditions underwent further epoxidation to a diepoxide. The position and configuration of the oxirane ring in the monoepoxide ($C_{28}H_{44}O$ by high-resolution mass spectrometry) followed from the NMR spectra. The ^{13}C NMR spectrum displays the signals of two olefinic methine atoms (δ(C) 125·99 and 131·83) and oxirane methine atom and quaternary carbon atoms (δ(C) 61·62 d, ^1J = 176 and 66·82 s). Irradiation of the signal of $H_{(3)}$ in the ^{1}H NMR spectrum afforded the vicinal coupling constant $J(1, 2) = 1{\cdot}9$ Hz which indicated β-configuration of the oxirane ring. This configuration is also indicated by the large shielding effect on the *cis*-oriented $H_{(10a)}$ which now appears at δ(H) 0·86. The monoepoxide has therefore structure *XXIV*. The second oxirane ring in the diepoxide is probably α-oriented, as we deduce from the very small vicinal coupling constant $J(2, 3) = 0{\cdot}7$ Hz and the relatively small shielding effect on the *cis*-$H_{(10a)}$ ($\Delta\delta$(H) = −0·15), compared with that induced by the β-1,10-oxirane ring ($\Delta\delta$(H) = = −0·92). We may therefore assign structure *XXV* to the diepoxide.

The second product of the acetolysis – the unsaturated acetate – was formed from the starting tosylate *VIII* by formal elimination of *p*-toluenesulphonic acid as the high resolution mass spectrum exhibits molecular ions $C_{30}H_{48}O_2^{+\bullet}$ at m/z 440. According to the mass and ^{13}C NMR spectra, the C/D ring system and the cholestane side chain were unaffected by the solvolytic rearrangement. The cyclopropane ring has also been preserved as documented by the signals of $C_{(4)}$, $C_{(4a)}$, and $C_{(5)}$ in the ^{13}C NMR spectrum (Table II). The bond connectivity in the former A/B ring

system followed from the NMR spectra. Irradiation of the unresolved three-proton multiplet of the cyclopropane protons affects the low-field mutltiplet of $H_{(3)}$ at δ(H) 5·09. Further doule resonance experiments led to the sequence $C_{(4)}H_{(4)}$—$C_{(3)}H_{(3)}$—$C_{(2)}H_{(2\alpha)}H_{(2\beta)}$—$C_{(1)}H_{(1)}$, which showed that the double bond is located

TABLE I

^{13}C NMR spectra of the diene *XXIII* and its derivatives, δ(C)

Atom[a]	*XXIII*	*XXXIII*	*XXIV*	*XXV*
$C_{(1)}$	122·35	122·33	61·62	61·40
$C_{(2)}$	122·62	122·33	125·99	54·48
$C_{(3)}$	135·03	135·03	131·83	54·25
$C_{(4)}$	22·69	22·65	23·01	22·44
$C_{(4a)}$	9·84	9·79	21·53	18·82
$C_{(5)}$	34·19	34·03	26·58	25·16
$C_{(6)}$	40·33	40·29	41·78	41·18
$C_{(7)}$	28·75	28·76	28·02	27·95
$C_{(8)}$	42·20	42·21	41·36	41·59
$C_{(9)}$	56·07	56·04	52·82	51·89
$C_{(10)}$	153·51	153·41	66·82	65·60
$C_{(10a)}$	35·25	—	37·03	36·65
$C_{(11)}$	28·04	28·04	24·60	24·19
$C_{(12)}$	28·33	28·33	29·41	28·77
$C_{(13)}$	43·74	43·74	43·71	43·55
$C_{(14)}$	55·11	55·12	55·39	55·24
$C_{(15)}$	24·38	24·38	24·30	24·50
$C_{(16)}$	40·14	40·15	39·83	39·68
$C_{(17)}$	56·57	56·58	56·38	56·30
$C_{(18)}$	12·51	12·51	12·42	12·37
$C_{(20)}$	35·82	35·81	35·80	35·77
$C_{(21)}$	18·66	18·66	18·57	18·55
$C_{(22)}$	36·16	36·17	36·09	36·05
$C_{(23)}$	23·85	23·85	23·81	23·79
$C_{(24)}$	39·53	39·53	39·51	39·49
$C_{(25)}$	28·02	28·01	28·00	27·99
$C_{(26)}$	22·83	22·82	22·81	22·80
$C_{(27)}$	22·58	22·57	22·56	22·54

[a] Assigned on the basis of signal multiplicities in the gated-decoupled spectra or from the "attached-proton test" phases[8,9]. The protonated cyclopropane and oxirane carbon atoms were assigned through ^1J(H, C) coupling constants. The signals of $C_{(13)}$ to $C_{(18)}$ and $C_{(20)}$ to $C_{(27)}$ were assigned by analogy with the ^{13}C NMR spectrum of 5-cholestane[7]. The assignment of the other methylene signals — $C_{(7)}$, $C_{(11)}$ and $C_{(12)}$ — is tentative and may be reversed within the corresponding column.

in the 1(10)-position. The protons at $C_{(10a)}$ appear as an siolated AB system, δ(H) 1·82, 2·28, J(10a, 10a) = 13·4 Hz. The signals of the latter two protons disappeared in the ^{1}H NMR spectrum of the labelled derivative *XXXIV*. Further information was provided by deuterium isotope shifts in the ^{13}C NMR spectrum of *XXXIV*. The signal of $C_{(10a)}$ (δ(C) 31·46 t in the unlabelled compound, Table II) is absent in the labelled analogue while those at δ(C) 145·54 s and 28·19 s are shifted upfield by 0·11 and 0·13 ppm, respectively. Hence the 10a-methylene is linked to the $C_{(5)}$ and $C_{(10)}$ quaternary atoms. Tertiary (γ) isotope shifts are also discernible for the signals of $C_{(1)}$ ($\Delta\delta$(C) = −0·02), $C_{(4)}$ (δ(C) = −0·07), $C_{(4a)}$ (δ(C) = −0·06), $C_{(6)}$ (δ(C) = −0·05), and $C_{(9)}$ (δ(C) = −0·02) (Table II), in line with the bond connectivity in the bridged AB system. The chemical shifts of the other carbon atoms were reproducible within 0·01 ppm. The unsaturated acetate has therefore structure *XI* and the corresponding alcohol structure *X*.

The configuration of the acetoxy group at $C_{(3)}$ was elucidated from double resonance experiments combined with lanthanide-induced shifts in the spectrum of the alcohol *X*. Second-order analysis of the ABXY spin system $H_{(1)}$–$J_{(2\alpha)}$–$H_{(2\beta)}$–$H_{(3)}$, obtained after irradiation of $H_{(4)}$, afforded the pertinent vicinal and allylic coupling constants which showed that one of the $C_{(2)}$ methylene protons (denoted $H_{(2\alpha)}$ had larger coupling constants with both $H_{(1)}$ and $H_{(3)}$. This relationship was found for both the acetate *XI* and the alcohol *X*. Since, however, the seven-membered ring in these compounds can adopt two stable conformations, the pseudoaxial orientation of $H_{(3)}$, compatible with the large vicinal coupling constants, can be accomplished for both $H_{(3\alpha)}$ and $H_{(3\beta)}$. The configurational assignment for $H_{(3)}$ was therefore based on the identity of the proton at $C_{(2)}$ showing the larger vicinal coupling constants. *In situ* complexation of the alcohol *X* with europium(III)-tris-(2,2-dimethyl-6,6,7,7,8,8,8-heptafluorooctane-3,5-dionate) ($Eu(fod)_3$) caused significantly larger induced shift of $H_{(2\alpha)}$ ($\Delta\delta$(H) = +1·86) than with the $H_{(2\beta)}$ ($\Delta\delta$(H) = = +1·00), which confirmed that the hydroxyl group had the same, α-configuration.

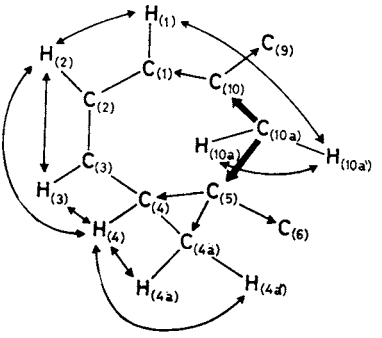


FIG. 1

Bond connectivity and couplings deduced from the NMR spectra of *XXIII* and *XXXIII*. Bold arrows — secondary isotope effects (beta shifts); normal arrows — tertiary isotope effects (gamma shifts); double sided arrows — proton–proton couplings

To get the corresponding 3β-oxygenated derivatives *XIX* and *XX* and their physico-chemical data as well we oxidized the alcohol *X* to the ketone *XVIII*. Borohydride reduction gave a mixture of two isomeric alcohols from which the 3β-isomer was isolated in about 70% yield. The NMR spectra of the 3β-acetoxy derivative *XX* when compared with the 3α-isomer *XI*, display some changes in the proton and carbon chemical shifts due to the reversed configuration at $C_{(3)}$. In the ^{1}H NMR

TABLE II

^{13}C NMR spectra of the unsaturated alcohol *X* and its derivatives, δ(C)

Atom[a]	*XI*	*XXXIV*	*XX*	*X*	*XVIII*
$C_{(1)}$	121·35	121·33	118·42	121·49	117·33
$C_{(2)}$	33·63	33·64	32·86	31·62	40·49
$C_{(3)}$	73·87	73·88	68·37	70·99	206·45
$C_{(4)}$	25·17	25·15	23·00	28·32	34·79
$C_{(4a)}$	19·01	18·95	17·94	18·72	23·95
$C_{(5)}$	28·19	28·06	28·92	27·74	33·46
$C_{(6)}$	41·42	41·37	42·31	41·51	41·98
$C_{(7)}$	28·55	28·55	29·93	28·89	29·38
$C_{(8)}$	40·54	40·55	40·91	40·58	40·75
$C_{(9)}$	57·12	57·10	54·31	56·99	54·19
$C_{(10)}$	145·54	145·43	151·57	146·02	15·77
$C_{(10a)}$	31·46	—	32·37	31·62	31·40
$C_{(11)}$	28·06	28·06	27·97	28·04	92·79
$C_{(12)}$	28·76	28·77	30·01	28·79	27·93
$C_{(13)}$	43·81	43·81	43·51	43·76	34·53
$C_{(14)}$	54·83	54·83	54·90	54·82	54·75
$C_{(15)}$	24·42	24·42	24·48	24·42	24·43
$C_{(16)}$	40·15	40·15	40·17	40·13	40·05
$C_{(17)}$	56·59	56·59	56·55	56·54	56·52
$C_{(18)}$	12·53	12·53	12·42	12·52	12·42
$C_{(20)}$	35·80	35·80	35·78	35·78	35·77
$C_{(21)}$	18·65	18·65	18·62	18·63	18·62
$C_{(22)}$	36·16	36·16	36·11	36·14	36·11
$C_{(23)}$	23·86	23·86	23·82	23·83	23·81
$C_{(24)}$	39·51	39·52	39·50	39·50	39·49
$C_{(25)}$	28·01	27·99	27·99	28·00	28·00
$C_{(26)}$	22·82	22·82	22·80	22·81	22·80
$C_{(27)}$	22·56	22·56	22·55	22·55	22·55
CH_3COO	21·49	21·49	21·45	—	—
CH_3COO	170·64	170·64	170·83	—	—

[a] See footnote in Table I.

spectrum the cyclopropane protons are resolved (δ(H) 0·82, 0·60, and 0·73 for $H_{(4)}$, $H_{(4a)}$, and $H_{(4a)}$, respectively) while those of the 2-methylene are nearly isochronous, so the information on the $J(2\alpha, 3)$ and $J(2\beta, 3)$ is lost. The signals of the10a-methylene protons are shifted slightly downfield compared with those of the 3α-acetate *XI*. In the ^{13}C NMR spectrum of the acetate *XX* (Table II) the signal of $C_{(4a)}$ is shifted upfield, while that of $C_{(5)}$ is shifted downfield.

The most polar products of the acetolysis of the tosylates *VIII* and *XVII* were evidently epimeric at $C_{(3)}$ as oxidation of the corresponding diols afforded the same hydroxy ketone. The acetates can be derived from the starting tosylates by formal substitution of the *p*-toluenesulphonyloxy group for an acetate as may be concluded from the mass spectra showing molecular ions at *m/z* 500. As follows from the NMR spectra of the 3β-hydroxy derivative *XIII*, the original cyclopropane ring is absent, no double bond was formed and one acetoxy group is linked to a methine group, while the other to a quaternary carbon atom. Since the C/D ring system and the cholestane side chain were untouched by solvolysis according to the mass and ^{13}C NMR spectra, the A/B ring system must have rearranged to a new saturated tricyclic ring structure. The closest vicinity of the original 19-methylene was elucidated from the ^{13}C NMR spectrum of the labelled erivative *XXXV* (Table III). There are two singlets corresponding by shift to $C_{(10)}$ (δ(C) 51·60) and $C_{(5)}$ (δ(C) 90·57) which undergo secondary isotope shift in the spectrum of *XXXV*, $\Delta\delta = -0{\cdot}15$ and $-0{\cdot}09$, respectively. The signal of $C_{(10a)}$, identified through deuterium labelling, appears at unusually low field (δ(C) 44·44) and resembles by its shift the bridge methylene carbon atoms in bicyclo[*n.m.*1]alkane systems[8].

Tertiary isotope shifts were found for the signals of methylene carbon atoms at δ(C) 33·09 ($\Delta\delta(C) = -0{\cdot}04$) and 37·74 ($\Delta\delta$(C) = 0·03) (Table III), while smaller shifts could not be safely discerned because of somewhat poorer reproducibility (0·02 ppm). Further information was obtained from the spectra of the hydroxy ketone *XXI* whose infrared spectrum shows a ν(C=O) band at 1 731 cm^{-1} which is indicative of cyclopentanone ring. Deuterium exchange of the enolizable hydrogen atoms in *XXI* (deuterium oxide, sodium deuteroxide, tetrahydrofuran, triethylbenzylammonium chloride, 20°C, 100 h) yielded clearly, after back-exchange of the hydroxyl hydrogen atom, a labelled derivative containing three deuterium atoms. Hence the oxo group is incorporated in an *ortho*-condensed five-membered ring to allow for enolization at both α-carbon atoms. The neighbourhood of the oxygen functions in the ketone *XXI* and its deuterated analogue was explored by lanthanide-induced shifts in the ^{1}H NMR spectra. Upon complexation with Eu(fod)$_3$, in the ketone *XXI* three methylene groups (δ(H) 5·78 d and 7·62 d, 5·28 dd and 6·95 m, 6·42 dd and 6·80 m) could be distinguished and assigned by decoupling, in addition to two other mutually uncoupled protons at δ(H) 7·52 and 6·80. The proton at δ(H) 7·52 shows two large couplings and belongs to another methylene group. Upon deuteration the signals of the methylene group (δ(H) 5·28, 6·95) and that of

the methine group at δ(H) 6·80 disappear, while the doublet of doublets at δ(H) 7·52 collapses to a doublet. From the labelling and lanthanide-induced-shift experiments follows the carbon–carbon connectivity in the A/B ring system (Fig. 2). The

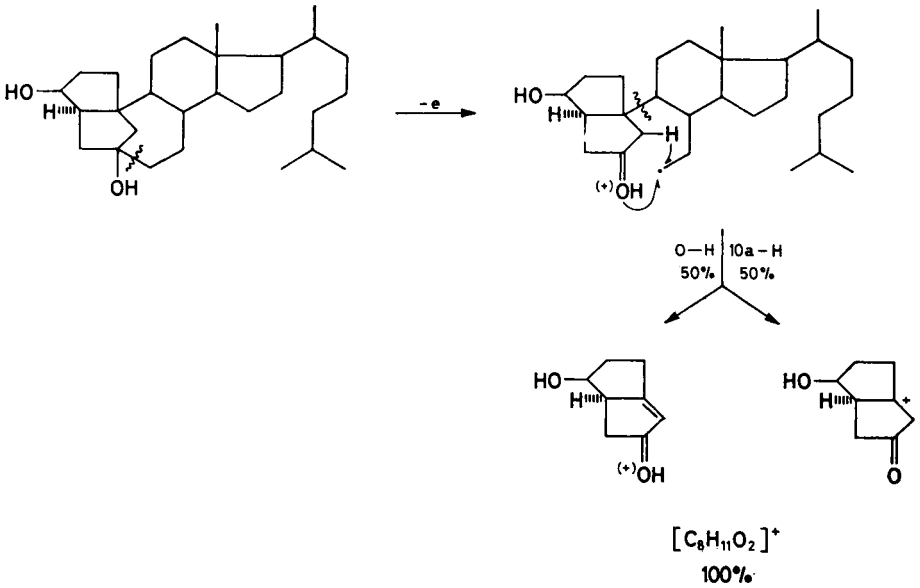
TABLE III

^{13}C NMR spectra of the 4β,10β-cycloderivatives *XIII*, *XXI*, and *XXXV*, γ(H)

Atom[a]	*XIII*	*XXXV*	*XXI* after deuterium exchange
$C_{(1)}$	33·09	33·05	44·06[b]
$C_{(2)}$	25·56[b]	25·58[b]	—
$C_{(3)}$	76·21	76·23	—
$C_{(4)}$	51·00	51·00	—
$C_{(4a)}$	37·81[b]	37·81[b]	43·67[b]
$C_{(5)}$	90·57	90·48	82·44
$C_{(6)}$	37·74	37·71	32·11[b]
$C_{(7)}$	25·12[b]	25·13[b]	25·30[b]
$C_{(8)}$	41·97	41·98	42·21
$C_{(9)}$	56·52	56·52	56·59
$C_{(10)}$	51·60	51·45	50·58
$C_{(10a)}$	44·44	—	45·12
$C_{(11)}$	28·09[b]	28·09[b]	28·09[b]
$C_{(12)}$	26·87[b]	26·87[b]	25·35[b]
$C_{(13)}$	43·55	43·55	43·44
$C_{(14)}$	56·00	56·02	56·07
$C_{(15)}$	24·64	24·64	24·72
$C_{(16)}$	40·69	40·70	40·64
$C_{(17)}$	56·52	56·53	56·52
$C_{(18)}$	12·68	12·68	12·63
$C_{(20)}$	35·83	35·84	35·85
$C_{(21)}$	18·49	18·49	18·50
$C_{(22)}$	36·02	36·03	36·03
$C_{(23)}$	23·84	23·85	23·82
$C_{(24)}$	39·48	39·49	39·50
$C_{(25)}$	27·98	27·98	28·01
$C_{(26)}$	22·81	22·81	22·82
$C_{(27)}$	22·54	22·54	22·57
CH_3COO	170·24	170·23	—
CH_3COO	170·78	170·77	—
CH_3COO	21·03	21·03	—
CH_3COO	22·22	22·22	—

[a] See footnote in Table I; [b] The assignment of the methylene signals is tentative and may be reversed within the corresponding column.

relative configuration at $C_{(3)}$ in the diols *XII* and *XIV* was assigned on the basis of the mass spectrum of the 3β-isomer *XII* and its [3-O—^{2}H] and [5-O—^{2}H] labelled derivative. The mass spectrum of this labelled diol shows a dominant elimination of ^2H_2O (55%) from the molecular ion under electron impact. This indicates that the hydroxy groups can come into interaction in a vibrationally excited molecular ion, which is feasible only for the 3β-OH, 4α-H, 5β-OH configuration in this diol obtained from the 3β-acetoxy tosylate *VIII*. Its mass spectrum and that of the ^{2}H labelled analogue also lend support to the above structural assignment. The base peak in the mass spectrum of the diol *XII* corresponds to $C_8H_{11}O_2^+$ ions that arise by cleavage of the $C_{(5)}$—$C_{(6)}$ bond (α-cleavage) followed by transfer of a hydrogen atom onto $C_{(6)}$ an final rupture of the weak $C_{(9)}$—$C_{(10)}$ bond (Scheme 1). According

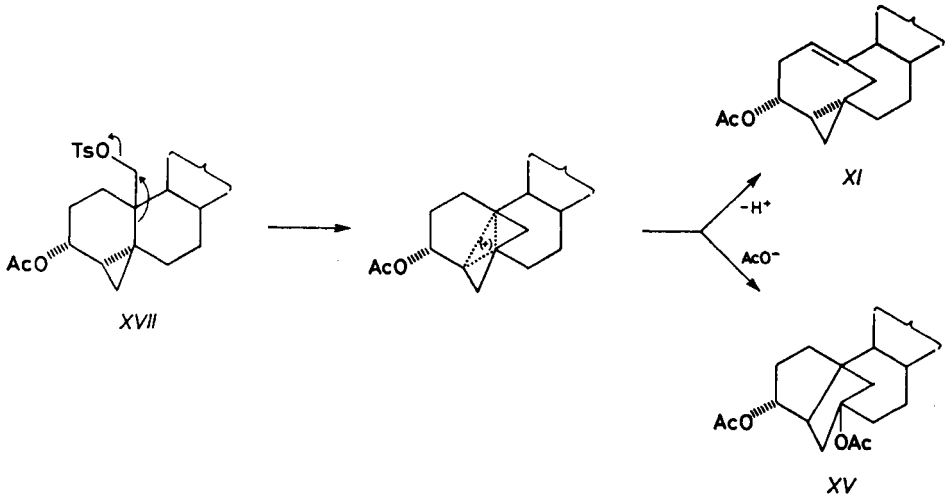


SCHEME 1

to the labelling, abut 50% of hydrogen atoms transferred onto the neutral fragment originate from the 5-OH group while the rest probably comes from the 10a-methylene group. The relative configurations at $C_{(3)}$ and $C_{(4)}$, as deduced from the mass spectra, are also consistent with the large sum of interaction constants of 3α-H ($W = 25$ Hz) which involves two *cis*-vicinal (large) and one *trans*-vicinal (small) couplings. In-line with this, the multiplet of 3β-H in the spectrum of the epimeric 3α-acetate *XV* is narrow ($W = 4{\cdot}5$ Hz).

On the basis of these spectral data we may consider the structures *XI*, *XIII*, *XV*, and *XXIII* for the products of the acetolyses of the tosylates *VIII* and *XVII* as

reasonably well established. The mechanism which gave rise to these structures is apparent (Scheme 2) and the conformation of the rings A and B in the 4,10-cyclo-



SCHEME 2

derivatives is shown in Fig. 3. There is, however, one experimental result which this mechanism does not well explain and that is the isolation of the same unsaturated acetate *XI* from the both epimeric tosylates *VIII* and *XVII*. According to our unpublished results analogous isomerization takes place also in the androstane series and further experimental material elucidating the mechanism of this reaction is reported separately[10].

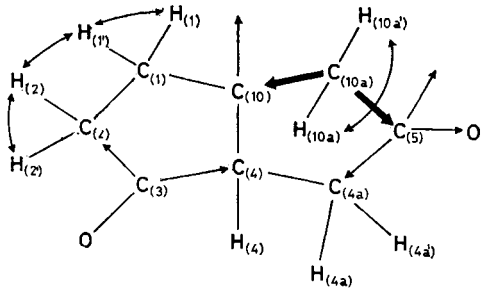


FIG. 2

Bond connectivity and couplings deduced from the NMR spectra and labelling in *XIII* and *XXI*. Denotation as in Fig. 1

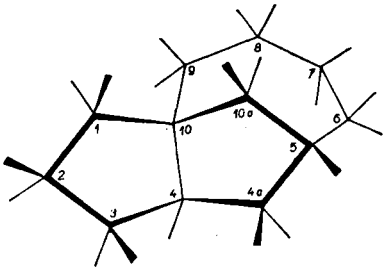


FIG. 3

Conformation of the rings A and B in the 4,10-cyclo derivatives

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform unless otherwise stated with an error of $\pm 2°$. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. Mass spectra were recorded on a Jeol D-100 double-focusing spectrometer (75 eV, 300 μA, 3 kV). The samples were introduced to the ion source *via* a direct inlet probe heated to the lowest temperature enabling evaporation (100 to 150°C). Accurate *m/z* values of ions were determined by the peak matching technique with perfluorokerosene as internal standard. The ^{1}H NMR, ^{2}H NMR, and ^{13}CNMR spectra were recorded on a Varian XL-200 spectrometer (200·057, 30·710, and 50·309 MHz for ^{1}H, ^{2}H, and ^{13}C, respectively, FT mode) in C^2HCl_3 with tetramethylsilane as internal reference. The chemical shifts are given on δ-scale. The identity of samples was checked by mixture melting point determination, by thin-layer chromatography and by spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate, water, drying over magnesium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40—60°C.

19-Hydroxy-4-cholesten-3-one 19-*p*-Toluenesulphonate (*II*)

The alcohol *I* (10 g) in pyridine (80 ml) was treated with *p*-toluenesulphonyl chloride (10 g) and allowed to stand at room temperature for 20 h. The mixture was decomposed with ice and water and the product was taken into ethyl acetate. The extract was worked up in the usual way and solvents were removed *in vacuo*. The residue was crystallized from acetone–ligroin to yield 9·2 g of *II*, m.p. 143—145°C, $[\alpha]_D^{20}$ +94° (*c* 1·6). For $C_{34}H_{50}O_4S$ (554·8) calculated: 73·60% C, 9·08% H, 5·78% S; found: 73·79% C, 8·99% H, 5·88% S.

4-Cholestene-3α,19-diol 19-*p*-Toluenesulphonate (*III*)

The tosylate *II* (3·3 g) in ethyl acetate (90 ml) and methanol (40 ml) was treated under stirring with sodium borohydride (600 mg), added in three portions within 30 min. Stirring was then continued for another 2 h, the mixture was neutralized with acetic acid and the solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate–water and the organic layer was worked up. Evaporation left 3·1 g of a product in which the 3α-isomer was the minor component. Chromatography over silica gel (250 g) in ligroin–ether (2 : 1) gave fractions with the lipophilic component. Working up and crystallization from ether–ligroin yielded 120 mg of *III*, m.p. 108—110°C, $[\alpha]_D^{20}$ +106° (*c* 1·2). IR spectrum: 3 615 (hydroxyl); 1 661 (double bond); 1 370, 1 190, 1 180 cm^{-1} (tosylate). For $C_{34}H_{52}O_4S$ (556·8) calculated: 73·33% C, 9·41% H, 5·75% S; found: 73·21% C, 9·30% H, 5·51% S.

4-Cholestene-3α,19-diol 3-Acetate 19-*p*-Toluenesulphonate (*IV*)

The alcohol *III* (100 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·3 ml) at room temperature for 20 h. The mixture was decomposed with ice anad the product was isolated with ether. Usual working up afforded a crude product which on crystallization from chloroform–methanol gave 65 mg of *IV*, m.p. 88—92°C (decomp.), $[\alpha]_D^{20}$ +158° (*c* 1·4). For $C_{36}H_{54}O_5S$ (598·9) calculated: 72·19% C, 9·08% H, 5·35% S; found: 72·01% C, 8·96% H, 5·03% S.

4-Cholestene-3β,19-diol 19-*p*-Toluenesulphonate (*V*)

Elution of the chromatography column after isolation of *III* with the same solvent mixture and crystallization from ether–ligroin gave 2·4 g of *V*, m.p. 106—107°C, $[\alpha]_D^{20}$ +63° (*c* 1·3).

IR spectrum: 3 620, 3 605 (hydroxyl)' 1 660 (double bond), 1 369, 1 190, 1 180 cm^{-1} (tosylate). For $C_{34}H_{52}O_4S$ (556·8) calculated: 73·33% C, 9·41% H, 5·75% S, found: 73·18% C, 9·30% H, 5·60% S.

5-Cholestene-3β,19-diol 3-Acetate 19-*p*-Toluenesulphonate (*VI*)

The alcohol *V* (200 mg) in pyridine (1 ml) was treated with acetic anhydride (0·6 ml) and allowed to stand at room temperature for 20 h. Decomposition with ice, isolation with ether and usual working up afforded a product which on crystallization from chloroform–methanol yielded 130 mg of *VI*, m.p. 105—106°C, $[\alpha]_D^{20}$ +28° (*c* 1·3). For $C_{36}H_{54}O_5S$ (598·9) calculated: 72·19% C, 9·08% H, 5·35% S; found: 72·12% C, 8·90% H, 5·51% S.

4β,5-Cyclopropano-5β-cholestane-3β,19-diol 19-*p*-Toluenesulphonate (*VII*)

A) The Zn–Cu couple (0·5%) was prepared by addition of zinc dust 30·5 g (Baker 60 to 200 mesh) into a solution of cupric acetate monohydrate (525 mg) in acetic acid (225 ml) at 50—60°C and shaking until the solution decolorized. The solvent was poured off, the metal was washed first with acetic acid (100 ml) and then decanted with eight portions of dry ether (100 ml each). The metal was then covered with dry ether (225 ml), iodine (75 mg) and diiodomethane (31·5 ml) were added and the mixture was refluxed in a nitrogen atmosphere under stirring for 3 h. A ter cooling off to the room temperature a solution of *V* (9·5 g) in dry ether (120 ml) was added and the mixture was stirred under nitrogen at room temperature for 3 h. The mixture was diluted with ether, poured into 5% sodium hydrogen carbonate, the ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvents were distilled off under reduced pressure. The residue was chromatographed on a silica gel column (650 g) in ligroin–ether (2 : 1). Fractions containing *VII* were combined and solvents removed. Crystallization from ether–ligroin afforded 7·5 g of *VII*, m.p. 104—105°C, $[\alpha]_D^{20}$ +3° (*c* 1·2). IR spectrum: 3 620 (hydroxyl); 3 062 (cyclopropane); 1 370, 1 190, 1 180 cm^{-1} (tosylate). ^1H NMR spectrum: 0·13 dd, 1 H (J = 9·2, 5·2); 0·62 s, 2 H; 0·78 dd, 1 H (J = 5·2, 5·0); 2·46 s, 3 H; 4·09, 4·20 m, 2 H, AB (J = 9·5); 4·32 m, 1 H (W = 14); 7·34 d, 2 H; 7·80 d, 2 H (J = 8·4). For $C_{35}H_{54}O_4S$ (570·8) calculated: 73·64% C, 9·53% H, 5·62% H, 5·62% S; found: 73·48% C, 9·40% H, 5·38% S.

B) The ketone *IX* (15 g) in ethyl acetate (450 ml) and methanol (180 ml) was treated under stirring with sodium borohydride (3 g) in the course of 15 min. The mixture was stirred for additional 1 h, neutralized with acetic acid and solvents removed *in vacuo*. The residue was dissolved in ethyl acetate and water and the ethyl acetate solution was worked up as usual. The crude reaction mixture consisted according to the TLC of two components, the 3β-isomer *IX* being the minor and polar product. The mixture wqs separated by column chromatography over silica gel (1·5 kg) in ligroin–ether (2 : 1). Fractions with the polar component were worked up and the product was crystallized from ether–ligroin to yield 1 g of *VII*, m.p. 103—104°C, $[\alpha]_D^{20}$ +34° (*c* 1·6), identical with the compound prepared as under *A*).

4β,5-Cyclopropano-5β-cholestane-3β,19-diol 3-Acetate 19-*p*-Toluenesulphonate (*VIII*)

The alcohol *VII* (2·8 g) was acetylated with acetic anhydride (9 ml) in pyridine (15 ml) and worked up in the usual way. The crude product was purified by column chromatography over silica gel (130 g) in ligroin–ether (9 : 1). Crystallization from ether–ligroin yielded 2 g of the diester *VIII*, m.p. 50—53°C, $[\alpha]_D^{20}$ −17° (*c* 1·5). IR spectrum: 3 060 (cyclopropane); 1 735, 1 251 (acetate); 1 599, 1 496, 1 191, 1 181 cm^{-1} (tosylate). For $C_{37}H_{56}O_5S$ (612·9) calculated: 72·50% C, 9·21% H, 5·23% S; found: 72·35% C, 9·18% H, 5·04% S.

19-Hydroxy-4β,5-cyclopropano-5β-cholestan-3-one 19-*p*-Toluenesulphonate (*IX*)

A) The alcohol *VII* (7 g) in acetone (600 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. Methanol was added to remove the excess oxidizing agent, the mixture was diluted with water (250 ml) and acetone was partly distilled off under reduced pressure. The organic material was extracted with ether and the ethereal solution was washed with 5% hydrochloric acid, water, and a sodium hydrogen carbonate solution and dried over magnesium sulphate. Evaporation of the solvent gave a crude product which was purified by chromatography on a silica gel column (440 g) in ligroin–ether (3 : 1). Working up of the corresponding fractions and crystallization from ether–ligroin yielded 6 g of *IX*, m.p. 74–65°C, $[\alpha]_D^{20}$ +76° (*c* 1·1). IR spectrum: 1 670 (cyclopropane); 1 371, 1 190, 1 180 cm^{-1} (tosylate). For $C_{35}H_{52}O_4S$ (568·8) calculated: 73·89% C, 9·21% H, 5·63% S; found: 74·03% C, 9·03% H, 5·62% S.

B) The alcohol *XVI* (100 mg) in acetone (10 ml) was oxidized with Jones' reagent as under *A*) Similar working up and crystallization from ether–ligroin gave 60 mg of *IX*, m.p. 73–75°C, $[\alpha]_D^{20}$ +76° (*c* 1·3), identical with the compound prepared as under *A*).

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-1(10)-en-3α-ol (*X*)

A) The acetate *XI* (250 mg) in methanol (30 ml) was treated with a solution of potassium carbonate (250 mg) in water (2 ml) and refluxed for 45 min. Water was added (5 ml) and methanol was removed *in vacuo*. The crystalls were separated, dissolved in ether and the ethereal solution was washed with water, dried, and ether was distilled off. The residue afforded on crystallization from methanol 140 mg of *X*, m.p. 143–144°C, $[\alpha]_D^{20}$ +89° (*c* 1·3). ^{1}H NMR spectrum: 0·42 to 0·60 m, 3 H (H-4, H-4a, H-4a′); 0·73 s, 3 H (H-18); 1·80 d, 1 H (H-10a, J = 13·0); 2·23 m, 1 H (H-2α, $J(2\alpha, 2\beta)$ = −16·9, $J(2\alpha, 3\beta)$ = 8·6, $J(2\alpha, 1)$ = 6·0); 2·26 d, 1 H (H-10a′, J(10a, 10a′) = = 13·0); 2·61 m, 1 H (H-2β, $J(2\beta, 1)$ = 4·6 $J(2\beta, 3\beta)$ = 4·4); 3·98 m, 1 H (H-3, W = 18·7); 5·23 m, 1 H (H-1, W = 10·6). Mass spectrum: $M^{+\cdot}$ 398. IR spectrum: 3 620 (hydroxyl); 3 055 (cyclopropane); 3 030, 1 657 cm^{-1} (double bond). For $C_{28}H_{46}O$ (398·6) calculated: 84·35% C, 11·63% H; found: 84·25% C, 11·54% H.

B) The ketone *XVIII* (500 mg) in ethyl acetate (15 ml) and methanol (6 ml) was treated with sodium borohydride (120 mg) under stirring. After 30 min the excess reducing agent was destroyed with acetic acid and solvents were partly removed *in vacuo*. The organic material was taken into ethyl acetate, the extract was washed with a sodium hydrogen carbonate solution, water, dried, and the solvent was evaporated. The reaction mixture consisted according to the TLC of *X* and *XIX*, the 3β-isomer *XIX* being the main component. Repeated chromatography over silica gel (30 g) in ligroin–ether (7 : 1) afforded fractions with the lipophilic compound. Working up and crystallization from methanol yielded 150 mg of *X*, m.p. 142–143°C, $[\alpha]_D^{20}$ +86° (*c* 1·1), identical in all respects with the compound prepared as under *A*).

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-1(10)-en-3α-ol 3-Acetate (*XI*)

A) Glacial acetic acid (100 ml) and acetic anhydride (10 ml) were refluxed with freshly fused potassium acetate (6·6 g) for 90 min. The tosylate *VIII* was then added and refluxed for additional 6 h. The mixture was decomposed with water (5 ml) and acetic acid was removed *in vacuo*. The organic material was taken into ether, the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried over magnesium sulphate and ether was distilled off. The residue (4·7 g) consisted of three main components next to traces of undefined products, as was shown by TLC. Chromatography on a silica gel column (500 g) in ligroin afforded fractions

with the lipophilic component from which 2·03 g of the crude diene *XXIII* were isolated. Elution with ligroin–ether (99 : 1) afforded fractions from which the crude acetate *XI* (950 mg) was obtained. Further elution afforded the crude diacetate *XIII* (540 mg). The crude *XI* was rechromatographed over silica gel (100 g) in ligroin to yield after working up of the corresponding fractions 650 mg of a product which after crystallization from ether–methanol gave 510 mg of *XI*, m.p. 96–98°C, $[\alpha]_D^{20}$ +77° (*c* 1·3). ^{1}H NMR spectrum: 0·55 m, 3 H (H-4, H-4a, H-4a'); 0·74 s, 3 H (18-H); 1·82 d, 1 H (H-10a', J(10a, 10a') = 13·4); 2·25 m, 1 H (H-2α, J(2α, 2β) = = −16·7, J(2α, 1) = 6·6, J(2α, 3β) = 8·8); 2·28 d, 1 H (H-10a, J(10a', 10a) = 13·4); 2·62 m, 1 H (H-2β, J(2β, 1) = 4·0, J(2β, 3β) = 5·4); 2·05 s, 3 H (acetate); 5·09 m, 1 H (H-3β, W = 21); 5·19 m, 1 H (H-1, W = 10·6). Mass spectrum; m/z (rel. intensity): 440 ($M^{+\cdot}$, $C_{30}H_{48}O_2$, 6), 398 (4), 380 (57), 365 (11), 352 (9), 341 (8), 339 (8), 267 (38), 247 (9), 225 (16), 43 (100). IR spectrum: 3 060 (cyclopropane); 1 734, 1 249 (acetate); 1 654 cm^{-1} (double bond). For $C_{30}H_{48}O_2$ (440·7) calculated: 81·76% C, 10·98% H; found: 81·63% C, 10·86% H.

B) The tosylate *XVII* (8 g) was submitted to the acetolytic conditions (120 ml of acetic acid, 12 ml of acetic anhydride, and 8 g of potassium acetate) as described under *A*). Similar working up and chromatography over silica gel (550 g) in ligroin yielded 1·8 g of the crude *XI*. Repeated chromatography over silica gel (100 g) in ligroin afforded 1·5 g of a product which after crystallization from acetone gave 1·2 g of *XI*, m.p. 95–97°C, $[\alpha]_D^{20}$ +76° (*c* 1·3), identical with the acetate prepared as under *A*).

4β,10β-Cyclo-5(10a)-homo-19-nor-5β-cholestane-3β,5-diol (*XII*)

A solution of *XIII* (90 mg) in methanol (5 ml) was treated with a solution of potassium hydroxide (80 mg), methanol (2 ml), and water (1 ml) and refluxed for 2 h. The excess alkali was removed with acetic acid, water was added (5 ml) and methanol was distilled off under reduced pressure. The solid product was extracted into ethyl acetate the solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was crystallized from ethyl acetate to yield 55 mg of *XII*, m.p. 207–209°C, $[\alpha]_D^{20}$ +46° (*c* 1·4). Mass spectrum, m/z (rel. intensity): 416 ($M^{+\cdot}$, $C_{28}H_{48}O_2$, 9), 398 (10), 383 (1), 380 (2), 370 (2), 357 (3), 317 (2), 285 (2), 243 (6), 227 (4), 225 (3), 139 ($C_8H_{11}O_2$, 100). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·57% C, 11·49% H.

4β,10β-Cyclo-5(10a)-homo-19-nor-5β-cholestane-3β,5-diol 3,5-Diacetate (*XIII*)

Elution of the chromatography column after isolation of *XI* under *A*) with ligroin–ether (95 : 5) gave 540 mg of the crude *XIII*. Repeated chromatography over 50 g of silica gel in ligroin–ether (95 : 5) yielded after working up of the corresponding fractions 370 mg of a product which after crystallization from methanol gave 210 mg of *XIII*, m.p. 103–105°C, $[\alpha]_D^{20}$ −10° (*c* 1·4). ^{1}H NMR spectrum: 0·70 s, 3 H (H-18); 1·98 s, 3 H (acetate), 2·03 s, 3 H (acetate); 2·42 m, 1 H (J(n, 3) = 8·5); 2·49 dd, 1 H (J = 13·0, 1·6); 4·79 m, 1 H (W = 25·5). Mass spectrum m/z (rel. intensity): 500 ($M^{+\cdot}$, $C_{32}H_{55}O_4$, 0·2), 440 (23), 425 (2), 398 (2), 380 (100), 365 (7), 352 (5), 327 (8), 313 (4), 300 (5), 295 (3), 285 (9), 267 (16), 247 (8), 240 (16), 227 (21), 226 (24), 225 (47), 211 (10), 191 (24), 178 (33). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·59% C, 10·32% H.

4β,10β-Cyclo-5(10a)-homo-19-nor-5β-cholestane-3α,5-diol (*XIV*)

The diacetate *XV* (200 mg) in methanol (40 ml) was refluxed with a solution of potassium hydroxide (200 mg) in methanol (5 ml) and water (1 ml) for 2 h. Excess alkali was removed with

acetic acid and solvents were distilled off *in vacuo*. The organic material was taken into ethyl acetate, the solution was washed with sodium hydrogen carbonate and worked up. The residue was crystallized from ethyl acetate to yield 120 mg of *XIV*, m.p. 201–203°C, $[\alpha]_D^{20}$ +62° (*c* 1·0 in ethanol). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·60% C, 11·46% H.

4β,10β-Cyclo-5(10a)-homo-19-nor-5β-cholestane-3α,5-diol 3,5-Diacetate (*XV*)

Elution of the chromatography column after isolation of *XI* under *B*) with ligroin–ether (95 : 5) afforded fractions with the most polar component of the solvolysis. The crude product (600 mg) was purified by column chromatography over 50 g of silica gel under similar conditions to afford 450 mg of a product which on crystallization from acetone gave 300 mg of *XV*, m.p. 102–103°C, $[\alpha]_D^{20}$ +35° (*c* 1·2). ^{1}H NMR spectrum: 0·72 s, 3 H (H-18); 1·96 s, 3 H (acetate); 2·01 s, 3 H (acetate); 2·42 m, 1 H; 2·45 m, 1 H; 4·75 m, 1 H ($W_{1/2}$ = 4·5). Mass spectrum: $M^{+\cdot}$ 500. IR spectrum: 1 739, 1 728, 1 249, 1 023 cm^{-1} (acetate). For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·68% C, 10·35% H.

4β,5-Cyclopropano-5β-cholestane-3α,19-diol 19-*p*-Toluenesulphonate (*XVI*)

Fractions with the lipophilic component from the chromatography of the preparation of *VII* under *B*) were combined, the solvent was evaporated and the residue (11·8 g) was crystallized from acetone–water to yield 8·9 g of *XVI*, m.p. 93–95°C, $[\alpha]_D^{20}$ +32° (*c* 1·3). IR spectrum: 3 625 (hydroxyl), 3 065 (cyclopropane), 1 369, 1 190, 1 180 cm^{-1} (tosylate). For $C_{35}H_{54}O_4S$ (570·8) calculated: 73·64% C, 9·53% H, 5·62% S; found: 73·51% C, 9·49% H, 5·30% S.

4β,5-Cyclopropano-5β-cholestane-3α,19-diol 3-Acetate 19-*p*-Toluenesulphonate (*XVII*)

The alcohol *XVI* (8·5 g) in pyridine (60 ml) was treated with acetic anhydride (25 ml) and allowed to stand at room temperature for 20 h. The mixture was decomposed with ice, diluted with water and the product was taken into ether. Usual working up gave 8·3 g of the noncrystalline *XVII*, $[\alpha]_D^{20}$ +33·5° (*c* 1·5). IR spectrum: 2 070 (cyclopropane); 1 736, 1 246 (acetate); 1 190, 1 180 cm^{-1} (tosylate). For $C_{37}H_{56}O_5S$ (612·9) calculated: 72·50% C, 9·21% H, 5·23% S; found: 72·39% C, 9·11% H, 4·90% S.

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-1(10)-en-3-one (*XVIII*)

A) The alcohol *X* (190 mg) in acetone (10 ml) was treated with excess Jones' reagent. After 10 min at room temperature the excess reagent was removed with methanol, water was added (5 ml) and acetone was partly distilled off. The crystalline product was taken into ether and the ethereal solution was worked up in the usual way. The residue (190 mg) was purified by column chromatography over 30 g of silica gel in ligroin–ether (97 : 3). Crystallization from methanol afforded 110 mg of *XVIII*, m.p. 120–122°C, $[\alpha]_D^{20}$ −120° (*c* 1·3). ^{1}H NMR spectrum: 0·75 s, 3 H (H-18); 2·07 dm, 1 H (10a-H, J_d = 13·5, WL = 3·8)' 2·62 d, 1 H (10a″-H, J(10a, 10a′) = = 13·5); 2·79 dd, 1 H (H-2α, J = 15·6, 7·2); 3·30 ddm, 1 H (H-2β, J = 15·6, 5·9); 5·38 dd, 1 H(H-1). ^{1}H NMR: (C_6^2Hy) 0·73 s, 3 H (H-18); 0·97 m, 2 H (H-4, H-4a); 1·92 d, 1 H (H-10a, J = 13·3); 2·46 d, 1 H (H-10a·); 3·00 ddd, 1 H (H-2α, J(2α, 2β) = −15·6, J(2α, 1) = 7·2, J = 1·3); 3·25 dd, 1 H (H-2β, J(2β, 1) = 6·0); 5·42 m, 1 H (W = 14). Solvent shifts $\delta(C^2HCl_3)$ − $\delta(C_{60}Hy)$: H-1 −0·04, H-2α −0·21, H-2β +0·05, H-10a +0·15, H-10a· +0·16, H-18 +0·02. Mass spectrum, *m/z* (rel. intensity): 396 ($M^{+\cdot}$, $C_{28}H_{44}O$, 100), 381 (8), 378 (4), 368 (51), 353 (11), 327 (10), 283 (22), 255 (41), 247 (8), 241 (17), 213 (21). IR spectrum: 3 070 (cyclopropane),

3 035, 1 644, 849 (double bond)' 1 691 cm^{-1} (carbonyl). For $C_{28}H_{44}O$ (396·6) calculated: 84·78% C, 11·18% H; found: 84·63% C, 11·05% H.

B) The alcohol *XIX* (80 mg) in acetone (6 ml) was oxidized with Jones' reagent as described under *A*). Similar working up, chromatography over silica gel (5 g) and crystallization from methanol afforded 30 mg of *XVIII*, m.p. 120—122°C, $[\alpha]_D^{20}$ —122° (*c* 1·2).

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-1(10)-en-3β-ol (*XIX*)

Elution of the chromatography after isolation of *X* under *B*) yielded fractions with the polar component. Working up and crystallization from methanol gave 280 mg of *XIX*, m.p. 124 to 126°C, $[\alpha]_D^{20}$ +64° (*c* 1·4). IR spectrum: 3 615, 1 032, 1 024 (hydroxyl); 3 055, 3 030 (cyclopropane and double bond); 1 653 cm^{-1} (double bond). For $C_{28}H_{46}O$ (398·6) calculated: 84·35% C, 11·63% H; found: 84·20% C, 11·51% H,

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-1(10)-en-3β-ol 3-Acetate (*XX*)

The alcohol *XIX* (150 mg) in pyridine (2 ml) was acetylated with acetic anhydride (0·6 ml) for 20 h at room temperature. The reaction mixture was decomposed with ice and water and the product was extracted with ether. Usual working up and crystallization from methanol yielded 115 mg of *XX*, m.p. 75—77°C, $[\alpha]_D^{20}$ +3° (*c* 1·4). ^{1}H NMR spectrum: 0·60 dd, 1 H (H-4a, *J*(4a, 4) = 8·7); 0·73 m, 1 H (H-4a'); 0·74 s, 3 H (H-18); 0·82 m, 1 H (H-4); 2·05 s, 3 H (acetate); 1·95 d, 1 H (H-10a, *J* = 13·1); 2·23 m, 2 H (H-2α, H-2β); 2·41 d, 1 H (H-10a', *J*(10a, 10a') = 13·1); 5·11 m, 1 H (H-3, *J*(3,4) = 7·8, *J*(3, 2α) + *J*(3, 2β) = 18·2); 5·24 m, 1 H (H-1, *W* = 14·6). Mass spectrum, *m*/*z* (rel. intensity): 440 ($M^{+\cdot}$, $C_{30}H_{48}O_2$, 5), 298 (6), 380 (73), 365 (11), 253 (10), 339 (15), 314 (6), 267 (45), 247 (10), 225 (19), 43 (100). IR spectrum: 3 060 (cyclopropane); 3 035, 1 653 (double bond); 1 736, 1 249 cm^{-1} (acetate). For $C_{30}H_{48}O_2$ (440·7) calculated: 81·76% C, 10·98% H; found: 82·03% C, 10·94% H.

5-Hydroxy-4β,10β-cyclo-5(10a)-homo-19-nor-5β-cholestan-3-one (*XXI*)

A) The diol *XII* (45 mg) in acetone (3 ml) was oxidized with Jones' reagent at room temperature for 10 min. Methanol was added to destroy the excess agent and solvents were distilled off. The product was taken into ethyl acetate and the extract was worked up in the usual way. Crystallization from methanol afforded 28 mg of *XXI*, m.p. 198—200°C, $[\alpha]_D^{20}$ —28° (*c* 1·1). ^{1}H NMR spectrum: 0·73 s, 3 H (H-18); 2·20 m, 2 H; 2·58 m, 1 H (*W* = 39). Mass spectrum, *m*/*z* (rel. intensity): 414 ($M^{+\cdot}$, $C_{28}H_{46}O_2$, 87), 396 (33), 260 (47), 259 (45), 241 (44), 165 (100), 137 (76). IR spectrum: 3 615, 3 470 (hydroxyl); 1 741, 1 721 cm^{-1} (carbonyl). CD spectrum: $\Delta\varepsilon_{300}$ —3·8. For $C_{28}H_{46}O_2$ (414·6) calculated: 81·10% C, 11·18% H; found: 80·92% C, 11·12% H.

B) Oxidation of *XIV* (100 mg) in acetone (10 ml) with Jones' reagent as described above afforded after similar working up and crystallization from methanol 64 mg of *XXI*, m.p. 199 to 201°C, $[\alpha]_D^{20}$ —29° (*c* 1·4).

5-Hydroxy-4β,10β-cyclo-5(10a)-homo-19-nor-5β-cholestan-3-one 5-Acetate (*XXII*)

The alcohol *XXI* (50 mg) in pyridine (1 ml) was treated with acetic anyhydride (0·3 m) and heated to 100°C for 4 h. Usual working up and crystallization from methanol gave 25 mg of *XXII*, m.p. 145—146°C, $[\alpha]_D^{20}$ —51° (*c* 1·3). IR spectrum: 1 741 (carbonyl); 1 738, 1 252 cm^{-1} (acetate). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 78·78% C, 10·42% H.

4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholesta-1(10),2-diene (*XXIII*)

A) Fractions with the most lipophilic component from the chromatography of the acetolysis of *VIII* (preparation of *XI* under *A*)) were worked up to yield 2·3 g of a crude product. Repeated chromatography over 200 g of silica gel in ligroin gave after working up of the corresponding fractions 1·7 g of a residue which on crystallization from ether–methanol yielded 1·35 g of *XXIII*, m.p. 70–72°C, $[\alpha]_D^{20}$ +379° (*c* 1·1). ^{1}H NMR spectrum: 0·05, 0·12 m, AB part of an ABX system, 2 H (H-4a, H-4a', J(4a, 4a') = −4·2, J(4a, 4) = 5·4, J(4a', 4) = 9·8); 0·76 s, 3 H (H-18); 0·85 m, 1 H (H-4); 1·78 d, 1 H (10a-H, J(10a, 10a') = −12·1); 2·33 d, 1 H (10a'-H); 5·52 m, 1 H (H-1, J(1, 2) = 3·9); 6·11 m, 1 H (H-2, J(2, 3) = 10·6, J(2, 4) = 2·1); 5·83 m, 1 H (H-3, J(3, 4) = 2·1). Mass spectrum, *m/z* (rel. intensity): 380 ($M^{+\cdot}$, $C_{28}H_{44}$, 37), 365 (10), 352 (8), 339 (3), 311 (5), 267 (45), 247 (11), 239 (9), 225 (26), 197 (52), 163 (52), 91 (100). IR spectrum: 3 065, 3 030, 3 005 (cyclopropane and double bonds); 1 638, 1 606 (conj. double bonds); 713 cm^{-1} (double bond). For $C_{28}H_{44}$ (380·6) calculated: 88·34% C, 11·65% H; found: 88·22% C, 11·53% H.

B) Fractions with the most lipophilic component from the chromatography of the acetolysis of *XVII* (preparation of *XI* under *B*) gave 2·6 g of a crude product which was purified by chromatography on a silica gel column (150 g) in ligroin to yield 2·2 g of a product which on crystallization from ether–methanol yielded 1·9 g of *XXIII*, m.p. 69–71°C, $[\alpha]_D^{20}$ +383° (*c* 1·4).

1β,10β-Epoxy-4β,5-cyclopropano-5(10a)-homo-19-nor-5β-cholest-2-ene (*XXIV*)

The diene *XXIII* (250 mg) in ether (5 ml) was treated at 18°C with a solution of *m*-chloroperbenzoic acid (120 mg) in ether (2 ml) and allowed to stand at the same temperature for 3 h. The mixture was diluted with with ether and the excess peracid was removed by extraction with a sodium carbonate solution. Evaporation of ether left 250 mg of a product which according to the TLC consisted of essentially one product. Chromatography over silica gel (25 g) in ligroin gave after crystallization from methanol–ether 190 mg of *XXIV*, m.p. 96–98°C, $[\alpha]_D^{20}$ +109° (*c* 1·3). ^{1}H NMR spectrum: 0·23 dd, 1 H (H-4a, J(4a, 4a') = −4·0, J(4a, 4) = 5·5); 0·64 dd, 1 H (H-4a', J(4a', 4) = 8·7); 0·75 s, 3 H (H-18); 0·86 d, 1 H (H-10a, J = 13·7); 2·56 dd, 1 H (H-10a', J(10a', 10a) = 13·7, $_9J$ = 0·8); 3·11 m, 1 H (H-1, W = 5); 5·61, 5·74 m, 2 H, AB part of an ABXY multiplet (H-2, H-3, J(2, 3) = 10·3, J(1, 2) = 1·9, J(3, 1) = 1·7, J(2, 4) = 1·7, $_9J$ = 0·8 and 0·9). Mass spectrum, *m/z* (rel. intensity): 396 (M^{+}!, $C_{28}H_{44}O$, 57), 381 (6), 378 (9), 368 (7), 353 (7), 339 (4), 327 (7), 315 (6), 311 (6), 283 (16), 265 (8), 255 (7), 247 (8), 43 (100). IR spectrum: 3 065, 3 015 (cyclopropane and double bond); 1 652, 691 (double bond); 877, 851 cm^{-1} (epoxide). For $C_{28}H_{44}O$ (396·6) calculated: 84·78% C, 11·18% H; found: 84·58% C, 10·85% H.

(1β,10β),(2α,3α)-Diepoxy-4β,5-cyclopropano-5(10a)-homo-19-nor-5β-cholestane (*XXV*)

A solution of *XIII* (500 mg) in ether (15 ml) was treated with *m*-chloroperbenzoic acid (650 mg) in ether (10 ml) and allowed to stand at 28°C for 48 h. The mixture was worked up as described in the foregoing experiment to yield a mixture of *XXIV* and *XXV* in which the more polar diepoxide predominated according to the TLC. It was chromatographed over silica gel (60 g) in ligroin and the fractions with the polar component were worked up and solvents removed to yield 310 mg of a product which on crystallization from ether–methanol gave 260 mg of *XXV*, m.p. 108–109°C, $[\alpha]_D^{20}$ +86° (*c* 1·3). ^{1}H NMR spectrum: 0·29 dd, 1 H (H-4a, J(4a, 4a') = −4·7, J(4a, 4) = 5·8); 0·69 dd, 1 H (H-4a', J(4a', 4) = 9·5); 0·71 d, 1 H (H-10a, J(10, 10a') = 14·1); 0·74 s, 3 H (18-H); 2·63 dm, 1 H (H-10a', J(10a, 10a') = 14·1, J(m) = 1); 3·07 m, B part of an ABCXY system, 1 H (H-3, J(2, 3) = 3·2, J(3, 4) = 0·7); 3·11 m, 1 H (H-1, W = 1·5); 3·12 m, 1 H (H-2, J(2, 1) ≅ 0·5, J(2, 4) = 0·7). Mass spectrum, *m/z* (rel. intensity): 412 ($M^{+\cdot}$, $C_{28}H_{44}O_2$,

9), 397 (2), 394 (2), 384 (3), 383 (3), 355 (5), 299 (7), 281 (5), 271 (5), 257 (5), 253 (7), 247 (7), 245 (7), 239 (7), 147 (53), 43 (100). IR spectrum: 3 065 (cyclopropane); 870, 854 cm^{-1} (epoxide). For $C_{28}H_{44}O_2$ (412·6) calculated: 81·50% C, 10·75% H; found: 81·36% C, 10·79% H.

3-Oxocholest-4-en-19-oic Acid Methyl Ester (*XXVI*)

A solution of *I* (12 g) in acetone (300 ml) was treated with excess Jones' reagent and allowed to stand at 45°C for 1 h. The mixture was treated with methanol to remove the excess agent, most of the solvents were distiled off *in vacuo* and the product was taken into ethyl acetate. The extract was washed with water, dried, and the solvent was evaporated. The residue was dissolved in methanol (40 ml) and treated with excess diazomethane in ether. After 10 min at room temperature the excess diazomethane was destroyed with acetic acid, the ethereal solution was washed with a sodium hydrogen carbonate solution water, dried over magnesium sulphate and ether was distilled off. The residue was chromatographed on a silica gel column (800 g) in benzene to yield after crystallization from methanol 8·5 g of *XXVI*, m.p. 79—80°C, $[\alpha]_D^{20}$ +154° (*c* 1·5) in accordance with the literature[11].

3β-Hydroxycholest-4-en-19-oic Acid Methyl Ester (*XXVII*)

The ketone *XVI* (9·7 g) in ethyl acetate (280 ml) and methanol (120 ml) was treated under stirring at +10°C with sodium borohydride, added in three portions in the course of 20 min. Stirring was then continued for another 30 min and the excess hydride was decomposed with acetic acid. Water (300 ml) was added and the product was taken into ethyl acetate. The extractwas washed with sodium hydrogen carbonate, then with water, dried, and solvent was evaporated. The residue (9·6 g) was chromatographed on a silica gel column in ligroin–ether (3 : 1). Working up of the corresponding fractions and crystallization from acetone–water gave 7·6 g of *XXVII*, m.p. 104—106°C, $[\alpha]_D^{20}$ +84° (*c* 1·6). IR spectrum: 3 620, 3 605, 1 035 (hydroxyl); 3 625, 1 662 (double bond); 1 726, 1 196, 1 172, 1 162 cm^{-1} (carboxyl). For $C_{28}H_{46}O_3$ (430·6) calculated: 78·09% C, 10·77% H; found: 77·93% C, 10·89% H.

3β-Hydroxy-4β,5-cyclopropano-5β-cholestan-19-oic Acid Methyl Ester (*XXVIII*)

The Zn–Cu couple (0·5%) was prepared by addition of zinc dust (24 g; Baker 60—200 mesh) into a solution of cupric acetate monohydrate (420 mg) in acetic acid (200 ml) at 105°C and shaking until the solution decolorized. The metal was further treated as described for the preparation of *VII* under *A*). Iodine (60 mg) and diiodomethane (24 ml) were added and the mixture was refluxed under stirring for 3 h. The alcohol *XXVII* (7·6 g) was then submitted to the Simmons–Smith methylenation. Stirring under nitrogen at room temperature for 6 h. and working up as described for *VII* under *A*) gave a crude product which was chromatographed over silica gel (600 g) in ligroin–ether (3 : 1) to yield, after working up of the corresponding fractions 6·72 g of a material which on crystallization from methanol afforded 6·40 g of *XXVIII*, m.p. 66—68°C, $[\alpha]_D^{20}$ +24° (*c* 1·3). IR spectrum: 3 620, 1 038 (hydroxyl); 3 065 (cyclopropane); 1 727, 1 204 (carboxyl); 1 632 cm^{-1} (ester). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·28% C, 10·90% H.

3β-Acetoxy-4β,5-cyclopropano-5β-cholestan-19-oic Acid Methyl Ester (*XXIX*)

The alcohol *XXVIII* (100 mg) in pyridine (1 ml) was treated with acetic anhydride (0·4 ml). After 20 h at room temperature the mixture was worked up in the usual way. Crystallization from methanol yielded 60 mg of *XXIX*, m.p. 79—80°C, $[\alpha]_D^{20}$ −11° (*c* 1·4). IR spectrum: 3 080,

3 010 (cyclopropane); 1 731, 1 252, 1 020 (acetate); 1 207 cm^{-1} (ester). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·36% H; found: 76·64% C, 10·35% H.

[19-$^2H_2$]-4β,5-Cyclopropano-5β-cholestane-3β,19-diol (*XXX*)

The acetate *XXIX* (2·5 g) in dry ether (250 ml) was treated with lithium aluminium deuteride (800 mg) and refluxed for 8 h. The mixture was decomposed with ethyl acetate and wet ether, washed with 5% hyddrochloric acid and worked up as usual. The curde product was chromatgraphed on a silica gel column (180 g) in ether–benzene (1 : 1) to yield after crystallization from methanol 1·55 g of *XXX*, m.p. 115—116°C, $[\alpha]_D^{20}$ 0°, identical with the unlabelled compound prepared previously[12]. ^1H NMR spectrum showed absence of the $C_{(19)}$-protons.

[19-$^2H_2$]-4β,5-Cyclopropano-5β-cholestane-3β,19-diol 19-*p*-Toluenesulphonate (*XXXI*)

The diol *XXX* (2 g) in pyridine (110 ml) was treated with *p*-toluenesulphonyl chloride (2·8 g) at 0°C and allowed to stand at 0°C for 18 h. The mixture was poured on ice containing 150 ml of conc. hydrochloric acid. The product was taken into ethyl acetate and worked up in the usual way. Chromatography over silica gel (100 g) in ligroin–ether (2 : 1) and crystallization from ether–ligroin afforded 1·62 g of *XXXI*, m.p. 106—108°C, $[\alpha]_D^{20}$ +4° (*c* 1·1).

[19-$^2H_2$]-4β,5-Cyclopropano-5β-cholestane-3β,19-diol
3-Acetate 19-*p*-Toluenesulphonate (*XXXII*)

The alcohol *XXXI* (1·6 g) in pyridine (15 ml) was acetylated with acetic anhydride (5 ml) at room temperature for 20 h. Usual working up gave 1·45 g of a product which was purified by column chromatography over silica gel (80 g) in ligroin–ether (9 : 1). Working up of the corresponding fractions and crystallization from ether–ligroin afforded 1·4 g of *XXXII*, m.p. 52—54°C, $[\alpha]_D^{20}$ −15° (*c* 1·2).

[10-$^2H_2$]-4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholesta-1(10),2-diene (*XXXIII*)

Acetic anhydride (1 ml) and acetic acid (12 ml) were refluxed with freshly fused sodium acetate (1 g) for 1 h. After cooling off 1·3 g of *XXXII* was added and refluxed for another 1 h. The mixture was then treated with water (1 ml) and after reflux for 20 min the solvents were removed *in vacuo*. The organic material was taken into ether, the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and ether was distilled off to leave 950 mg of a residue which according to the TLC contained *XXXIII*, *XXXIV*, and *XXXV*. The mixture was chromatographed over silica gel (120 g) in ligroin. Fractions with the lipophilic product were combined, solvent was distilled off and the residue (360 mg) was crystallized from ether–methanol to afford 250 mg of the labelled diene *XXXIII*, m.p. 71—73°C, $[\alpha]_D^{20}$ +381° (*c* 1·1). Mass spectrum, *m/z* (rel. intensity): 382 ($M^{+\cdot}$, $C_{28}H_{42}{}^2H_2$, 48), 367 (7), 352 (5), 311 (4), 269 (33), 247 (7), 227 (14), 165 (30), 43 (100).

[10a-$^2H_2$]-4β,5-Cyclopropano-5(10a)-homo-19-nor-5β-cholest-
-1(10)-en-3α-ol 3-Acetate (*XXXIV*)

Elution of the chromatography from the foregoing experiment with the same solvent afforded fractions with the component of medium polarity. Working up gave 70 mg of a residue which was crystallized from ether–methanol to yield 40 mg of the acetate *XXXIV*, m.p. 96—98°C, $[\alpha]_D^{20}$ +75° (*c* 0·8). Mass spectrum, *m/z* (rel. intensity): 442 ($M^{+\cdot}$, $C_{30}H_{46}{}^2H_2O_2$, 4), 400 (3), 382 (46), 367 (8b, 343 (5), 339 (6), 329 (3), 269 (34), 247 (8), 243 (7), 227 (15), 43 (100).

[10a-$^2H_2$]-4β,10β-Cyclo-5(10a)-homo-19-nor-5β-cholestane-3β,5-diol 3,5-Diacetate (*XXXV*)

Further elution of the chromatography from the foregoing experiment with ligroin–ether (99 : 1) yielded fractions with the most polar product. Combination of these fractions and evaporation of the solvents left 24 mg of a residue which on crystallization from methanol afforded 16 mg of *XXXV*, m.p. 102—104°C, $[\alpha]_D^{20}$ −10° (*c* 0·7). Mass spectrum, *m/z* (rel. intensity): 502 ($M^{+\cdot}$, $C_{32}H_{50}{}^2H_2O_4$, 0·2), 442 (32), 427 (2), 400 (3), 382 (49), 381 (37), 380 (22), 367 (7), 329 (8), 288 (6), 287 (9), 269 (11), 247 (10), 242 (9), 241 (10), 229 (16), 228 (14), 227 (30), 226 (12), 192 (19), 179 (23), 57 (100).

The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Sýkorová and Mrs E. Šípová under the direction of Dr V. Pechanec. The IR *spectra were recorded by Mrs K. Matoušková under the direction of Dr J. Smolíková. The* CD *spectra were recorded by Dr S. Vašíčková.*

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Translated by the author (J.F.).