ELECTROPHILIC ADDITION TO THE 5,6-DOUBLE BOND IN A-NOR-3,5-SECOSTEROIDS*

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The stereochemistry of epoxidation, Simmons–Smith methylenation and addition of bromine and hypobromous acid to 5,6-unsaturated A-nor-3,5-secosteroids was studied. The additions proceed from both sides of the molecule and, the β-oriented positively charged intermediate is regularly cleaved under participation by the substituent at $C_{(3)}$ to the corresponding oxa derivative *II* or to the lactones *VI* and *XI*. Cleavage of the cyclopropano derivative *XVI* with thallium(III) acetate was accompanied by Westphalen rearrangement and lead to the 5-membered lactone *XXI*. The structures of the products were established by spectral and chemical means and the mechanisms of reactions observed are discussed.

In the course of our studies[1] on reactivity of the 5,6-double bond in A-nor-3,5-secosteroids we became interested in some types of addition reactions. In this paper we describe our results obtained on studying additions of bromine and hypobromous acid as well as epoxidation and Simmons–Smith methylenation of these unsaturated derivatives.

Epoxidation of the olefin[2] *I* afforded the α-epoxide *IV* as the main product together with about 30% of 4-oxa-5β-cholestan-6β-ol (*II*) which represents the product of cleavage of the β-oriented oxonium intermediate with participation by the oxygen of the 3-hydroxyl group. The structure of this oxa derivative follows from the ^{1}H NMR spectrum as well as from the spectrum of the corresponding acetate *III*; whereas in the olefin *I* the protons at $C_{(3)}$ appear as a triplet at 3·58 ppm, in the oxa derivative *II* these protons are represented by two multiplets at 3·40 ppm and 3·92 ppm. The resonance of the 6α-proton forms a multiplet located also at 3·92 ppm but in the acetate *III* this multiplet is shifted upfield to 4·85 ppm and shows $W_{1/2}$ of 7 Hz. The 5β-proton in the acetate *III* appears as a doublet at 3·16 ppm with J = = 3 Hz. The protons at $C_{(5)}$ and at $C_{(6)}$ are therefore equatorial and the acetoxy group has 6β configuration and axial conformation in agreement with the proposed structure *III*.

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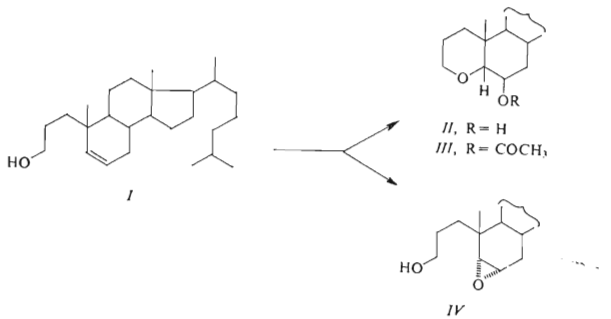
Epoxidation of the ester[2] *V* gave somewhat different results. Next to the α-epoxide *XII* which formed here the minor product of the reaction, also the β-epoxide *X* was isolated. However, the main product of the epoxidation was the lactone *VI*. Like the oxa derivative *II*, this lactone originated from cleavage of the β-oriented oxonium intermediate under participation – in this case – by the carboxy ester group. The lactone *VI* is also the only product of the fission of the β-epoxide *X* which proceeds smoothly for example on contact with adsorbent. The ^{1}H NMR spectrum of this lactone showed a broad singlet ($W_{1/2}$ = 3 Hz) at 4·08 ppm which was attributed to the 5β- and 6α-protons. After acetylation to the acetate *VII* the resonances separated to a doublet at 4·14 ppm with J = 2·8 Hz (equatorial 5β-H) and to a multiplet at 5·05 ppm ($W_{1/2}$ = 7·8 Hz, 6α-H, equatorial).

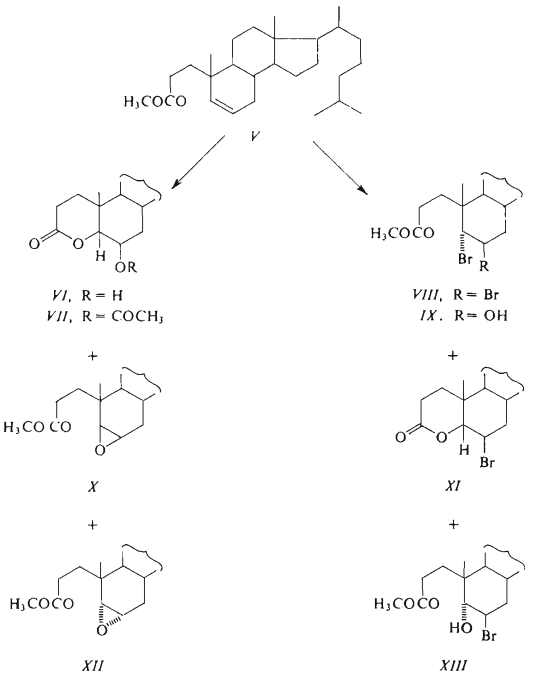


I *IV*

The results of epoxidation are in close analogy to the addition of bromine and hypobromous acid to the 5,6-double bond in these secosteroids. Addition of bromine yielded the diaxial dibromo derivative *VIII* as the main product and the bromolactone *XI* in about 35% yield. Here again the β-oriented ionic intermediate underwent diaxial opening under participation by the ester group, giving rise to the lactone *XI*. In this bromolactone the protons at $C_{(5)}$ and $C_{(6)}$ appear, like in the lactone *VI*, as a broad singlet as observed by Boris and Uskoković[3] in similar compounds in the androstane series. In analogy to these results hypobromous acid addition afforded the bromohydrin *IX* as the main product next to the bromolactone *XI* and the bromohydrin *XIII*. This bromohydrin is unstable and transforms easily to the bromolactone *XI* when treated with silica gel. The electrophilic additions to these 5,6-unsaturated secosteroids proceed from both sides of the molecule in contrast to the normal steroid series where the rear attack always predominates. Models suggest that this is a result of both the steric hindrance of the α-side of the molecule by the

10α-oriented side chain as well as absence of the 4β-hydrogen. This axial hydrogen together with the 10β-methyl group is mainly responsible for the preferred α-attack of the 5,6-double bond in steroids.

Our next interest was Simmons–Smith methylenation of these unsaturated seco-steroids. The course of this reaction as well as its stereochemistry is strongly influenced by presence or absence of an allylic hydroxyl group. If such a group is present the reaction proceeds stereospecifically in high yields, and under mild conditions, usually at room temperature[1,4–6]. However, if the hydroxyl group is protected or not close enough to the double bond the reaction requires drastic conditions, gives rise to both isomers and the yields are much lower. Some examples of this effect are presented in Table I which shows that also the 19-hydroxyl group is sterically well oriented to participate in the methylenation of the 5,6-double bond[7]. Our first concern was



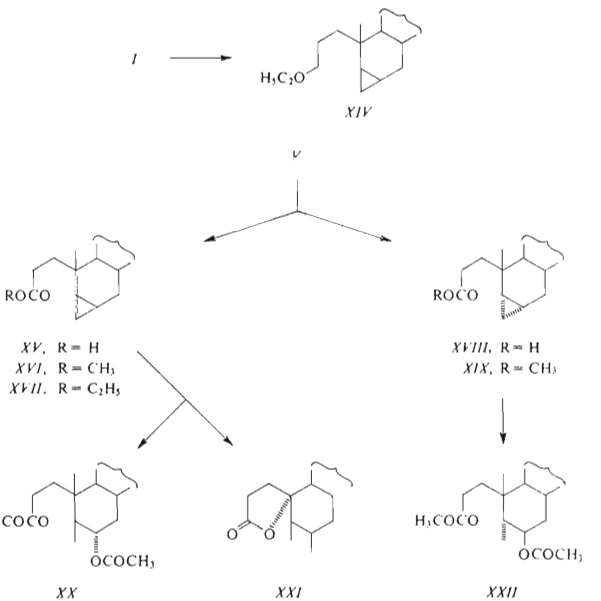
therefore methylenation of the unsaturated alcohol *I*. Under mild conditions the starting material was recovered unchanged. At higher temperatures etherification of the hydroxyl group took place and the only adduct isolated in a very low yield was the cyclopropano derivative *XIV*. The configuration of the cyclopropane ring follows from the ^{1}H NMR spectrum in which the signal of the 19-protons appears at 0·83 ppm. This chemical shift of the 19-protons is characteristic of the β-cyclopropano derivatives in these secosteroids[1] (Table II). Methylenation of the unsaturated ester *V* afforded the cyclopropano derivatives *XVI* (7%) and *XIX* (2%) together with the ethyl ester *XVII*. The 19-protons in the derivative *XVI* resonate at 0·85 ppm (β-configuration of the cyclopropane ring) whereas in the isomeric compound *XIX* the signal of the 19-protons appears at 1·04 ppm. This proves clearly the configurations of the cyclopropane rings in the adducts *XVI* and *XIX*.

In agreement with the structures assigned on the basis of spectral evidence are the results of fission of our cyclopropane derivatives with thallium(III) acetate in acetic acid. The 5α,6α-derivative *XIX* afforded a product of diaxial opening of the cyclopropane ring – the acetate *XXII* – the structure of which follows from spectral data: the ^{1}H NMR spectrum shows presence of a secondary methyl group and a secondary acetoxy group. The signal of the proton at $C_{(6)}$ appears at 4·827 ppm as a doublet of doublets of doublets with identical coupling constants of 2·8 ± 0·2 Hz.

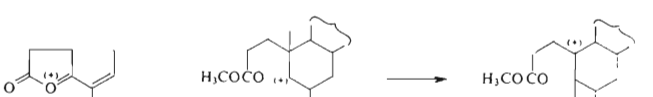
TABLE I

Simmons–Smith methylenation of 5,6-unsaturated steroids

Starting material	α-Adduct %	β-Adduct %	Conversion %
5-Cholesten-7β-ol (ref.[6])	0	100	61
5-Cholesten-7α-ol (ref.[6])	100	0	41
3β-Acetoxycholest-5-en-7β-ol (ref.[10])	0	100	72
3β-Acetoxycholest-5-en-7α-ol (ref.[10])	100	0	53
Methyl 17β-benzoyloxy-7β-hydroxy-A-nor--3,5-secoandrost-5-en-3-oate (ref.[1])	0	100	56
Methyl 17β-benzoyloxy-7α-hydroxy-A-nor--3,5-secoandrost-5-en-3-oate (ref.[1])	100	0	76
3β-Acetoxycholest-5-en-19-ol (ref.[7])	2	98	65
3β-Acetoxycholest-5-ene (ref.[11])	42	58	33
Cholest-5-en-3β-ol (ref.[11])	54	46	12
3β-Acetoxyandrost-5-en-17-one (ref.[12])	27	73	11
3β-Acetoxy-17β-benzoyloxyandrost-5-ene (ref.[12])	19	81	20
3β-Acetoxypregn-5-en-20-one (ref.[13])	44	56	13
3β,19-Diacetoxycholest-5-ene (ref.[7])	0	0	0



This proves 6α-equatorial orientation of this proton and corroborates the structure *XXII*. Clevavage of the 5β,6β-cyclopropane derivative *XVI* gave two products. The minor product was again an acetate with a secondary methyl group and a secondary acetoxy group. In this case however, the proton adjacent to the acetoxy group is represented by a doublet of doublets of doublets with $J = 11{\cdot}1$ Hz, $J' = 11{\cdot}1$ Hz and $J'' = 4{\cdot}8$ Hz, This proton, like the acetoxy group are therefore at $C_{(6)}$, the proton is 6β-axial and the acetoxy group is 6α-equatorial. The second product contained neither the cyclopropane ring nor the methoxy or acetoxy group. The IR spectrum



showed presence of a five membered lactone ring and, in addition, the ^{1}H NMR spectrum detected two secondary methyl groups represented by two doublets with coupling constants of 7·6 Hz and 6·9 Hz. This proves the structure of this second product as the lactone *XXI*. Mass spectrum showed a base peak of *m/z* 139 corresponding to the fragment $[C_8H_{11}O_2]^+$ possessing the structure *XXIII*. Evidently, in the ionic intermediate *XXIV*, formed by axial opening of the 5β,6β-cyclopropane ring, the strong 1,3-diaxial interaction between the $C_{(6)}$ and $C_{(10)}$ methyl groups is relieved in a Westphalen type rearrangement. The newly formed carbocation *XXV* then undergoes stabilisation to the lactone *XXI* under participation of the ester group. Similar rearrangement was observed also by Lund and Edward[8] and Kočovský and Černý[9].

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H NMR spectra were recorded on the Tesla 60 MHz instrument in deuteriochloroform unless otherwise stated and corrected to tetramethylsilane. The chemical shift is given in ppm. The mass spectra were recorded on the mass spectrometer AEI MS 902. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC), and by infrared and ^{1}H NMR spectra. Plates with 200 × 200 × 0·7 mm silica gel layer were used for preparative TLC. Usual working up of a solution implies washing the solution with water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulphate, and evaporation of the solvent *in vacuo*. Ligroin refers to the fraction of b.p. 40—62°C.

TABLE II

19-Proton signals in ^{1}H NMR spectra of 5,6-cyclopropano derivatives (ppm)

Compound	19-H	*Δ*
Derivatives of methyl A-nor-3,5-secoandrostan-3-oate		
7α-Hydroxy (ref.[1])	0·86	
5α,6α-Cyclopropano-7α-hydroxy (ref.[1])	1·06	0·20
7β-Hydroxy (ref.[1])	0·89	
5β,6β-Cyclopropano-7β-hydroxy (ref.[1])	0·91	0·02
Derivatives of methyl A-nor-3,5-secocholestan-3-oate		
Unsubstituted (ref.[14])	0·85	
5α,6α-Cyclopropano (*XVIII*)	1·04	0·19
5β,6β-Cyclopropano (*XV*)	0·85	0·00

4-Oxa-5β-cholestan-6β-ol (*II*)

A solution of the olefin *I* (280 mg) in ether (15 ml) was treated with a solution of perphthalic acid (460 mg) in ether (8 ml) and allowed to stand at room temperature for 20 h. The excess peracid was removed by extraction with 5% sodium carbonate and the ethereal solution was dried and ether removed. The residue was purified by preparative TLC on 8 plates of silica gel in ligroin–ether (1 : 1). The zones with the lipophilic compound were worked up to yield 78 mg of the oily oxa derivative *II*, $[\alpha]_D^{20}$ +26° (*c* 1·23). IR spectrum: 3 635, 1 055, 1 033, 1 003, 987 (hydroxyl), 1 101 cm^{-1} (C—O—C). ^1H NMR spectrum: 0·68 (s, 18-H), 0·91 (d, J = 5 Hz, 21-H), 0·85 (d, J = 5·7 Hz, 26-H and 27-H), 0·99 (s, 19-H), 3·10 (d, J = 2·7 Hz, 5β-H), 3·26 to 3·65 (m, 1-H and 3-H), 3·70—3·14 (m, 1-H and 3-H). For $C_{26}H_{46}O_2$ (390·6) calculated: 79·94% C, 11·87% H; found: 78·21% C, 11·16% H.

4-Oxa-5β-cholestan-6β-ol 6-Acetate (*III*)

The alcohol *II* (55 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0·6 ml) at room temperature for 18 h. The mixture was decomposed with ice and water, the product was taken into ether, and the ethereal solution was washed with 5% hydrochloric acid. Usual working up and evaporation of the solvent afforded a product which was crystallised from methanol to yield 24 mg of the acetate *III*, m.p. 117—120°C, $[\alpha]_D^{20}$ +2° (*c* 0·93). IR spectrum: 1 741, 1 241, 1 035 (acetate), 1 100 cm^{-1} (C—O—C). ^1H NMR spectrum: 0·67 (s, 18-H), 0·84 (d, J = 5·5 Hz, 26-H and 27-H), 0·88 (s, 19-H), 0·89 (d, J = 5 Hz, 21-H), 2·05 (s, $OCOCH_3$), 3·16 (d, J = 3 Hz, 5β-H), 3·27 (m, 1-H and 3-H), 3·80—4·18 (m, 1-H and 3-H), 4·85 (m, $W_{1/2}$ = 7 Hz, 6α-H). For $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·41% C, 11·12% H.

5α,6α-Oxido-A-nor-3,5-secocholestan-3-ol (*IV*)

The zone with the polar component after isolation of the oxa derivative *II* by preparative TLC were worked up and extracted with ether. Evaporation of the solvent yielded 113 mg of the oily epoxide *IV*, $[\alpha]_D^{20}$ +3° (*c* 1·36). IR spectrum: 3 630, 3 420, 1 060 (hydroxyl), 1 024, 1 016, 935 cm^{-1} (epoxide). ^1H NMR spectrum: 0·62 (s, 18-H), 0·96 (s, 19-H), 0·86 (d, J = 5·7 Hz, 26-H and 27-H), 2·82 (d, J = 4·5 Hz, 5β-H), 3·10 (dd, J = 4·5 Hz, J' = 4·5 Hz, 6β-H), 3·65 (t, J = 5·8 Hz, 3-H). For $C_{26}H_{46}O_2$ (390·6) calculated: 79·94% C, 11·87% H; found: 79·71% C, 11·51% H.

Methyl A-Nor-3,5-seccocholest-5-en-3-oate (*V*)

To recover the ester *V* from the lactone *XI* and the bromohydrins *IX* and *XIII* or their mixtures following procedure applied: 1 g of the material in acetic acid (25 ml) was heated for 20 min to 80°C under stirring with zinc dust (5 g). The metal was filtered off and the filtrate was diluted with water. The product was extracted into ether and the ethereal solution was worked up as usual. Evaporation of the solvent left 850 mg of bromine free product which was dissolved in methanol (85 ml), treated with conc. hydrochloric acid (4 ml) and set aside for 18 h. Methanol was removed under reduced pressure, the residue was treated with water, and the product was isolated with ether in the usual way. The residue after evaporation of ether was purified by column chromatography over silica gel (50 g) in ligroin–ether (19 : 1) to yield 700 mg of the olefin *V*.

5α,6β-Dihydroxy-A-nor-3,5-secocholestan-3-oic Acid Lactone (*VI*)

a) *From the olefin* V: Elution of the chromatography after isolation of the epoxide *X* gave fractions with the polar compound. Working up and crystallization from methanol yielded 295 mg

of the lactone *VI*, m.p. 154–157°C, $[\alpha]_D^{20}$ −8° (*c* 1·32). IR spectrum (chloroform): 3 615 (hydroxyl), 1 728, 1 260, 1 050, 1 027, 1 014 cm^{-1} (—O—). ^1H NMR spectrum: 0·69 (s, 18-H), 0·85 (*d*, *J* = 6 Hz, 26-H and 27-H), 1·16 (s, 19-H), 2·45 (dd, J = 6 Hz, *J'* = 7 Hz, 2-H), 4·08 (s, $W_{1/2}$ = = 3 Hz, 5β-H and 6α-H). For $C_{26}H_{44}O_3$ (404·6) calculated: 77·18% C, 10·96% H; found: 76·72% C, 10·54% H.

b) *From epoxide* X: The epoxide *X* (20 mg) was applied in chloroform solution on a plate of silica gel and after 2 h the plate was developed by benzene–ether (9 : 1). Detection (morin, UV light) showed presence of a compound corresponding in polarity to the lactone *VI* and absence of the starting epoxide. Working up of the zone gave 18 mg of the lactone *VI*.

6β-Acetoxy-5α-hydroxy-A-nor-3,5-secocholestan-3-oic Acid Lactone (*VII*)

The lactone *VI* (40 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (0·5 ml) for 18 h at room temperature. Usual working up and crystallisation from methanol yielded 38 mg of the acetate *VII*, m.p. 135–136°C, $[\alpha]_D^{20}$ −9° (*c* 0·9). CD in methanol $\Delta\varepsilon_{208}$ −0·96. IR spectrum: 1 749, 1 248, 1 041 (C=O lactone), 1 201 cm^{-1} (—O—). ^1H NMR spectrum: 0·70 (s, 18-H), 0·85 (d, *J* = 6 Hz, 26-H and 27-H), 1·07 (s, 19-H), 2·05 (s, acetate), 2·46 (dd, *J* = 6 Hz, *J'* = 8 Hz, 2-H), 4·14 (d, *J* = 2·8 Hz, 5β-H), 5·05 (m, $W_{1/2}$ = 7·8 Hz, 6α-H). For $C_{28}H_{46}O_4$ (446·6) calculated: 75·29% C, 10·38% H; found: 75·08% C, 10·42% H.

Methyl 5α,6β-Dibromo-A-nor-3,5-secocholestan-3-oate (*VIII*)

A solution of the ester *V* (150 mg) in carbon tetrachloride (1 ml) was treated with a solution of bromine (60 mg) in the same solvent (0·2 ml). After 5 min at room temperature the mixture was diluted with chloroform, washed with 2% sodium thiosulphate, and worked up in the usual ways. The residue after evaporation of the solvents contained two products. Separation by preparative TLC on four plates of silica gel in benzene gave after working up of the corresponding zones the lipophilic component which was crystallised from methanol to afford 132 mg of the dibromo derivative *VIII*, m.p. 95–97°C, $[\alpha]_D^{20}$ +7° (*c* 1·0). IR spectrum: 1 740, 1 435, 1 170 $\tilde{c}m^{-1}$ (—$COOCH_3$), ^1H NMR spectrum: 0·71 (s, 18-H), 0·86 (d, *J* = 6 Hz, 26-H and 27-H), 1·40 (s, 19-H), 3·64 (s, methoxyl), 4·43 (d, *J* = 2 Hz, 5β-H), 4·92 (dd, *J* = 2 Hz, *J'* = 4 Hz, 6α-H). For $C_{27}H_{46}Br_2O_2$ (562·5) calculated: 57·65% C, 8·24% H, 28·43% Br; found: 58·07% C, 8·45% H, 28·11% Br.

Methyl 5α-Bromo-6β-hydroxy-A-nor-3,5-secocholestan-3-oate (*IX*)

The zones with the polar component after isolation of the lactone *XI* under *b*) were worked up and the product was crystallised from methanol to afford 88 mg of the bromohydrin *IX*, m.p. 115 to 117°C, $[\alpha]_D^{20}$ +12° (*c* 1·3). IR spectrum: 3 620 (hydroxyl), 1 740, 1 725 (sh), 1 436, 1 194, 1 169 cm^{-1} (—$COOCH_3$). ^1H NMR spectrum: 0·67 (s, 18-H), 0·85 (d, *J* = 6 Hz, 26-H and 27-H), 1·21 (s, 19-H), 3·65 (s, methoxyl), 3·98 (d, *J''* = 2 Hz, 5β-H), 4·34 (dd, *J* = 2 Hz, *J'* = 4Hz, 6α-H). For $C_{27}H_{47}BrO_3$ (499·6) calculated: 64·90% C, 9·48% H; found: 64·51% C, 9·61% H.

Methyl 5β,6β-Oxido-A-nor-3,5-secocholestan-3-oate (*X*)

Elution of the chromatography after isolation of the α-epoxide *XII* with the same solvent mixture yielded fractions with the polar compound. Working up gave 190 mg of the epoxide *X* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ −7·5° (*c* 1·3). IR spectrum: 1 745, 1 437, 1 201, 1 170 cm^{-1} (—$COOCH_3$). ^1H NMR spectrum: 0·62 (s, 18-H), 0·86 (d, *J* = 5·6 Hz, 26-H and

27-H), 0·89 (d, J = 5 Hz, 21-H), 0·97 (s, 19-H), 2·16–2·53 (m, 2-H), 2·81 (d, J = 4 Hz, 5α-H), 3·19 (m, $W_{1/2}$ = 8 Hz, 6α-H), 3·65 (s, —$COOCH_3$). For $C_{27}H_{46}O_3$ (418·6) calculated: 77·46% C, 11·08% H; found: 78·01% C, 10·90% H.

6β-Bromo-5α-hydroxy-A-nor-3,5-secocholestan-3-oic Acid Lactone (*XI*)

a) *From the olefin* VI *with bromine*: The zones with the polar compound after preparative TLC of the dibromo derivative *VIII* were worked up the product was crystallized from methanol to give 53 mg of the lactone *XI*, m.p. 112–114°C $[\alpha]_D^{20}$ + 1° (*c* 1·3). IR spectrum (chloroform): 1 755, 1 196, 1 018 cm^{-1}. ^1H NMR spectrum: 0·72 (s, 18-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 1·35 (s, 19-H), 2·43 (m, 2-H), 4·40 (broad s, 5β-H and 6α-H). For $C_{26}H_{43}BrO_2$ (467·5) (calculated: 66·79% C, 9·27% H; found: 66·15% C, 9·09% H.

b) *From the olefin* VI *with hypobromous acid*: The olefin *VI* (155 mg) in dioxane (4·5 ml) was treated with 5% perchloric acid (0·7 ml) and N-bromoacetamide (140 mg). After stirring for 1 h at room temperature the mixture was diluted with water and the product was taken into ether. The ethereal solution was washed with 5% sodium thiosulphate and worked up as usual. The product after evaporation of ether was chromatographed on four plates of silicagel in ligroin–ether (9 : 1). The zones with the lipophilic component were worked up and the residue was crystallised from methanol to yield 63 mg of the lactone *XI*, m.p. 112–114°C, identical with the product obtained as under *a*).

Methyl 5α,6α-Oxido-A-nor-3,5-secocholestan-3-oate (*XII*)

The olefin *V* (750 mg) in ether (50 ml) was treated with a solution of perphthalic acid (1·5 g) in ether (22 ml) and allowed to stand at room temperature for 20 h. The excess peracid was removed by extraction with 5% sodium carbonate and the ethereal solution was worked up in the usual way. The residue consisted according to the TLC of four components. It was chromatographed on a silica gel column (300 g) in ligroin–ether (7 : 1). Fractions with the most lipophilic component were combined and the solvent removed to afford 165 mg of the epoxide *XII* resisting all attempts at crystallisation, $[\alpha]_D^{20}$ −2° (*c* 1·1). IR spectrum: 1 743, 1 436, 1 199, 1 172 (—COO.CH_3), 959 cm^{-1} (epoxide). ^1H NMR spectrum: 0·62 (s, 18-H), 0·86 (d, J = 5·5 Hz, 26-H and 27-H), 0·97 (s, 19-H), 2·28–2·62 (m, 2-H), 2·75 (d, J = 4·5 Hz, 5β-H), 3·06 (dd, J = 4·5 Hz, J' = 4·5 Hz, 6β-H), 3·67 (s, methoxyl). For $C_{27}H_{46}O_3$ (418·6) calculated: 77·46% C, 11·08% H; found: 78·03% C, 10·84% H.

Methyl 6β-Bromo-5α-hydroxy-A-nor-3,5-secocholestan-3-oate (*XIII*)

The zones with the polar product after preparative TLC of the lactone *XI* under *b*) were worked up to yield after evaporation of the solvent 32 mg of the oily bromohydrin *XIII*, $[\alpha]_D^{20}$ 0° (*c* 1·1). IR spectrum: 3 620 (hydroxyl), 1 740, 1 435, 1 195, 1 170 cm^{-1} (—$COOCH_3$). ^1H NMR spectrum: 0·68 (s, 18-H), 0·87 (d, J = 6 Hz, 26-H and 27-H), 1·23 (s, 19-H), 3·67 (s, methoxyl), 3·98 and 4·36 (two m, $W_{1/2}$ = 8 Hz and 7·5 Hz, 5β-H and 6α-H).

5β,6β-Cyclopropano-3-ethoxy-A-nor-3,5-secocholestane (*XIV*)

0·7% Zn–Cu couple was prepared by adding zinc dust (4 g) into a solution of cupric acetate monohydrate (120 mg) in acetic acid (5 ml) at 50–60°C and shaking until the solution decolorised. Fresh acetic acid was added (5 ml) and the sedimented zinc was decanted with eight portions (5 ml each) of ether. The olefin *I* (1 g) in ether (25 ml) and diiodomethane (4·6 ml) was then

added to the couple in an 100 ml autoclave and heated in boiling water for 7 h. After cooling off to room temperature the mixture was diluted with ether, the metal was filtered off and washed well with ether. The ethereal solution was washed with 5% sodium hydrogen carbonate, water, 5% hydrochloric acid, 5% sodium hydrogen carbonate, 5% sodium thiosulphate, water, dried, and the solvents were distilled off under reduced pressure. The residue was chromatographed on a silica gel column (50 g) in ligroin–ether (19 : 1). Fractions with the lipophilic component were combined, solvents removed, and the mixture of the adducts with unreacted material was dissolved in ether (20 ml). A solution of perphthalic acid (200 mg) in ether (3 ml) was added, and allowed to stand at room temperature for 18 h. The excess peracid was removed by extraction with 5% sodium carbonate and the ethereal solution was worked up. The residue after evaporation of the solvent was purified by preparative TLC on four plates of silica gel in ligroin–ether (19 : 1). The zones with the lipophilic component were worked up, extracted with ether, and solvent was distilled off to yield 14 mg of the cyclopropano derivative *XIV* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ +2·7° (*c* 1·46). IR spectrum: 3 075 (cyclopropane), 1 115, 1 076, 1 040 cm^{-1} (ether). ^1H NMR spectrum: −0·09 to +0·45 (m, cyclopropane protons), 0·59 (s, 18-H), 0·83 (s, 19-H), 0·86 (d, J = 5·5 Hz, 26-H and 27-H), 1·21 (t, J = 7 Hz, CH_3—CH_2), 3·76 (q, J = 7 Hz, CH_3—CH_2). For $C_{29}H_{52}O$ (416·7) calculated: 83·58% C, 12·58% H; found: 82·91% C, 12·30% H.

5β,6β-Cyclopropano-A-nor-3,5-secocholestan-3-oic Acid (*XV*)

Elution of the chromatography after isolation of the lactone *XXI* with ligroin–ether (1 : 1) gave 390 mg of the acid *XV*. Crystallisation from acetone afforded analytical sample, m.p. 95—98°C $[\alpha]_D^{20}$ 0° (*c* 0·8). IR spectrum: 3 400—2 400, 1 714 (carboxyl), 3 075 cm^{-1} (cyclopropane, ^1H NMR spectrum: 0·00—0·50 (cyclopropane protons), 0·62 (s, 18-H), 0·87 (s, 19-H), 0·87 (d, J = 5·2 Hz, 26-H and 27-H), 2·06—2·65 (m, 2-H). For $C_{27}H_{46}O_2$ (calculated: 80·54% C, 11·52% H; found: 80·36% C, 11·14% H.

Methyl 5β,6β-Cyclopropano-A-nor-3,5-secocholestan-3-oate (*XVI*)

a) *From the olefin* V: the Zn–Cu couple was prepared from zinc dust (3 g) as described for the preparation of the cyclopropano derivative *XIV*. The olefin *V* (750 mg) in ether (25 ml) and diiodomethane (4·6 ml) was heated with the couple in the autoclave for 11 h to 100°C. The mixture was worked up as described above and the residue was chromatographed over silica gel (200 g) in ligroin–ether (33 : 1). Fractions with the component corresponding in polarity to the starting material were combined, solvents removed, and the residue (650 mg) was dissolved in dioxane (19 ml). The solution was treated with 5% perchloric acid (2·8 ml) and N-bromoacetamide (560 mg) and stirred for 1 h at room temperature. The mixture was diluted with water and the product was taken into ether. The ethereal solution was washed with 5% sodium thiosulphate and worked up in the usual way. The oily residue (700 mg) after evaporation of the solvent was chromatographed on a silica gel column (200 g) in ligroin–ether (33 : 1). The fractions with the polar components afforded after working up a mixture of the bromohydrins *IX* and *XIII* and lactone *XI* which was transformed to the olefin *V* as described above. The lipophilic fractions containing the adducts *XVI*, *XVII*, and *XIX* were combined to yield after evaporation of the solvents 84 mg of a residue which was dissolved in chloroform (1·5 ml). The solution was treated with hydrochloric acid (0·5 ml) in methanol (5 ml) and allowed to stand at room temperature for 48 h. The products were isolated with ether and worked up as usual to afford a mixture of methyl esters *XVI* and *XIX*. The mixture was separated on four plates of silica gel in pentane–ether (24 : 1). The zones with the lipophilic adduct gave after working up 59 mg of the β-cyclopropano derivative *XVI* (oil), $[\alpha]_D^{20}$ −16° (*c* 0·74). IR spectrum: 3 070 (cyclopropane), 1 745,

1 438, 1 196, 1 173 cm^{-1} (methyl ester). ^1H NMR spectrum: 0·05–0·50 (m, cyclopropane protons), 0·60 (s, 18-H), 0·85 (s, 19-H), 0·86 (d, J = 6 Hz, 26-H and 27-H), 3·67 (s, methoxyl). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·49% C, 11·41% H.

b) *From the acid* XV: The acid *XV* (18 mg) in ether (5 ml) was treated with a solution of diazomethane in ether. After 10 min at room temperature the excess diazomethane was removed with acetic acid, the mixture was diluted with ether and worked up in the usual way to yield 18 mg of the methyl ester *XVI*, $[\alpha]_D^{20}$ −15° (*c* 1·14).

Ethyl 5β,6β-Cyclopropano-A-nor-3,5-secocholestan-3-oate (*XVII*)

The olefin *V* (750 mg) was submitted to the Simmons–Smith methylenation as described in the foregoing experiment under *a*). Similar working up afforded the mixture of adducts *XVI*, *XVII*, and *XIX* which was not treated with methanolic hydrochloric acid and was separated on 8 plates of silica gel in pentane–ether (24 : 1). The corresponding zones were combined, extracted with ether, and solvent was removed to afford 18 mg of the ethyl ester *XVII* which resisted all attempts at crystallisation; $[\alpha]_D^{20}$ −14° (*c* 1·12). IR spectrum: 3 075 (cyclopropane), 1 738, 1 184 cm^{-1} (ethyl ester). ^1H NMR spectrum: 0·05–0·50 (m, cyclopropane protons), 0·60 (s, 18-H), 0·85 (s, 19-H), 0·86 (d, J = 5·7 Hz, 26-H and 27-H), 2·04–2·58 (m, 2-H), 1·25 (t, J = 7 Hz, O—CH_2——CH_3), 4·11 (q, J = 7 Hz, O—CH_2—CH_3). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·92% C, 11·32% H.

5α,6α-Cyclopropano-A-nor-3,5-secocholestan-3-oic Acid (*XVIII*)

Elution of the chromatography after isolation of the acetate *XXII* with ligroin–ether (1 : 1) yielded 71 mg of the acid *XVIII*. Crystallisation from acetone afforded 31 mg of the analytical sample, m.p. 142–144°C, $[\alpha]_D^{20}$ +13° (*c* 0·75). IR spectrum: 3 065 (cyclopropane), 3 400–2 400, 1 730, 1 711 cm^{-1} (carboxyl). ^1H NMR spectrum: −0·16 to +0·06 and 0·38–0·53 (two m, cyclopropane protons), 0·62 (s, 18-H), 0·87 (d, J = 5 Hz, 26-H and 27-H), 0·89 (d, J = 5 Hz, 21-H), 1·06 (s, 19-H), 2·29–2·68 (m, 2-H). For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H, found: 80·72% C, 11·15% H.

Methyl 5α,6α-Cyclopropano-A-nor-3,5-secocholestan-3-oate (*XIX*)

a) *From the olefin* V: Working up of the zones with the polar component obtained on preparation of the β-cyclopropano derivative *XVI* and crystallisation of the product from chloroform–methanol yielded 17 mg of the α-cyclopropano derivative *XIX*, m.p. 89–91°C, $[\alpha]_D^{20}$ +10 (*c* 1·20). IR spectrum: 3 065 (cyclopropane), 1 744, 1 437, 1 198, 1 170 cm^{-1} (methyl ester). ^1H NMR spectrum: −0·16–0·00 and 0·39–0·60 (two m, cyclopropane protons), 0·61 (s, 18-H), 0·85 (d, J = 5·7 Hz, 26-H and 27-H), 1·04 (s, 19-H) 3·66 (s, methoxyl). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·62% C, 11·22% H.

b) *From the acid* XVIII: The acid *XVIII* (35 mg) in ether (5 ml) was treated with excess diazomethane in ether and allowed to stand for 10 min at room temperature. The excess diazomethane was decomposed with acetic acid, the reaction mixture was diluted with ether, and worked up in the usual way. Crystallisation from chloroform–methanol yielded 37 mg of the ester *XIX*, m. p. 88–90°C, $[\alpha]_D^{20}$ +9° (*c* 1·16).

Methyl 6α-Acetoxy-5β-methyl-A-nor-3,5-secocholestan-3-oate (*XX*)

A solution of the cyclopropano derivative *XVI* (2·4 g) in acetic acid (48 ml) was refluxed with thallium(III) acetate (4·8 g) for 146 h. After cooling off to room temperature the mixture was

diluted with water and the product was isolated with ether. Usual working up afforded a product which was chromatograohed over silica gel (480 g) in ligroin–ether (25 : 1) to afford fractions with the unchanged starting cyclopropano derivative *XVI* (1·6 g). Further elution with ligroin–ether (9 : 1) gave fractions with the polar product. Working up gave 20 mg of the oily ester *XX*, $[\alpha]_D^{20}$ +36° (*c* 0·76). IR spectrum: 1 740, 1 247, 1 025 (acetate), 1 745, 1 432, 1 190, 1 173 cm^{-1} (methyl ester). ^1H NMR spectrum (200 MHz Varian instrument): 0·639 (s, 18-H), 0·806 (s, 19-H), 0·824 (d, J = 7·3 Hz, 5-methyl), 0·859 and 0·863 (two d, J = 6·6 Hz, 26-H and 27-H), 0·892 (d, J = 6·6 Hz, 21-H), 2·037 (s, acetate), 3·667 (s, methyl ester), 4·723 (ddd, J = 11·1 Hz, J' = = 11·1 Hz, J'' = 4·8 Hz, 6β-H). For $C_{30}H_{52}O_4$ (476·7) calculated: 75·58% C, 11·00% H; found: 75·08% C, 10·72% H.

5β,6β-Dimethyl-10α-hydroxy-A,19-bisnor-3,5-secocholestan-3-oic Acid Lactone (*XXI*).

Elution of the chromatography after preparation of the acetate *XX* with ligroin–ether (9 : 1) yielded fractions with the polar component. Working up gave 32 mg of the oily lactone *XXI*, $[\alpha]_D^{20}$ 0° (*c* 1·11). IR spectrum: 1 776, 1 248, 1 234, 1 217, 1 181, 989 (five membered lactone). Mass spectrum: m/z 387 (M−CH_3), 331 (M−CH_3−C_3H_4O), 289 (M−C_8H_{17}), 247 (M− −$C_{11}H_{25}$, side chain and D-ring), base peak: 139 $[C_8H_{11}O_2]^+$. ^1H NMR spectrum (200 MHz Varian instrument, C_6D_6): 0·576 (s, 18-H), 0·606 and 0·786 (two d, J = 7·6 Hz and J = 6·9 Hz, 5-methyl and 6-methyl), 0·946 (d, J = 6·7 Hz, 26-H and 27-H), 0·969 (d, J = 6·5 Hz, 21-H), 2·14 (m, 2-H). For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·57% C, 11·70% H.

Methyl 6β-Acetoxy-5α-methyl-A-nor-3,5-secocholestan-3-oate (*XXII*)

The α-cyclopropano derivative *XXII* (400 mg) in acetic acid (8 ml) was refluxed with thallium(III) acetate (800 mg) for 140 h. After cooling of the reaction mixture was poured into water and the product was taken into ether. Usual working up afforded a mixture which was chromatographed over silica gel (160 g) in ligroin–ether (24 : 1). The fractions with the lipophilic component gave 230 mg of the starting cyclopropano derivative. Further elution with the same solvent mixture gave after working up of the corresponding fractions 26 mg of the oily acetate *XX*, $[\alpha]_D^{20}$ +16 (*c* 0·86). IR spectrum: 1 732, 1 438, 1 172 (methyl ester), 1 742, 1 250, 1 024 cm^{-1} (acetate). ^1H NMR spectrum (200 MHz Varian instrument): 0·691 (s, 18-H), 0·862 and 0·867 (two *d*, J = 6·6 Hz, 26-H and 27-H), 0·902 (d, J = 7·5 Hz, 5-methyl), 0·906 (d, J = 6·2 Hz, 21-H), 1·015 (s, 19-H), 2·037 (s, acetate), 3·660 (s, methyl ester), 4·827 (ddd, J = 2·8 ± 0·2 Hz, 6α-H). For $C_{30}H_{52}O_4$ (476·7) calculated: 75·58% C, 11·00% H; found: 75·10% C, 10·81% H.

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