NEIGHBORING GROUP PARTICIPATION AND REARRANGEMENT IN HYPOBROMOUS ACID ADDITION TO 10β-VINYL CHOLESTANE DERIVATIVES*

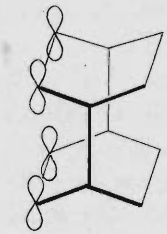
Pavel Kočovský[a] and František Tureček[b]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6 and*
[b] *The J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences 121 38 Prague 2*

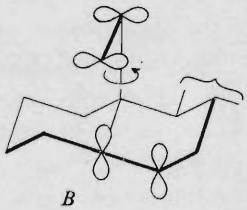
Received April 2nd, 1981

Hypobromous acid addition to the diene *VII* yields two epimeric dibromo 6β,19a-epoxides, *XVI* (main product) and *XVII*, *via* the intermediary bromohydrin *XIII*. Products due to C—C bond formation were not observed. This fact is attributed to the mutual perpendicular arrangement of π-orbitals of the two double bonds in the diene *VII*. Hypobromous acid action upon the 5α,6β--diol *IX* and the dimethoxy derivative *X* afforded analogous products of 6(O)^n participation by the 6β-substituent, *i.e.* the cyclic ethers *XXII*, *XXIII* and *XXIV*, *XXV*, Under the same conditions the 6β-acetoxy derivative *XI* gave a mixture of the cyclic ethers *XXII* and *XXIII* as products of 6(O)^n participation, and the rearranged ketone *XXVI*. Mechanism of this rearrangement is discussed.

Electrophilic addition to the double bond can be strongly influenced by intramolecular participation of other functionalities in the substrate molecule. For instance, the tricyclic diene *I* is known[1-9] to react with some electrophiles with double participation of π-electrons of the double bond and of the ester group to afford the cyclized products *II* and *III*. On acid treatment the related epoxide *IV* also yields a product of cyclization. The smooth cyclization was attributed to an appropriate arrangement of π-orbitals of both double bonds in *I* which enables the colinear overlap necessary for the concerted cyclization and formation of a new C—C bond (model *A*).

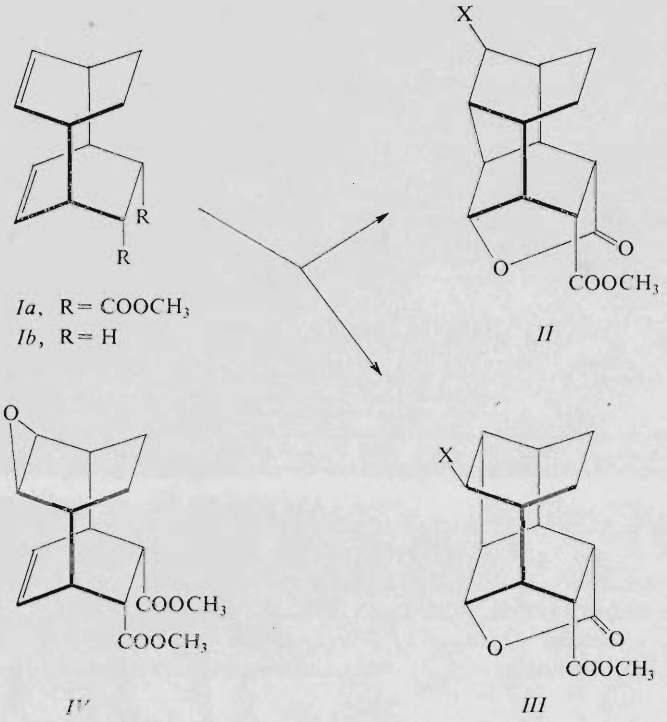


A



B

* Part CCLIII in the series On Steroids; Part CCLII: This Journal *46*, 2906 (1981).



Ia, R = $COOCH_3$
Ib, R = H

II

IV

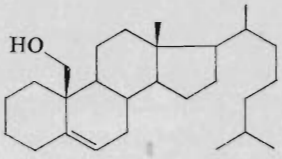
III

In order to check the conclusions inferred from the investigation of the rigid molecule of *I*, we prepared the model compound *B* in which the π-orbitals lay in two mutually perpendicular planes. If the theory of colinearity is correct (model *A*), *C*—*C* bond formation should be suppressed in concerted electrophilic addition.

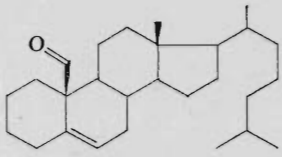
Syntheses of Model Compounds

5-Cholesten-19-ol[10,11] (*V*) was oxidized to the aldehyde *VI* which on Wittig reaction afforded the diene (*VII*, model *B* compound). This diene reacted selectively with 3-chloroperoxybenzoic acid to give the single 5α,6α-epoxide *VIII*. Neither the 5β,6β-epoxide nor the product of the reaction of the vinyl group were formed (in accordance with the behavior of the 3β-acetoxy analog[12]). In 5,6-unsaturated steroids with a methyl group at the 10β-position, the 5β,6β epoxide arises as minor product of epoxidation by means of various peroxy acids. The enhanced stereoselectivity of the epoxidation of the 10β-vinyl derivative *VII* is probably due to a larger steric hindrance of the 5,6-double bond by the vinyl group from the β-side. The nonreactivity of the vinyl group can be explained as follows: 10β-Vinyl group must be approached by the reagent from the direction parallel to the plane of the steroid skeleton (Fig. 1). This approach is hindered by axial hydrogen atoms in positions 2β, 4β, 8β and 11β.

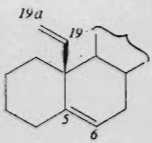
By contrast, the 5,6-double bond is approached perpendicularly to the plane of steroid skeleton and no similar hindrance is operative. This explanation is in line with our observation that the diene *VII* does not react with 9-borabicyclo[3.3.1]nonane[13] which is known to hydroborate vinyl groups selectively in the presence of other double bonds.



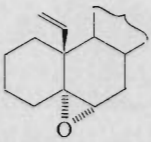
V



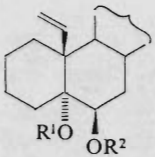
VI



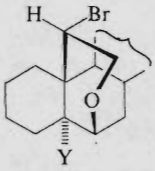
VII



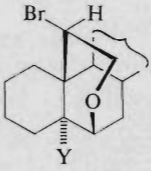
VIII



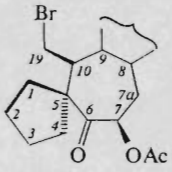
IX, $R^1 = H$, $R^2 = H$
X, $R^1 = CH_3$, $R^2 = CH_3$
XI, $R^1 = H$, $R^2 = Ac$



XVI, Y = Br
XXII, Y = OH
XXIV, Y = OCH_3



XVII, Y = Br
XXIII, Y = OH
XXV, Y = OCH_3



XXVI

The epoxide *VIII* was cleaved with aqueous perchloric acid in dioxane to give the diaxial diol *IX* which on methylation with methyl iodide and sodium hydride afforded the dimethoxy derivative *X*. On treatment with acetic anhydride in pyridine the diol *IX* furnished the monoacetate *XI*.

Reaction of the Model Compounds VII, IX – XI *with Hypobromous Acid*

When treated with hypobromous acid (generated *in situ* from N-bromoacetamide and perchloric acid in aqueous dioxane) the diene *VII* afforded a mixture of the

cyclic dibromo ethers *XVI* and *XVII* in a 83 : 17 ratio (determined by ^{1}H-NMR spectroscopy) which resisted all attempts at separation. Formation of products with a new C—C bond was not observed. The diol *IX* reacted with hypobromous acid similarly to yield a mixture of the cyclic ethers *XXII* and *XXIII* in *c.* 90 : 10 ratio (determined by ^{1}H-NMR spectra). Under the same conditions, the dimethoxy derivative *X* furnished a mixture of *XXIV* and *XXV* in a 78 : 22 ratio. The reaction of the acetate *XI* with hypobromous acid was found to be more complex. Again, the ethers *XXII* and *XXIII* were formed in a 95 : 5 ratio (44%). As a third product we isolated the rearranged spirocyclic ketone *XXVI* (47%). This compound is derived from cyclopentane-1'-spiro-5-(7a-homo-des-A-cholestane). It has to be noted that numbering of carbon atoms in this system is not genetically related to that in the starting 10β-vinyl derivative, *e.g.* $C_{(10)}$ in *XXVI* corresponds to $C_{(19)}$ in *XI*, $C_{(19)}$ in *XXVI* corresponds to $C_{(19a)}$ in *XI*, *etc.*

The structure of *XVI* and *XVII* was deduced from the mass and ^{1}H-NMR spectra. The mass spectrum of the mixture of *XVI* and *XVII* contains molecular ions *m/z* 556, 558, 560 of low relative intensity, thus confirming the presence of two bromine atoms and of an additional ring. The high mass region displays fragment ions due to subsequent losses of bromine (*m/z* 477, 479), hydrogen bromide (*m/z* 397) and of the $C_{(19)}$—$C_{(19a)}$—O bridge (*m/z* 355). The ^{1}H-NMR spectrum of the major component *XVI* shows three doublets of doublets in the low-field region: 19-H_1 (δ = 4·69), 19a—H_2 (δ = 3·92) and 19a—H_3 (δ = 3·69). The values of the vicinal coupling constants ($J_{1,2}$ = 9·1 Hz, $J_{1,3}$ = 3·7 Hz) confirm the antiperiplanar arrangement of the bromine and oxygen atoms in *XVI*. Similarly, the component *XVII* exhibits the 19-H_1 as a doublet of doublets (δ = 4·23 H'_1) coupled to the $C_{(19a)}$ methylene protons (δ = 3·74 H'_2 and δ = 3·56 H'_3, $J'_{1,2}$ = 9·5 Hz, $J'_{1,3}$ = 4·1 Hz). Again, this points to antiperiplanar position of the bromine and oxygen atoms. The values of the vicinal coupling constants in both *XVI* and *XVII* are consistent with two structures: In the first, the oxygen-containing six-membered ring assumes the chair conformation with equatorial (19*S*)-bromine. In the second, the heterocycle is in a boat conformation with equatorial (19*R*)-bromine. The structural as-

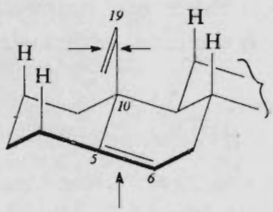


FIG. 1

Approach of the reagent to the 5,6-double bond and to 10β-vinyl in model compound *B*

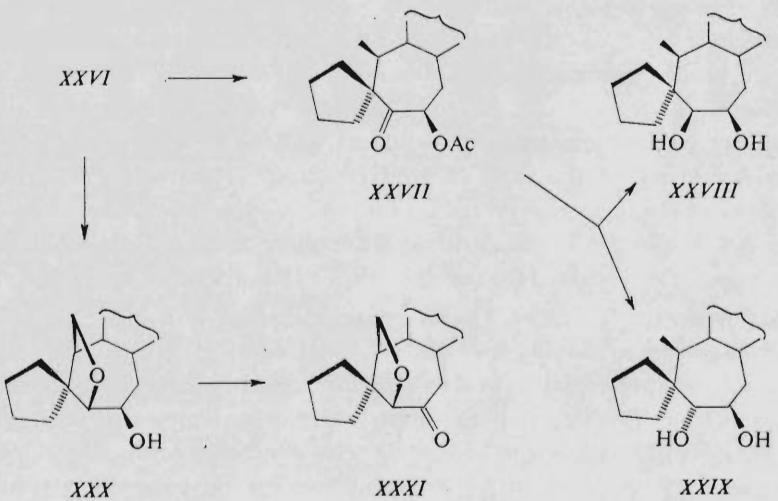
signment in *XXVI* was based on the coupling constants of the 6α-H (δ = 4·14 d). The latter proton appears as a doublet which suggests that the B-ring in *XVI* is somewhat flattened so that the torsional vicinal angle of the 6α-H and 7β-H approaches 90°. This flattening is probably due to the combined effects of steric compression of 19a-*endo* and 8β-hydrogens as well as to the presence of the axial 5α-bromine. In the second isomer *XVII*, the steric interactions 2β-H...Br and 4β-H...19a-*exo*-H cannot be released by flattening the B-ring and, in accordance, the 6α-H occurs as a multiplet.

The structure of *XXII* and *XXIII* follows again from the mass and ^{1}H-NMR spectra. The mass spectrum of the mixture of *XXII* and *XXIII* contains ions *m/z* 496, 494 ($C_{28}H_{47}BrO_2$, $M^{+\cdot}$), 415 $(M-Br)^+$, 397 $(M-Br-H_2O)^+$, 371 $(M-Br-C_2H_4O)^+$ and 217, 215 ($C_9H_{12}BrO$). The elemental composition of the molecular ion suggests that a new ring was closed. The presence of the abundant C_9H_{12}.BrO ion indicates $C_{(6)}-C_{(10)}$ bridging in analogy with mass spectra of oxygen-bridged steroids described earlier[15]. The ^{1}H-NMR spectrum of *XXII* shows a pattern very similar to that of *XVI*. The proton at $C_{(19)}$ (δ = 4·61, H_1) is coupled to two adjacent protons of the $C_{(19a)}$ methylene group (δ = 3·90, H_2 and δ = 3·68, H_3), the corresponding vicinal coupling constants being 9·5 Hz and 3·3 Hz for $J_{1,2}$ and $J_{1,3}$, respectively. The 6α-H forms a doublet (δ = 3·97, J = 3·8 Hz). In analogy with *XVI* we conclude that *XXII* contains the heterocycle in chair conformation with an equatorial (19*S*) bromine. The less abundant isomer *XXIII* corresponds to the (19*R*) epimer with the boat conformation of the oxygen-containing ring as documented by appropriate vicinal coupling constants of the 19- and 19a-protons. Unfortunately, the signal of the 6α-H of *XXIII* overlaps with that of *XXII* so that the multiplicity of the former could not be determined. The structure of the methoxy derivatives *XXIV* and *XXV* was deduced from their mass and ^{1}H-NMR spectra in the same manner as described for the alcohols *XXII* and *XXIII*.

The mass spectrum of *XXVI* exhibits molecular ions *m/z* 538, 536 ($C_{30}H_{49}$.BrO_3) and fragments arising by loss of C_3H_5 (*m/z* 497, 495), acetic acid (*m/z* 478, 476), bromine (*m/z* 457), *m/z* 428 $(M-Br-CHO)^{+\cdot}$ and *m/z* 397 $(M-Br-CH_3CO_2.H)^+$. The spectrum revealed that the acetoxy group was preserved in *XXVI* but still the addition of hypobromous acid must have proceeded with a ring or double bond formation. IR spectrum of *XXVI* shows two carbonyl stretching bands that correspond to a keto (ν(C=O) = 1 720 cm^{-1}) and an acetoxy (ν(C=O) = 1 746 cm^{-1}) group. In the low-field region of the ^{1}H-NMR spectrum of *XXVI* there are only three signals corresponding to the acetate methine (δ = 5·38 dd, J = 8·9 and 7·4 Hz) and to a bromomethyl group (δ = 3·87 dd, J = 9·8 and 2·0 Hz and δ = 3·61 dd, J = 9·8 and 9·8 Hz). The downfield shift of the acetate methine is due to the vicinity of the carbonyl group. From the above data it was clear that the A and B rings must have rearranged to create the carbonyl group. Since the former AB part of the skeleton of *XXVI* includes two ring-plus-double-bond equivalents (apart

from the ketone and acetate carbonyls), the AB unit is either bicyclic or monocyclic with a tetrasubstituted double bond. The latter possibility was excluded by the ^{13}C-NMR spectrum of *XXVI*. At 50·3 MHz, all twenty seven skeletal sp^3 carbons are resolved leaving no possibility for the presence of any double bond. Moreover, the compound *XXVI* reacted neither with 3-chloroperoxybenzoic acid nor with potassium permanganate solution.

In order to confirm the proposed structure of *XXVI* we carried out some chemical transformations. Reduction of *XXVI* with both zinc in acetic acid and tri-n-butyltin hydride led to clean dehalogenation affording the acetoxy ketone *XXVII*. The mass spectrum of *XXVII* shows the corresponding molecular ion *m/z* 458 ($C_{30}H_{50}O_3$, $M^{+\bullet}$) and fragments *m/z* 430 $(M-CO)^+$, 417 $(M-C_3H_5)^+$, 398 $(M-CH_3CO_2H)^{+\bullet}$, 370 $(M-CH_3CO_2H-CO)^{+\bullet}$, 330 $(M-CH_3CO_2H—C_5H_8)^{+\bullet}$ and 301 $(M-CH_3.CO_2H—CO—C_5H_9)^+$. In the ^{1}H-NMR spectrum of *XXVII* the protons of the bromomethyl group are absent and a new methyl doublet arises at $\delta = 1{\cdot}10$ ($J = 7{\cdot}1$ Hz). In agreement with this finding the $C_{(19)}$ as a new methyl is found in the ^{13}C-NMR spectrum of *XXVII* at $\delta = 17{\cdot}64$.



Further reduction of *XXVII* with lithium aluminum hydride afforded a nonseparable mixture of two diols *XXVIII* (75%) and *XXIX* (25%). The ^{1}H-NMR spectrum of *XXVIII* displays two mutually coupled — CH(OH)-methine protons at $\delta = 4{\cdot}05$ (ddd, $J = 7{\cdot}2$, 3·3 and 2·3 Hz) and $\delta = 3{\cdot}62$ (d, $J = 3{\cdot}3$ Hz). The doublet of doublets of doublets was assigned to the 7α-H while the doublet corresponds to the 6α-H. In *XXIX* the 6β-H also appears as a doublet at $\delta = 3{\cdot}18$ ($J = 9{\cdot}0$).

Direct reduction of *XXVI* with lithium aluminum hydride is accompanied by intramolecular displacement of the bromine atom so that a new oxygen-containing ring is formed (compound *XXX*). This was confirmed by the mass spectrum of *XXX*: *m/z* 416 ($C_{28}H_{48}O_2$, $M^{+\bullet}$), 398 $(M-H_2O)^{+\bullet}$, 356 $(M-H_2O-C_3H_6)^{+\bullet}$, 368 $(M-H_2O-CH_2O)^{+\bullet}$, 317 $(M-H_2O-C_6H_9)^+$, 274 $(M-H_2O-C_8H_{12}O)^{+\bullet}$ and 137 $(C_9H_{13}O)^+$. The ^{1}H-NMR spectrum agrees well with the proposed structure of *XXX* showing the 7α-H (δ = 4·03 ddd, J = 5·0, 3·1 and 3·0 Hz), 6α-H (δ = 3·76 d, J = = 5·0 Hz) and 19-methylene protons (δ = 4·17 dd, J = 8·1 and 7·7 Hz, and δ = = 3·67 dd, J = 7·7 and 1·0 Hz). The geminal coupling constant of the latter two protons confirms that the —CH_2—O— bridge is a part of a five-membered ring.

Oxidation of *XXX* with both Jones' reagent and – rather surprisingly – periodic acid afforded the ketone *XXXI*. The structure of *XXXI* is supported by the mass spectrum: *m/z* 414 ($C_{28}H_{46}O_2$, $M^{+\bullet}$), 386 $(M-CO)^{+\bullet}$, 355 $(M-CO-CH_2OH)^+$, 317 $(M-CO-C_5H_9)^+$ and 123 ($C_8H_{11}O$) and, namely, by the ^{1}H-NMR spectrum. The 6α-H appears as a singlet at δ = 3·79, the 7aα-H and 7aβ-H are also distinguished at δ = 2·66 (dd, 11·8 and 9·7 Hz) and δ = 2·14 (d, J = 11·8 Hz), respectively. The 19-protons occur at δ = 4·33 (dd, J = 8·5 and 6·2 Hz) and δ = 3·92 (d, J = = 8·5 Hz). By irradiating the 19-*exo*-proton (δ = 4·33), the 10-H can be identified at δ = 1·89 (d, J = 6·2 Hz). Since that latter proton occurs only as a doublet, the vicinal torsion angle 10α-H...9α-H must be close to 90° which is also clearly seen on the relaxed Dreiding model of *XXXI*.

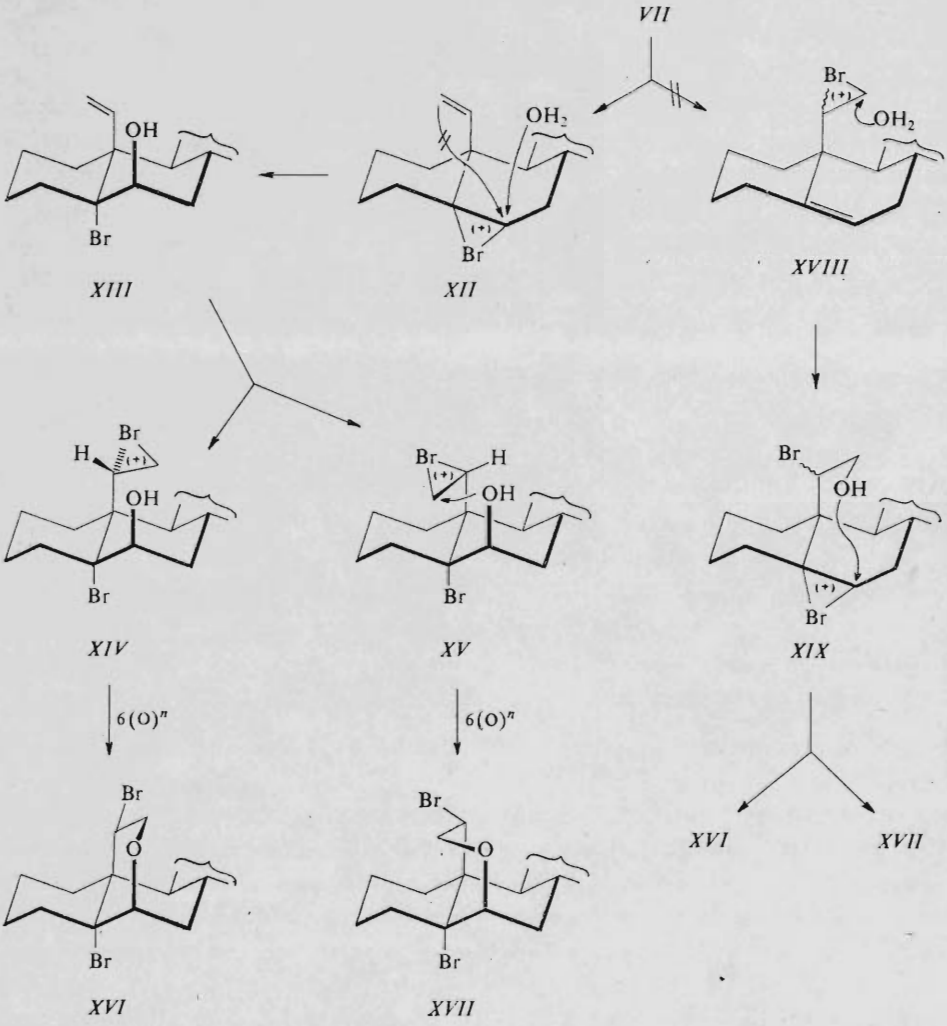
Summarizing, the spectral data of *XXVI*–*XXXI* strongly support the proposed structure *XXVI* and exclude all relevant alternatives.

Discussion of the Mechanism

The formation of the dibromo epoxides *XVI* and *XVII* from the diene *VII* may be *a priori* explained by two different mechanistic routes. In the first route, formation of the 5α,6α-bromonium ion *XII* is assumed. This ion is cleaved by water to give the intermediate diaxial bromohydrin *XIII*. No π-orbital participation of the vinyl group which would have led to the C—C bond formation was observed. On reaction with second equivalent of hypobromous acid two epimeric bromonium ions, *XIV* and *XV*, may be expected to rise. The cleavage of the former ion in an anti-Markovnikov manner with participation by the 6β-hydroxyl in a $6(O)^n$ process leads to the main product, the cyclic ether *XVI*. The epimeric ion *XV* gives the second cyclic ether *XVII*. The reactivity of the 10β-vinyl group is probably enhanced by participation of the neighboring 6β-hydroxyl group present in the intermediate bromohydrin *XIII*.

An alternative reaction path leading to the same products could be also assumed. This would comprise formation of the 19,19a-bromonium ion *XVIII* in the first step, followed by an anti-Markovnikov cleavage to produce the intermediate bromo-

hydrins *XIX*. On reaction with second equivalent of the reagent, *XIX* would give again the cyclic ethers *XVI* and *XVII*.

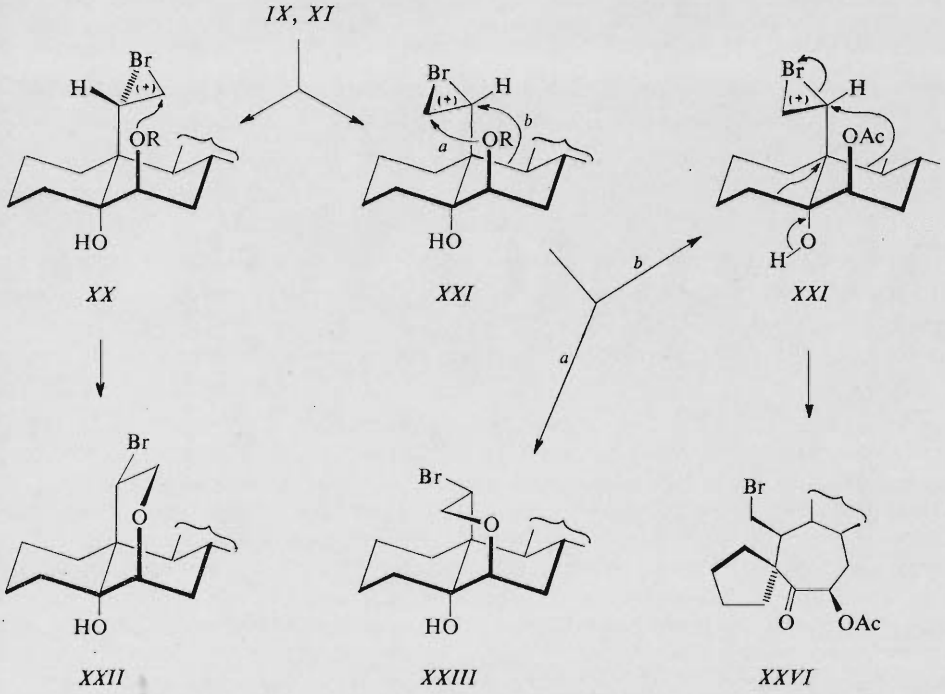


The second route can be excluded on the basis of the following considerations. As we have shown above, the 5,6-double bond is more reactive than the 10β-vinyl and there is no obvious reason for reversal of the reactivity order in hypobromous acid addition. Moreover, in closely related compounds[13], the opening of a 5α,6α--bromonium ion by the 19a-hydroxyl group takes place at $C_{(5)}$ in contrast to the

reaction course from *XIX* to *XVI* and *XVII*. All this makes the second alternative improbable and strongly favors the proposed reaction sequence.

The anti-Markovnikov cleavage of the bromonium ions *XIV* and *XV* by the neighboring 6β-hydroxyl is probably caused by steric hindrance at $C_{(19)}$ and by better steric approach of participating hydroxyl to $C_{(19a)}$ than to $C_{(19)}$ so that the reaction at $C_{(19a)}$ is preferred.

Hypobromous acid addition to the unsaturated diol *IX* proceeds *via* two epimeric bromonium ions *XX* and *XXI* (R = H) which are further cleaved at $C_{(19a)}$ to give the corresponding products of 6(O)^n participation (*XXII* and *XXIII*). The dimethoxy derivative *X* reacts analogously furnishing the cyclic ethers *XXIV* and *XXV*. The solvolytic loss of the methyl group during the cleavage of the bromonium ion is a common reaction as we have shown earlier[11,13,15–20].



In contrast to the diene *VII*, diol *IX* and dimethoxy derivative *X*, the monoacetate *XI* reacts with hypobromous acid in a more complex way. In the first step, we assume the formation of two epimeric bromonium ions *XX* and *XXI* (R = Ac). The (19*S*)-epimer *XX* is cleaved by the ether oxygen of the 6β-acetoxy group in a normal way of 6(O)^n participation to afford the cyclic ether *XXII*. On the other hand, 6β-acetoxyl-assisted fission of the epimeric bromonium ion *XXI* is relatively very slow which results in formation of only trace amount of *XXIII* in the reaction mixture.

Instead, the (19*R*)-bromonium ion *XXI* is rearranged *via* shifts of carbon-carbon bonds (see arrows in *XXI*), the reaction being finished by conversion of the 5α--hydroxyl to a keto group. The facile rearrangement of *XXI* can be explained by the antiperiplanarity of migrating bonds, *i.e.* $C_{(19)}$—Br, $C_{(9)}$—$C_{(10)}$ and $C_{(4)}$—$C_{(5)}$, $C_{(9)}$—$C_{(10)}$, which is imposed by both the stereochemistry of addition and the rigidity of the AB ring junction. The rearrangement of the (19*R*)-bromonium ion *XXI* is probably enabled by a decreased nucleophilicity of the ether oxygen of the 6β-acetoxy group which makes the competing $6(O)^n$ participation much slower than in the 6β-hydroxy and 6β-methoxy derivatives[17].

When comparing the two models *A* and *B*, it is obvious that in the former system the parallel double bonds are held together by the rigid tricyclic frame work, while in the model *B* the vinyl group may rotate about the $C_{(10)}$—$C_{(19)}$ bond. Now, a question arises whether the reluctance against π-participation of the vinyl group is not due to an unfavorable rotamer population. Although the barriers to rotation of the 10β-vinyl group are unknown in this particular case, numerous analogies[16–21] show that the rotamer population is not the decisive factor for other functional groups (*i.e.* 19-hydroxy methoxy and acetoxy) possessing an inherent participation ability.

In concluding, model *B* brought evidence that the perpendicularly oriented double bonds did not undergo any C—C bond formation when attacked by an electrophile. The addition of hypobromous acid to this diene system proceeds in a stepwise manner the second addition being controlled by intramolecular participation of the hydroxyl group introduced by the first equivalent of the reagent.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa or at 20°C/26 Pa. Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 or on a Perkin–Elmer spectrometers in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were measured on a Varian XL-200 apparatus (200·05 MHz FT-mode) and on a Tesla B 476 (60 MHz) instrument at 25°C in deuteriochloroform with tetramethylsilane as internal reference. Chemical shifts are given in δ (ppm) scale. Coupling constants were taken from the first-order analysis; in all cases they were checked by double resonance experiments. ^{13}C-NMR spectra were measured on Varian XL-200 apparatus (50·3 MHz, FT-mode) using the square-wave proton decoupling mode. Mass spectra were recorded on a JEOL JMS D-100 spectrometer at 75 eV. The samples were introduced using a direct inlet heated to 120—150°C, the ion source was maintained at 150°C. Elemental compositions of all reported ions were determined by peak matching method using perfluorokerosene as a reference. The decompositions of metastable ions in the 1st field-free region were monitored by using the accelerating voltage scan method. The CD spectra were recorded on a Dichrographe II (Jouan-Roussel) in dioxane unless otherwise stated. The identity of the samples prepared by different routes was checked by mixture melting point determination, thin-layer chromatography (TLC), infrared, ^{1}H-NMR and mass spectra. Usual workup of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5% aqueous potassium

hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent in vacuo.

5-Cholesten-19-al (*VI*)

The alcohol[11] *V* (1 g) was dissolved in acetone (20 ml) and treated with Jones reagent at room temperature for 5 min. The excess reagent was decomposed with methanol, the mixture was diluted with ether and water, the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried and the solvent was evaporated. The residue was crystallized from a mixture of acetone and methanol to yield the aldehyde *VI* (660 mg), m.p. 104—105°C, $[\alpha]_D^{20}$ —170° (*c* 2·6). ^{1}H-NMR spectrum: 0·61 (3 H, s, 18-H), 5·74 (1 H, brd d, J = = 6 Hz, 6-H), 9·62 (1 H, s, 19-H). For $C_{27}H_{44}O$ (384·7) calculated: 84·31% C, 11·53% H; found 84·14% C, 11·67% H.

19-Nor-10β-vinyl-5-cholestene (*VII*)

Sodium hydride (70 mg) was dissolved in dimethyl sulfoxide (5 ml) with stirring and heating at 65°C for 3 h. Triphenylmethylphosphonium iodide (1·2 g) was then added at 0°C and the mixture stirred at room temperature for 1 h. A solution of the aldehyde *VI* (700 mg) in ether (5 ml) was added, ether was distilled off and the resulting solution was heated at 70°C for 4 h while stirring. The mixture was cooled, diluted with ether and water and the ethereal layer was worked up as usual. The residue was crystallized from a mixture of ether and acetone to give the diene *VII* (450 mg), m.p. 51—53°C, $[\alpha]_D^{20}$ —137° (*c* 1·8). ^{1}H-NMR spectrum: 0·61 (3 H, s, 18-H), 5·48 (1 H, m, W = 10 Hz, 6-H), 5·40 (3 H, m, W = 90 Hz, 19-H and 19a-H). Mass spectrum: m/z 382 ($C_{28}H_{46}$, $M^{+\cdot}$), 367, 355, 353, 269, 227. For $C_{28}H_{46}$ (382·7) calculated: 87·88% C, 12·12% H; found: 87·59% C, 12·03% H.

5,6α-Epoxy-19-nor-10β-vinyl-5α-cholestane (*VIII*)

The diene *VII* (5 g) was dissolved in chloroform (30 ml) and treated with 3-chloroperoxybenzoic acid (3 g) at room temperature overnight. The mixture was diluted with ether and water, the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on silica gel (200 g) using a mixture of light petroleum and benzene (95 : 5). The corresponding fractions were collected and evaporated to yield the oily epoxide *VIII* (4·1 g), $[\alpha]_D^{20}$ —40° (*c* 2·1). ^{1}H-NMR spectrum: 0·50 (3 H, s, 18-H), 2·98 (1 H, d, J = 4 Hz, 6β-H), 5·40 (3 H, m, W = 70 Hz, 19-H and 19a-H). For $C_{28}H_{46}O$ (398·7) calculated: 84·36% C, 11·63% H; found: 84·19% C, 11·41% H.

19-Nor-10β-vinyl-5α-cholestane-5,6β-diol (*IX*)

The epoxide *VIII* (2 g) was dissolved in dioxane (40 ml) and water (2 ml) and treated with a solution of 70% perchloric acid (2 ml) in water (2 ml) at room temperature for 2 h. The mixture was diluted with ether and water, the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated, to yield the oily diol *IX* (1·8 g), $[\alpha]_D^{20}$ +27° (*c* 4·9). ^{1}H-NMR spectrum: 0·57 (3 H, s, 18-H). 3·60 (1 H, m, W = 10 Hz, 6α-H), 5·10 (2 H, m, W = 40 Hz, 19a-H), 6·60 (1 H, m, W = 35 Hz, 19-H). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·56% C, 11·49% H.

19-Nor-10β-vinyl-5,6β-dimethoxy-5α-cholestane (*X*)

The diol *IX* (350 mg) was dissolved in 1,2-dimethoxyethane (10 ml) and treated with sodium hydride (100 mg) and methyl iodide (1 ml) at 60°C for 30 min while stirring. The mixture was decomposed with water, diluted with ether and water, and the ethereal layer was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (3 : 1) and the solution filtered through a column of aluminum oxide. The column was washed with the same mixture of solvents and the combined filtrates were evaporated, to give the oily *X* (310 mg), $[\alpha]_D^{20}$ +2° (*c* 3·6). ^{1}H-NMR spectrum: 0·55 (3 H, s, 18-H), 3·12 (1 H, m, 6α-H), 3·12 (3 H, s, CH_3O), 3·29 (3 H, s, CH_3O), 5·00 (2 H, m, W = 40 Hz, 19a-H), 6·60 (1 H, m, W = 35 Hz, 19-H). For $C_{30}H_{52}O_2$ (456·8) calculated: 81·52% C, 11·48% H; found: 81·29% C, 11·33% H.

19-Nor-10β-vinyl-5α-cholestane-5,6β-diol 6-Monoacetate (*XI*)

The diol *IX* (400 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (0·5 ml) at room temperature overnight. The mixture was decomposed with ice and water, the product extracted with ether and the ethereal solution was worked up as usual, to yield the oily acetate *XI* (370 mg), $[\alpha]_D^{20}$ +9° (*c* 3·7). ^{1}H-NMR spectrum: 0·55 (3 H, s, 18-H), 2·06 (3 H, s, CH_3CO_2), 4·80 (1 H, m, W = 10 Hz, 6α-H), 5·20 (2 H, m, W = 35 Hz, 19a-H), 6·40 (1 H, m, W = 40 Hz, 19-H). For $C_{30}H_{50}O_3$ (470·7) calculated: 79·10% C, 10·71% H; found: 78·94% C, 10·66 %H.

Addition of Hypobromous Acid to Compounds *VII*, *IX*—*XI*

The unsaturated compound (0·5 mmol) was dissolved in dioxane (5 ml) and water (0·5 ml) and treated with 10% perchloric acid (0·4 ml) and N-bromoacetamide (80 mg, 0·6 mmol or 160 mg, 1·2 mmol) for 30 min at room temperature. The mixture was diluted with ether and water, the ethereal solution was washed successively with water, 5% aqueous potassium hydrogen carbonate solution, 5% aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was chromatographed on three silica gel plates (20 × 20 cm) using a mixture of light petroleum and ether (90 : 10) or a mixture of light petroleum, ether and acetone (85 : 10 : 5) as eluent. Zones containing the desired compound were collected, eluted with ether, and evaporated. The yields are given in the text.

(19*S*)-5,19-*Dibromo*-6β,10β-(*epoxyethano*)-19-*nor*-5α-*cholestane* (*XVI*): ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 3·69 (1 H, dd, J = 10·3 and 3·7 Hz, 19a-*exo*-H), 3·92 (1 H, dd, J = 10·3 and 9·1 Hz, 19a-*endo*-H), 4·14 (1 H, d, J = 4·0 Hz, 6α-H), 4·69 (1 H, dd, J = 9·1 and 3·7 Hz, 19-H). Mass spectrum (in a mixture with *XVII*): *m/z* 556, 558, 560 ($M^{+\cdot}$), 541, 543, 545 $(M—CH_3)^+$, 477, 479 $(M—Br)^+$, 459, 461 $(M—Br—H_2O)^+$, 397 $(M—Br—HBr)^+$, 380 $(M—2\,Br—H_2O)^{+\cdot}$, 355 $(M—2\,Br—C_2H_3O)^+$.

(19*R*)-5,19-*Dibromo*-6β,10β-(*epoxyethano*)-19-*nor*-5α-*cholestane* (*XVII*): ^{1}H-NMR spectrum: 0·69 (3 H, s, 18-H), 3·56 (1 H, dd, J = 10·1 and 4·1 Hz, 19a-H), 3·73 (1 H, dd, J = 10·1 and 10 Hz, 19a-H), 4·12 (1 H, m, overlapped by other signals, 6α-H), 4·23 (1 H, dd, J = 9·5 and 4·1 Hz, 19-H).

(19*S*)-6β,10β-(*epoxyethano*)-19-*bromo*-19-*nor*-5α-*cholestan*-5-*ol* (*XXII*): ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 3·68 (1 H, dd, J = 10·0 and 3·3 Hz, 19a-*exo*-H), 3·79 (1 H, d, J = 3·8 Hz, 6α-H), 3·90 (1 H, dd, J = 10·0 and 9·5 Hz, 19a-*endo*-H), 4·61 (1 H, dd, J = 9·5 and 3·3 Hz, 19-H). Mass spectrum (in a mixture with *XXIII*): *m/z* 494, 496, ($M^{+\cdot}$, $C_{28}H_{47}BrO_2$), 415 $(M—Br)^+$, 397 $(M—Br—H_2O)^+$, 371 $(M—Br—C_2H_4O)^+$, 215, 217 $(C_9H_{12}BrO)^+$).

(19*R*)-6β,10β-(*epoxyethano*)-19-*bromo*-19-*nor*-5α-*cholestan*-5-ol (*XXIII*): ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 3·56 (1 H, dd, J = 10·0 and 3·6 Hz, 19a-H), 3·78 (1 H, d, overlapped by other signals, 6α-H), 4·29 (1 H, dd, J = 9·0 and 3·6 Hz, 19-H).

(19*S*)-5-*Methoxy*-6β,10β-(*epoxyethano*)-19-*bromo*-19-*nor*-5α-*cholestane* (*XXIV*): ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 3·17 (3 H, s, CH_3O), 3·67 (1 H, dd, J = 10·2 and 3·2 Hz, 19a-*exo*-H), 3·91 (1 H, dd, J = 10·2 and 9·8 Hz, 19a-*endo*-H), 3·95 (1 H, d, J = 4·0 Hz, 6α-H), 4·62 (1 H, dd, J = 9·8 and 3·2 Hz, 19-H). Mass spectrum (in a mixture with *XXV*): *m/z* 508, 510 ($M^{+\cdot}$, $C_{29}H_{49}BrO_2$), 429 $(M—Br)^+$, 397 $(M—Br—CH_3OH)^+$, 386 $(M—Br—C_2H_3O)^{+\cdot}$, 354 $(397 — C_2H_3O)^{+\cdot}$, 215, 217 $(C_9H_{12}BrO)^+$.

(19*R*)-5-*Methoxy*-6β,10β-(*epoxyethano*)-19-*bromo*-19-*nor*-5α-*cholestane* (*XXV*): ^{1}H-NMR spectrum: 0·71 (3 H, s, 18-H), 3·17 (3 H, s, CH_3O), 3·54 (1 H, dd, J = 10·1 and 3·4 Hz, 19a-H), 3·77 (1 H, dd, J = 10·1 and 9·8 Hz, 19a-H), 3·95 (overlapped by other signals, 6α-H), 4·27 (1 H, dd, J = 9·8 and 3·4 Hz, 19-H).

Cyclopentane-1′-*spiro*-5-(7β-*acetoxy*-19-*bromo*-7a-*homo*-*des*-A-*cholestan*-6-*one*) (*XXVI*): $[\alpha]_D^{20}$ —9° (*c* 4·8). ^{1}H-NMR spectrum: 0·66 (3 H, s, 18-H), 2·12 (3 H, s, CH_3CO_2), 3·61 (1 H, dd, J = 9·8 and 9·8 Hz, 19-H), 3·87 (1 H, dd, J = 9·8 and 2·0 Hz, 19-H), 5·38 (1 H, dd, J = 8·9 and 7·4 Hz, 7α-H). ^{13}C-NMR spectrum: 12·10, 18·56, 20·57, 22·52, 22·76, 23·73, 24·52, (2 C), 25·45, 27·84, 27·94, 32·48, 33·94, 35·64, 35·99, 36·41, 37·27, 38·38, 38·49, 39·43, 39·94, 42·37, 47·90, 54·87, 56·04, 56·20, 60·98, 75·44, 172·8. Mass spectrum: *m/z* 536, 538 ($M^{+\cdot}$, $C_{30}H_{49}BrO$), 495, 497, $(M—C_3H_5)^+$, 476, 478 $(M—CH_3CO_2H)^{+\cdot}$, 457 $(M—Br)^+$, 435, 437, $(M—CH_3CO_2H—C_3H_5)^+$, 428 $(M—Br—CHO)^{+\cdot}$, 415 $(M—C_3H_5—HBr)^+$, 397 $(M—CH_3CO_2H—Br)^+$, 379 $(397—H_2O)^+$, 369 $(397—CO)^+$, 368 $(428—CH_3CO_2H)^{+\cdot}$. IR spectrum: 1 242, 1 720, 1 746 cm^{-1}. CD spectrum (dioxane): $\Delta\varepsilon$ = +2·37, 288 nm. For $C_{30}H_{49}BrO_3$ (537·6) calculated: 67·02% C, 9·19% H, 14·86% Br; found: 66·84% C, 9·23% H, 14·99% Br.

Cyclopentane-1′-spiro-5-(7β-acetoxy-7a-homo-des-A-cholestan-6-one) (*XXVII*)

The bromide *XXVI* (40 mg) in benzene (5 ml) was refluxed with a benzene solution of tributyltin hydride (0·2 ml; 31 mg/ml) in the presence of a catalytic amount of 2,2′-bis(azo-2-methylpropionitrile) for 2 h. The mixture was filtered through a column of aluminum oxide and the filtrate was evaporated. The residue was chromatographed on one plate of silica gel (10 × 20 cm) using a mixture of light petroleum, ether and acetone (9 : 1 : 1). The corresponding zone was eluted with ether and evaporated to yield the oily *XXVII*, $[\alpha]_D^{20}$ —18° (*c* 3·2). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 1·10 (3 H, d, J = 7·1 Hz, 19-H), 2·13 (3 H, s, CH_3CO_2), 5·52 (1 H, dd, J = 6·4 and 5·2 Hz, 7α-H). ^{13}C-NMR spectrum: 11·94, 17·64, 18·61, 20·94, 22·58, 22·81, 23·84, 25·02, 25·74, 26·44, 27·84, 28·10, 30·30, 32·31, 34·44, 35·73, 36·06, 37·32, 37·59, 39·51, 40·08, 42·22, 45·63, 49·77, 56·33 (2 C), 61·61, 76·80, 177·08, 205·10. Mass spectrum: *m/z* 458 ($M^{+\cdot}$, $C_{30}H_{50}O_3$), 430 $(M—CO)^{+\cdot}$, 417 $(M—C_3H_5)^+$, 398 $(M—CH_3CO_2H)^{+\cdot}$, 370 $(M—CH_3CO_2H—CO)^{+\cdot}$, 330 $(398 — C_5H_8)^{+\cdot}$, 301 $(370 — C_5H_9)^+$. IR spectrum (chloroform): 1 250, 1 416, 1 712, 1 738 cm^{-1}. CD spectrum (dioxane): $\Delta\varepsilon$ = —1·54, 288 nm. For $C_{30}H_{50}O_3$ calculated: 78·55% C, 10·99% H; found: 78·41% C, 11·08% H.

Reduction of the Acetoxy Ketone *XXVII*

The ketone *XXVII* (20 mg) was dissolved in ether (5 ml) and treated with lithium aluminum hydride (50 mg) at room temperature overnight. The mixture was decomposed with water, diluted with ether and 5% aqueous hydrochloric acid and the ethereal phase was worked up as usual. The residue was chromatographed on a plate of silica gel (20 × 10 cm) with a mixture

of light petroleum, ether and acetone (80 : 10 : 10). Corresponding zone was eluted with ether to yield a nonseparable mixture of the diols *XXVIII* and *XXIX* (12 mg).

Cyclopentane-1′-spiro-5-(7a-homo-des-A-cholestan-6β,7β-diol) (*XXVIII*)

^{1}H-NMR spectrum: 0·70 s (3 H, s, 18-H), 0·93 (3 H, d, J = 8·2 Hz, 19-H), 3·62 (1 H, d, J = 3·3 Hz, 6α-H), 4·05 (1 H, ddd, J = 7·2 Hz, J = 3·3 Hz, J = 2·3 Hz, 7α-H).

Cyclopentane-1′-spiro-5-(7a-homo-des-A-cholestan-6α,7β-diol) (*XXIX*)

^{1}H-NMR spectrum: 0·66 (3 H, s, 18-H), 3·18 (1 H, d, J = 9 Hz, 6β-H), 3·68 (1 H, ddd, J = 9·0 Hz, J = 9·0 Hz, J = 2·8 Hz, 7α-H).

Cyclopentane-1′-spiro-5(6β,19-epoxy-7a-homo-des-A-cholestan-7β-ol) (*XXX*)

The ketone *XXVI* (50 mg) in ether (5 ml) was treated with lithium aluminum hydride (50 mg) at room temperature overnight. The mixture was decomposed with water, diluted with ether and 5% aqueous hydrochloric acid and the ethereal layer was worked up as usual. The residue was chromatographed on one preparative silica gel plate (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zone was eluted with ether and the eluate was evaporated. The residue was crystallized from aqueous acetone to afford the epoxide *XXX* (27 mg), m.p. 150—152°C. ^{1}H-NMR spectrum: 0·73 (3 H, s, 18-H), 3·67 (1 H, dd, J = 7·7 and 1·0 Hz, 19-*endo*-H), 3·76 (1 H, d, J = 5·0 Hz, 6α-H), 4·03 (1 H, ddd, J = 5·0 and 3·0 Hz, J = 3·1 Hz, 7α-H), 4·17 (1 H, dd, J = 7·7 and 8·1 Hz, 19-*exo*-H). Mass spectrum: m/z 416 ($M^{+\cdot}$, $C_{28}H_{48}O_2$), 398 ($M-H_2O)^{+\cdot}$, 368 ($M-H_2O-CH_2O)^{+\cdot}$, 356 ($M-H_2O-C_3H_6)^{+\cdot}$, 317 ($M-C_6H_{11}O)^+$, 274 ($M-C_8H_{14}O_2)^{+\cdot}$, 137 $(C_9H_{13}O)^+$. IR spectrum (chloroform): 3 425, 3 615 cm^{-1}. For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·63% C, 11·69% H.

Cyclopentane-1′-spiro-5-(6β,19-epoxy-7a-homo-des-A-cholestan-7-one) (*XXXI*)

The alcohol *XXX* (25 mg) in acetone (3 ml) was treated with Jones' reagent at room temperature for 5 min. The excess of reagent was decomposed with methanol, the mixture was diluted with ether and water, the ethereal layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on one preparative silica gel plate (10 × 20 cm) using a mixture of light petroleum, ether and acetone (85 : 10 : 5) as eluent. The corresponding zone was eluted with ether and the eluate was evaporated to afford oily ketone *XXXI* (23 mg), $[\alpha]_D^{20}$ —58° (c 2·0). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 1·89 (1 H, d, J = 6·2 Hz, 10α-H), 2·14 (1 H, d, J = 11·8 Hz, 7aβ-H), 2·66 (1 H, dd, J = 11·8 and 9·7 Hz, 7aα-H), 3·79 (1 H, s, 6α-H), 3·92 (1 H, d, J = 8·5 Hz, 19-*endo*-H), 4·33 (1 H, dd, J = = 8·5 and 6·2 Hz, 19-*exo*-H). Mass spectrum: m/z 414 ($M^{+\cdot}$, $C_{28}H_{46}O_2$), 386 $(M-CO)^{+\cdot}$, 355 $(M-CO-CH_2OH)^+$, 317 $(M-CO-C_5H_9)^+$, 305 $(M-C_7H_9O)^+$, 123 $(C_8H_{11}O)^+$. For $C_{28}H_{46}O_2$ (414·7) calculated: 81·10% C, 11·18% H; found: 81·02% C, 11·31% H.

The elemental analyses were carried out in the Analytical Laboratory of this Institute (under the direction of Dr J. Horáček). The 60 MHz ^{1}H-NMR *spectra were recorded by Mrs J. Jelínková and Mrs M. Snopková. The* IR *spectra were recorded by Mrs K. Matoušková, and interpreted by Dr S. Vašíčková. The* CD *spectra were recorded and interpreted by Dr S. Vašíčková.*

REFERENCES

1. Kondo A., Yamane T., Ashida T., Kanematsu K.: J. Org. Chem. *43*, 1180 (1978).
2. Zefirov N. S., Kirin V. N., Koz'min A. S., Bodrikov I. V., Potekhin K. A., Kurkutova E. N.: Tetrahedron Lett. *1978*, 2617.
3. Sasaki T., Kanematsu K., Kondo A.: J. Org. Chem. *39*, 2246 (1974).
4. Sasaki T., Kanematsu K., Kondo A., Nishitani Y.: J. Org. Chem. *39*, 3569 (1974).
5. Zefirov N. S., Sadovaya K. N., Kirin V. N., Koz'min A. S., Bodrikov I. V.: Zh. Org. Khim. *13*, 228 (1977).
6. Zefirov N. S., Koz'min A. S., Kirin V. N., Zhdankin V. V., Bodrikov I. V.: Zh. Org. Khim. *14*, 2615 (1978).
7. Sasaki T., Kanematsu K., Kondo A.: J. Chem. Soc., Perkin Trans. 1, *1976*, 2516.
8. Osawa E., Aigami K., Inamoto U.: Tetrahedron *34*, 509 (1978).
9. Garratt D. G., Ryan M. D., Beaulieu P. L.: J. Org. Chem. *45*, 839 (1980).
10. Sasaki T., Kanematsu K., Kondo A.: J. Org. Chem. *40*, 1642 (1975).
11. Kočovský P.: This Journal *45*, 3008 (1980).
12. Cubberley B. W., Guest I. G., L. Jones J. G., Marples B. A.: J. Chem. Soc., Perkin Trans. 1, *1977*, 1916.
13. Kočovský P.: This Journal, in press.
14. Garratt D. G., Ryan M. D., Kabo A.: Can. J. Chem. *58*, 2329 (1980).
15. Tureček F., Kočovský P.: This Journal *45*, 274 (1980).
16. Kočovský P., Černý V.: This Journal *43*, 1924 (1978).
17. Kočovský P., Kohout L., Černý V.: This Journal *45*, 559 (1980).
18. Kočovský P.: Tetrahedron Lett. *21*, 555 (1980).
19. Kočovský P., Černý V.: This Journal *45*, 3023 (1980).
20. Kočovský P., Černý V.: This Journal *45*, 3030 (1980).
21. Kočovský P., Starý I.: Unpublished results.

Translated by V. Černý.