PARTICIPATION OF 19-SUBSTITUENTS IN ELECTROPHILIC ADDITIONS TO 6,7-UNSATURATED 5α-CHOLESTANE AND B-HOMO-5α-CHOLESTANE DERIVATIVES; A CASE OF COMPETITION BETWEEN THE PARTICIPATION OF AN AMBIDENT NEIGHBORING GROUP AND EXTERNAL NUCLEOPHILE ATTACK

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Hypobromous acid action upon the 6,7-unsaturated 19-substituted 5α-cholestanes *Va—Vc* results in the formation of two types of products, the cyclic ethers *IX* as products of 5(O)^n participation of the 19-substituent, and the bromohydrins *X*. All these compounds are formed from the 6α,7α-bromonium ions *Va'—Vc'*. Under the same conditions the B-homo-5α-cholestane derivatives *VIIa—VIIc* afforded solely the cyclic ethers *XIV* as products of 5(O)^n participation of the 19-substituent in the cleavage of the bromonium ions *VIIa'—VIIc'*. Acid cleavage of the 6α,7α-epoxides *VIb* and *VIc* with aqueous perchloric acid or hydrobromic acid gave two types of products, *i.e.* the cyclic ethers *XI* and the diols *XII* or bromohydrines *XIII*. The cyclic ethers *XI* arise by 5(O)^n participation of the 19-substituent. The B-homo-6α,7α-epoxide *VIIIc* on cleavage with aqueous perchloric acid gave solely the cyclic ether *XVc* and by treatment with hydrobromic acid *VIIIc* afforded the mixture of *XVc*, as the main product, and of the bromohydrin *XVIc*. Discussed is the similarity of the bromonium ion cleavage with the fission of the corresponding epoxides, the mechanism of these reactions and the difference in the behavior of the isomeric olefins *Ia—c*, *IIIa—c*, *Va—c* and *VIIa—c* and epoxides *IIb,c*, *IVb,c*, *VIb,c* and *VIIIb,c*. The competition between ambident neighboring group participation and external nucleophile attack is discussed as well as the dependence of the products ratio on the nucleophilicity of the attacking species.

In preceding papers[1-12], we dealt with the participation of hydroxyl, methoxyl and acyloxy groups in electrophilic additions to a double bond; the action of hypobromous acid has been selected for systematic study. Electrophilic additions to the double bond are generally influenced by many factors that can be classified as steric, electronic and polar[13-26]. These factors remain important also when participation is involved but intervention of a participating neighboring group may alter the relative importance of these factors and introduces some new aspects. Of particular importance is to establish how the reaction course is modified by the character of the participating group, its orientation and its distance from the reaction center.

* Part CCXXVI in the series On Steroids; Part CCXXV: This Journal *45*, 274 (1980).

We have chosen steroid compounds with participating group standardly located at $C_{(19)}$. A suitable approach to investigation of these questions is the successive introduction of the following structural modifications: a) Changes in the participating group; b) changes in the location of the double bond; c) changes in the size of A- or B-ring.

Our previous work[3-12] demonstrated that competition with an external nucleophile is a good measure of the participation ability of the functional group. We also demonstrated the existence of a close analogy between the reactivity of the intermediary bromonium ion[27-34] and that of the protonated epoxide ring[35-45]. In the present paper we compare the behaviour of 19-substituted 6,7-unsaturated steroid models of the normal series with those of the B-homo series.

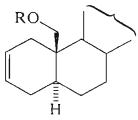
On treatment with hypobromous acid (generated *in situ* from N-bromoacetamide and perchloric acid in aqueous dioxane), the 6,7-unsaturated alcohol *Va* gave the cyclic ether *IXc* (Table I). Under the same conditions methoxy and acetoxy derivatives *Vb* and *Vc* gave a mixture of the cyclic ether *IXb* or *IXc* and of the bromohydrin *Xb* or *Xc* (Table I). Application of the same conditions to seven-membered B-ring derivatives *VIIa–VIIc* afforded the cyclic ethers *XIVb* or *XIVc*. No other products were detected by thin-layer chromatography (Table I).

On treatment with perchloric acid, the 6α,7α-epoxides *VIb* (or *VIc*) were cleaved to give a mixture of the cyclic ether *XIb* (or *XIc*) with the diol *XIIb* (or *XIIc*). On treatment with hydrobromic acid, the epoxides *VIb* (or *VIc*) furnished a mixture of the cyclic ether *XIb* (or *XIc*) with the bromohydrin *XIIIb* (or *XIIIc*) (Table II). We were unable to prepare the analogous 19-methoxy epoxide *VIIIb* with the seven-membered B-ring on epoxidation of the olefin *VIIb*. Instead, treatment of *VIIb* with peroxy acids even in buffered solution, gave the cyclic ether *XVb* directly. Cleavage of the 19-acetoxy epoxide *VIIIc* with aqueous perchloric acid in dioxane solution gave the analogous cyclic ether *XVc*. On treatment with hydrobromic acid, *VIIIc* gave a mixture of the cyclic ether *XVc* with the bromohydrin *XVIc* (Table II).

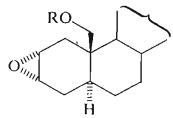
Structure of Reaction Products

The cyclic ether *IXc* is identical with a compound prepared in a different manner by an unequivocal route (*cf.* the synthetic part). The ^{1}H-NMR spectrum of the cyclic ether *IXb* reveals the presence of one methoxyl group; multiplets of CH—O and CH—Br have the same shape as those in *IXc* (Table III). The mass spectrum is in full agreement with the structure *IXb* (characteristic fragmentation of the bridged B-ring) as described in another paper[46].

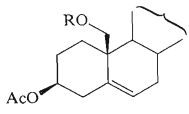
The ^{1}H-NMR spectrum of the bromohydrin *Xc* shows signals of two acetoxy groups. Multiplets corresponding to CH—OH and CH—Br protons have a shape very similar to those in the cyclic ether *IXc* and indicate diaxial orientation of the substituents in positions 6 and 7. The alternative structure, namely 6β-Br-7α-OH,



Ia, R = H
Ib, R = CH_3
Ic, R = Ac



IIb, R = CH_3
IIc, R = Ac



IIIa, R = H
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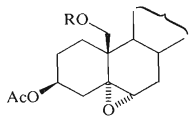
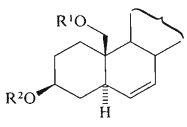
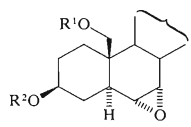
IIIc, R = Ac



IVb, R = CH_3
IVc, R = Ac



Va, R^1 = H, R^2 = Ac
Vb, R^1 = CH_3, R^2 = CH_3
Vc, R^1 = Ac, R^2 = Ac



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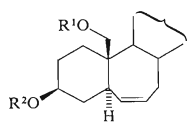
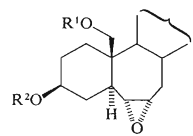
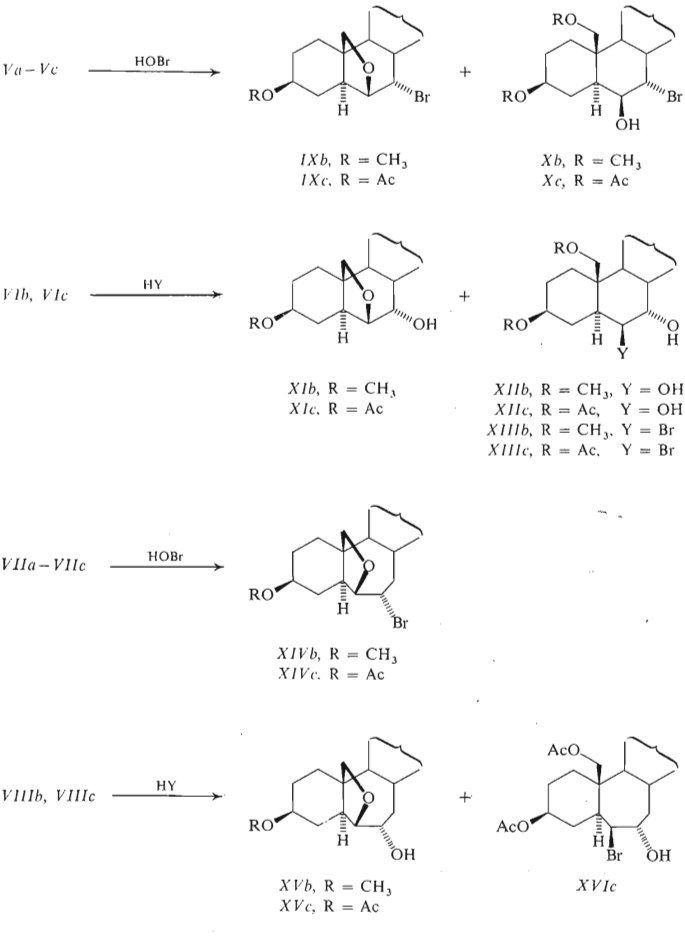
VIc, R^1 = Ac, R^2 = Ac

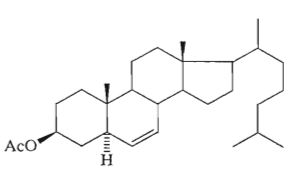


VIIa, R^1 = H, R^2 = Ac
VIIb, R^1 = CH_3, R^2 = CH_3
VIIc, R^1 = Ac, R^2 = Ac

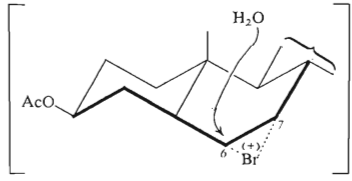


VIIIb, R^1 = CH_3, R^2 = CH_3
VIIIc, R^1 = Ac, R^2 = Ac


Va – Vc
HOBr
RO
H
O
Br
+
RO
H
OH
Br
IXb, R = CH3
IXc, R = Ac
Xb, R = CH3
Xc, R = Ac
VIb, VIc
HY
RO
H
O
OH
+
RO
H
OH
Y
XIb, R = CH3
XIc, R = Ac
XIIb, R = CH3, Y = OH
XIIc, R = Ac, Y = OH
XIIIb, R = CH3, Y = Br
XIIIc, R = Ac, Y = Br
VIIa – VIIc
HOBr
RO
H
O
Br
XIVb, R = CH3
XIVc, R = Ac
VIIIb, VIIIc
HY
RO
H
O
OH
+
AcO
AcO
H
Br
OH
XVb, R = CH3
XVc, R = Ac
XVIc



XXI



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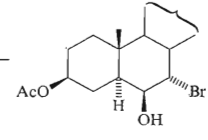

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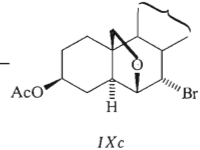
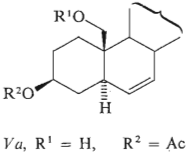
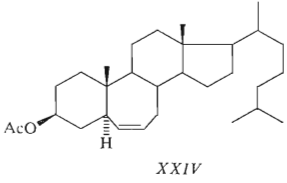


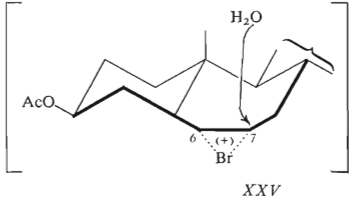
IXc



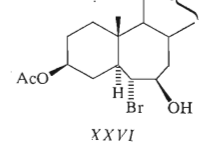
Va, R^1 = H, R^2 = Ac
Vb, R^1 = CH_3, R^2 = CH_3
Vc, R^1 = Ac, R^2 = Ac
Vd, R^1 = H, R^2 = H
Ve, R^1 = CH_3, R^2 = Ac



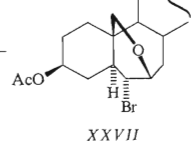
XXIV



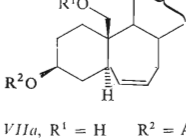
XXV



XXVI



XXVII



VIIa, R^1 = H R^2 = Ac
VIIb, R^1 = CH_3, R^2 = CH_3
VIIc, R^1 = Ac, R^2 = Ac
VIId, R^1 = H, R^2 = H
VIIe, R^1 = CH_3, R^2 = Ac
VIIf, R^1 = Ac, R^2 = CH_3
VIIg, R^1 = Ac, R^2 = H

is excluded on the basis of the IR spectrum: Strong intramolecular hydrogen bonding ($3550\ cm^{-1}$) is only possible in the structure *Xc*. Similarly the ^{1}H-NMR spectrum of the compound *Xb* proves the presence of two methoxyl groups but other signals are analogous to *Xc*. The IR spectrum shows the presence of a strong hydrogen bridge at $3470\ cm^{-1}$.

The ^{1}H-NMR spectrum of the cyclic ether *XIc* demonstrates the presence of only one acetoxyl. The IR spectrum shows no indication of an intramolecular hydrogen bridge. This fact points to the axial arrangement of both the 6-oxygen bond and 7--hydroxyl and leads to the 6β,19-epoxy-7α-hydroxy structure *XIc*. Moreover, the alternate 6α-hydroxy-7β,19-epoxy structure is ruled out by B-ring fragmentation in the

TABLE I

Yields and Ratios of Products of Hypobromous Acid Addition to the Olefins *V* and *VII*

Starting compound	Products, % of the total yield			Total yield %
	IX	*X*	*XIV*	
Va	100	—	—	96
Vb	93	7	—	89
Vc	92	8	—	94
VIIa	—	—	100	93
VIIb	—	—	100	91
VIIc	—	—	100	90

TABLE II

Yields and Ratios of Epoxide *VI* and *VIII* Cleavage Products

Starting compound	Reagent	Products, % of the total yield					Total yield %
		XI	*XII*	*XIII*	*XV*	*XVI*	
VIb	$HClO_4/H_2O$	95	5	—	—	—	92
VIb	HBr/H_2O	91	—	9	—	—	87
VIc	$HClO_4/H_2O$	74	26	—	—	—	93
VIc	HBr/H_2O	8	—	92	—	—	88
VIIIb	$HClO_4/H_2O$	—	—	—	~100	—	—
VIIIc	$HClO_4/H_2O$	—	—	—	100	—	93
VIIIc	HBr/H_2O	—	—	—	92	8	92

mass spectrum[4,6] and by the splitting pattern of the CH—O protons in the ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum of *XIb* shows the presence of one methoxyl, other spectral characteristics being analogous to *XIc*.

The IR spectrum of the diol *XIIc* proves the presence of one free (3621 cm^{-1}) and one bridged hydroxyl group (3546 and sh 3580 cm^{-1}). These characteristics are in agreement only with the diaxial structure *XIIc* where 6β-OH is hydrogen-bonded to 19-$COCH_3$. Small quantity of the diol *XIIb* did not permit accurate measurement of hydrogen bonding but the value of optical rotation and consideration of the mode of formation led to the above formula.

In the bromohydrin *XIIIc*, presence of two acetoxy groups is indicated by the ^{1}H-NMR spectrum. The α-configuration of the epoxide group in the parent compound *VIc* permits the formation of either the 6β-Br−7α-OH product *XIIIc* or 6α-OH−7β-Br derivative. This second possibility is ruled out by the IR spectrum which reveals the presence of a free hydroxyl (3625 cm^{-1}). In the 6α-OH−7β-Br bromohydrin, the hydrogen bridge between equatorial bromine and hydroxyl should be expected. The minor product of hydrogen bromide action upon the epoxide *VIb* was obtained in only a small quantity and could not be brought to crystallization. Therefore, its structure *XIIIb* is only tentative but is in agreement with a positive Beilstein test, migration rate in thin-layer chromatography, and its mode of formation.

The ^{1}H-NMR spectrum of the ether *XIVc* shows the presence of only one acetoxy

TABLE III

^{1}H-NMR Data of the Products of Hypobromous Acid Addition and of Epoxide Cleavage

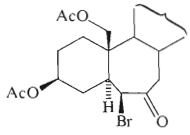
Compound	18-H	19-H[a]	6-H (*W* in Hz)	7-H (*W* in Hz)
IXb	0·71	3·87	4·00 m (20)[b]	4·00 m (20)[b]
IXc	0·73	3·91	4·05 m (18)[b]	4·05 m (20)[b]
Xb	0·72	3·57	3·95 m (21)	4·35 m (10)
Xc	0·69	4·39	3·89 m (18)	4·15 m (9)
XIb	0·65	4·67	3·70 m (18)	3·60 m (12)
XIc	0·66	3·69	3·73 m (13)	3·65 m (10)
XIIc	0·64	4·28	3·65 m[b]	3·65 m[b]
XIIIc	0·70	4·54	4·05 m (15)	3·80 m (13)
XIVb	0·65	3·72	4·00 m (16)	4·18 m (7)
XIVc	0·68	3·73	4·00 m (17)	4·15 m (6)
XVb	0·65	3·66	3·70 m (10)	3·55 m (35)
XVc	0·67	3·69	3·76 m (9)	3·62 m (30)
XVIc	0·68	4·30	4·25 m (25)	3·85 m (30)

[a] Center of AB system; [b] overlapped signals.

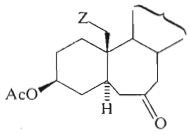
group whereas no band of hydroxyl is present in the IR spectrum. Two alternative structures may be considered: 6β,19-epoxy-7α-Br (*XIVc*) or 6α-Br-7β,19-epoxy (*XXVII*). The second may be excluded since *XXVII* has been prepared in a different way, and the two compounds were found not identical. Structure *XIVc* is thus derived indirectly but is further supported by mass spectrometric evidence[46]. Similar arguments may also be applied to *XIVb*. The ^{1}H-NMR spectrum reveals the presence of only one methoxyl; multiplets associated with CH—O and CH—Br protons have the same shape and width as those in the spectrum of *XIVc*.

The ^{1}H-NMR spectrum of *XVc* proves the presence of one acetoxy group. Treatment with trichloroacetyl isocyanate shows the presence of one hydroxyl. No indication of hydrogen bonding is apparent from the IR spectrum and only the band of free hydroxyl at 3622 cm^{-1} was found. On the other hand, the epimeric 7β-alcohol[46] shows a strong intramolecular hydrogen bridge. For *XVb*, analogous spectral data are characteristic: The ^{1}H-NMR spectrum demonstrates the presence of one methoxyl group. The shape, width and chemical shift of the multiplets of CH—O and CH—OH are the same as in *XVc*.

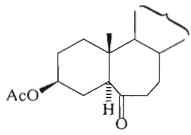
The ^{1}H-NMR spectrum of the bromohydrin *XVIc* shows signals of two acetoxy groups and the multiplets associated with CH—OH and CH—Br groupings. In view of the α-configuration of the epoxide ring in the starting compound *VIIIc*, two structures of the bromohydrin are possible: 6β-Br-7α-OH (*XVIc*) or 6α-OH-7β-Br. Neither ^{1}H-NMR nor mass spectrum can unequivocally decide between these two structures. The bromohydrin *XVIc* was therefore oxidized to the bromo ketone *XVII* and the latter was reduced with zinc in acetic acid to afford the ketone *XVIII*. The mass spectrum of *XVIII* contains molecular ions of low abundance, *m/z* 516, and significant fragment ions *m/z* 456 $(M-CH_3COOH)^{+\cdot}$, 438 $(456-H_2O)^{+\cdot}$, 414 $(456-CH_2CO)^{+\cdot}$, 396 $(M-2\ CH_3COOH)^{+\cdot}$, 389 $(56-C_5H_7)^{+\cdot}$, 378 $(396-H_2O)^{+\cdot}$, 368 $(396-CO)^{+\cdot}$, 356 $(414-C_3H_6O)^{+\cdot}$, 149 $(C_{10}H_{13}O)^+$ and 134 $(C_9H_{10}O)^{+\cdot}$. The loss of C_3H_6O (ions *m/z* 356) suggests that *XVIII* contains a —CH_2—CO—CH_2— subunit in analogy to other steroidal ketones[47]. In order to confirm the proposed structure of *XVIII*, mass spectra of two isomeric model ketones[48], *XIX* and *XX*, were investigated. The spectrum of the 7-oxo derivative *XIX* displayed abundant fragments *m/z* 398 $(M-CH_3COOH)^{+\cdot}$, 380 $(398-H_2O)^{+\cdot}$, 356 $(398-CH_2CO)^{+\cdot}$, 344 $(398-C_4H_6)^{+\cdot}$, 340 $(398-C_3H_6O)^{+\cdot}$, 331 $(398-C_5H_7)^+$, 151 $(C_{10}H_{15}O)$ and 135 $(C_9H_{11}O)^+$. The fragmentation pattern of the 6-oxo derivative *XX* differed considerably from those of *XVIII* and *XIX* showing prominent ions *m/z* 332 $(398-C_5H_6)$, while $(398-C_3H_6O)^{+\cdot}$, $C_{10}H_{15}O^+$ and $C_9H_{11}O^+$ ions were of negligible abundance. The skeletal fragmentations leading to ions $C_9H_{10}O^{+\cdot}$, $C_{10}H_{13}O^+$ and $C_9H_{11}O^+$, $C_{10}H_{15}O^+$ for *XVIII* and *XIX*, respectively, are depicted in Scheme 1. From comparison of the mass spectra of *XVIII*, *XIX* and *XX* it follows that *XVIII* has the keto group located at $C_{(7)}$. The bromohydrin in question must therefore be formulated as 6β-Br-7α-OH structure *XVIc*.



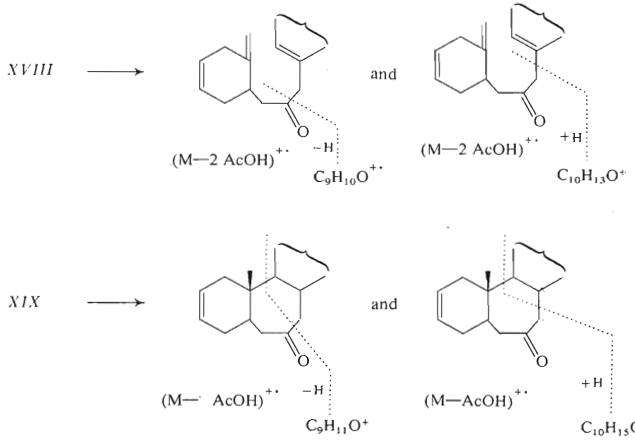
XVII



XVIII, Z = OAc
XIX, Z = H



XX



SCHEME 1

Hypobromous Acid Addition

Addition of hypobromous acid to the 6,7-unsaturated 19-substituted derivatives *Va*–*Vc* commences by formation of the 6α,7α-bromonium ions *Va'*–*Vc'* (Scheme 2). No products of 6β,7β-bromonium ion cleavage could be found in the reaction mixtures. Stereoelectronic control of opening the 6α,7α-bromonium ions *V'* should lead to a diaxial derivative so that the cleavage should occur at $C_{(6)}$ by an attack from the β-side. In the 19-hydroxy and 19-methoxy ions *Va'* and *Vb'* there are two possibilities that can accomodate these requirements: *1*) Intramolecular attack by the

Ia, X = $Br^{(+)}$, R = H
Ib, X = $Br^{(+)}$, R = CH_3
Ic, X = $Br^{(+)}$, R = Ac
Ib', X = $HO^{(+)}$, R = CH_3
Ic', X = $HO^{(+)}$, R = Ac

IIIa', X = $Br^{(+)}$, R = H
IIIb', X = $Br^{(+)}$, R = CH_3
IVb', X = $HO^{(+)}$, R = CH_3

IIIc', X = $Br^{(+)}$
IVc', X = $HO^{(+)}$

VIIa', X = $Br^{(+)}$, R = H
VIIb', X = $Br^{(+)}$, R = CH_3
VIIc', X = $Br^{(+)}$, R = Ac
VIIIb', X = $HO^{(+)}$, R = CH_3
VIIIc, X = $HO^{(+)}$; R = Ac

Va', X = $Br^{(+)}$, R = H
Vb', X = $Br^{(+)}$, R = CH_3
Vc', X = $Br^{(+)}$, R = Ac
VIb', X = $HO^{(+)}$, R = CH_3
VIc', X = $HO^{(+)}$, R = Ac

IX, XI

X, XII, XIII

XIV, XV

XVI

XXVII

SCHEME 2

19-oxygen which by $5(O)^n$ participation would yield the cyclic ether *IX* (for notation *cf.* ref.[8]). 2) Attack by water as external nucleophile leading to the bromohydrin *X*. In the 19-acetoxy derivative *Vc*, the 19-substituent as internal nucleophile may attack the reaction center analogously to give the cyclic ether *IX* but, in addition, it offers one more competitive possibility: The reaction center at $C_{(6)}$ may be attacked also by the carbonyl oxygen of the ester grouping in the $7(O)^{\pi,n}$ participation process.

The 19-alcohol *Va* gave solely the cyclic ether *IXc* which fact is in agreement with the previous observation that treatment of alcohols *Ia* and *IIIa* with hypobromous acid proceeds also with 100% $5(O)^n$ participation. 19-Methoxy and 19-acetoxy derivatives *Vb* and *Vc* give, along with the cyclic ether *IX*, a small quantity of the bromohydrin *X*. Formation of the bromohydrin *Xb* from *Vb* is due to external attack by a water molecule on the corresponding bromonium ion. However, formation of the bromohydrin *Xc* may either proceed by the same mechanism or may be due to internal attack by $7(O)^{\pi,n}$ participation. Since in both cases (*Vb* and *Vc*) the ratio of the cyclic ether *IX* to the bromohydrin *X* is practically identical (Table I), it is likely that also the bromohydrin *Xc* is formed from the 19-acetoxy derivative *Vc* by the attack of a water molecule as external nucleophile and $7(O)^{\pi,n}$ participation does not occur.

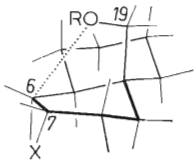
In homologous B-homo derivatives *VIIa–VIIc*, analogous initial formation of 6α,7α-bromonium ion *VII'* should be predicted. In the 19-unsubstituted 6,7-unsaturated B-homo derivative *XXIV*, the 6α,7α-bromonium ion *XXV* is assumed to be formed predominantly under conditions of hypobromous acid addition[48,49]. Cleavage of the latter ion with water as external nucleophile proceeds mainly at $C_{(7)}$ yielding the bromohydrin *XXVI* as a major product of the addition[49]. Fission at $C_{(6)}$ is also operative, though only to a limited extent[48,49]. This lack of regiospecificity in the fission of the 6α,7α-bromonium ion may be attributed to conformational nonhomogeneity of the seven-membered B-ring ion *XXV*. In contrast with 19-substituted steroids bearing a six-membered B-ring we may expect additional competition between attack at $C_{(6)}$ and $C_{(7)}$. The following processes could compete: *1*) Cleavage at $C_{(6)}$ with $5(O)^n$ participation which would yield the cyclic ether *XIV*; *2*) external attack by water at $C_{(6)}$ which would afford a bromohydrin; *3*) $7(O)^{\pi,n}$ participation of the ester grouping (only in the acetate *VIIc*) which would give the same bromohydrin; *4*) cleavage at $C_{(7)}$ with $6(O)^n$ participation which would yield the cyclic ether *XXVII*; *5*) external attack by water at $C_{(7)}$ which would furnish a bromohydrin.

Experimentally, we have found that the reaction is surprisingly smooth. Both *VIIa* and *VIIc* give rise to the cyclic ether *XIVc* and similarly *VIIb* yields the cyclic ether *XIVb*. These compounds are products of regiospecific fission of the 6α,7α-bromonium ion *VII'* at $C_{(6)}$, solely with $5(O)^n$ participation. The B-ring of the bromonium ion *VII'* may *a priori* exist in two conformations, $C_{(9)}$-chair and $C_{(7)}$-twist-boat (Fig. 1). For a potential $5(O)^n$ participation in the first conformation the distance between $C_{(6)}$ and the 19-oxygen is 0·25 nm, whereas the distance for $6(O)^n$ partici-

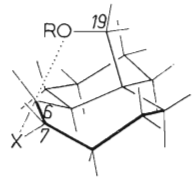
pation between the $C_{(7)}$ reaction center and 19-oxygen atom is 0·31 nm. Therefore, $5(O)^n$ participation is favored in this conformation. In the second conformation, the distance between $C_{(6)}$ and the 19-oxygen is 0·30 nm whereas the distance between $C_{(7)}$ and the 19-oxygen is 0·27 nm. The fact that the distance from $C_{(7)}$ is smaller than from $C_{(6)}$ could be favourable for $6(O)^n$ participation but concomitant strong steric interference with 7aβ-hydrogen hinders the approach of the 19-substituent. Inspection of Dreiding models shows that in the $C_{(9)}$-chair conformation the distance of the 19-oxygen from $C_{(6)}$ is practically the same as in the six-membered B-ring analog *V*, *i.e.* 0·25 nm, but the 19-oxygen lies in the plane of the bromonium ion ring (Fig. 1). By contrast, in the six-membered B-ring analog the 19-oxygen must approach the reaction center in a line declined from this plane by about 15° (angle of approach). This case appears to be strong evidence for the view that the zero angle of approach is the reason why in the fission of all three bromonium ions *VIIa'* – *VIIc'* no process other than $5(O)^n$ participation is operative.

Fission of the Epoxides

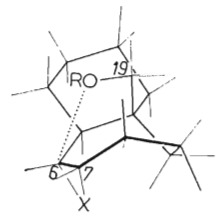
Similarly as in the 6α,7α-bromonium ions *Va'* – *Vc'*, two or three reaction pathways may be expected in the fission of the protonated 6α,7α-epoxides *VIb'* and *VIc'*. In the cleavage of the protonated 19-methoxy epoxide *VIb'* with perchloric acid in aqueous dioxane (where water is the external nucleophile), $5(O)^n$ participation as the almost sole reaction pathway leads to the cyclic ether *XIb*. Only a small proportion of the diol *XIIb* (product of external attack) is present (Table II). The product of participation (*XIb*) largely predominates over the product of external attack (*XIIIb*) even when the epoxide is cleaved with hydrogen bromide and the epoxide ring is thus exposed to the action of a nucleophile (Br^-) much stronger than water.



V' and *VI'*



VII' and *VIII'*, $C_{(9)}$-Chair



VII' and *VIII'*, $C_{(7)}$-Twist Boat

FIG. 1
Conformations of the Ions *V'*—*VIII'*

A different situation arises in the 19-acetoxy analog *VIc'*. When the epoxide ring is cleaved with aqueous perchloric acid, the content of the $5(O)^n$ participation product *XIc* is somewhat lower (Table II). This result may be attributed first to decreased nucleophilicity of the ether oxygen of the ester grouping and secondly to the possibility of a competitive $7(O)^{\pi,n}$ participation of the acetoxy group. The product of $7(O)^{\pi,n}$ participation (*XIIc*) should be identical with the product of external attack but we did not establish which mechanism is responsible for the formation of the diol *XIIc*. The question of $7(O)^{\pi,n}$ participation thus remains open. When the epoxide *VIc'* is cleaved with hydrogen bromide, external nucleophile attack markedly predominates (Table II).

In the B-homo series, the participation reaction is extremely easy. Our attempts at preparing the 19-methoxy epoxide *VIIIb* were thus unsuccessful, since under epoxidation conditions this compound undergoes rapid cyclization to *XVb*. This reaction proceeds in the absence of a strong nucleophile as exclusive $5(O)^n$ participation. Aqueous perchloric acid splits the 19-acetoxy ion *VIIIc'* solely with $5(O)^n$ participation of the 19-substituent to give the cyclic ether *XVc*. It is of interest to compare this result with the cleavage of the analogous compound *VIc* with six-membered B-ring under the same conditions. Here, the product of $5(O)^n$ participation is accompanied by 26% of the diol *XIIc* as a product of external attack. This difference may be explained by considering the angles of approach of the 19-oxygen in B-homo and normal series as discussed above. Thus, $5(O)^n$ participation is more favored in the B-homo- than in the normal series. Moreover, the approach of the external nucleophile to $C_{(6)}$ seems to be more sterically shielded in the first than in the second case.

The reaction of 19-acetoxy epoxide *VIIIc* with hydrogen bromide proceeds again predominantly with $5(O)^n$ participation under formation of the cyclic ether *XVc*. In addition to this compound, a certain but small amount of the product of external nucleophile attack, the bromohydrin *XVIc*, was isolated. This example demonstrates the importance of the angle of approach of the participating group to the reaction center. If this angle is small (approx. 0° in *VIIIc*) the internal attack is preferred over the external one even if the externally attacking species is a strong nucleophile (*e.g.* Br^-). In the compound *VIc*, this angle is larger (approx. 15°) and the external attack by Br^- becomes dominant. In 5α,6α-epoxides *IVb* and *IVc*, where both the angle and the distance increased to 30° and 0·31 nm, respectively, the $5(O)^n$ participation is no longer operative and only the product of external attack was isolated (Table IV).

General Considerations

The addition of hypobromous acid to the olefins *I*, *III*, *V* and *VII* proceeds via intermediary bromonium ions *I'*, *III'*, *V'* and *VII'* the fission of which by internal or

external nucleophile attack is similar to the cleavage of the protonated epoxides *II'*, *IV'*, *VI'* and *VIII'* (Table IV). It is pertinent to note that here is one point at which the cleavage of epoxides does not exactly parallel the cleavage of bromium ions. Whereas the epoxides can be isolated and are used in pure condition, the bromonium ions may be accompanied by their epimers and this may influence the results. In Ta-

TABLE IV
Neighboring Group Participation in the Cleavage of the Ions *I'*—*VIII'*

Ion[a,b]	Neighb. group	X[b]	Y[b]	Mode of reaction			Distance[d] (nm)	Angle of approach
				5(O)[n]	6(O)[π,n]	external[c]		
Ia'	OH	Br^+	H_2O	100	—	—	0·26	~15°
Ib'	OCH_3	Br^+	H_2O	100	—	—	0·26	~15°
Ic'	OAc	Br^+	H_2O	88	—	12	0·26	~15°
IIIa'	OH	Br^+	H_2O	100	—	—	0·31	~30°
IIIb'	OCH_3	Br^+	H_2O	100[e]	—	—	0·31	~30°
IIIc'	OAc	Br^+	H_2O	—	87[f]	13[f]	0·31	~30°
Va'	OH	Br^+	H_2O	100	—	—	0·26	~15°
Vb'	OCH_3	Br^+	H_2O	93	—	7	0·26	~15°
Vc'	OAc	Br^+	H_2O	92	—	8	0·26	~15°
VIIa'	OH	Br^+	H_2O	100	—	—	0·25	~ 0°
VIIb'	OCH_3	Br^+	H_2O	100	—	—	0·25	~ 0°
VIIc'	OAc	Br^+	H_2O	100	—	—	0·25	~ 0°
IIb'	OCH_3	HO^+	H_2O	68	—	32	0·26	~15°
IIc'	OAc	HO^+	H_2O	60	—	40	0·26	~15°
IVb'	OCH_3	HO^+	H_2O	27	—	73	0·31	~30°
IVc'	OAc	HO^+	H_2O	—	97	3	0·31	~30°
VIb'	OCH_3	HO^+	H_2O	95	—	5	0·26	~15°
VIc'	OAc	HO^+	H_2O	74	—	26	0·26	~15°
VIIIb'	OCH_3	HO^+	H_2O	100	—	—	0·25	~ 0°
VIIIc'	OAc	HO^+	H_2O	100	—	—	0·25	~ 0°
IIb'	OCH_3	HO^+	Br^-	48	—	52	0·26	~15°
IIc'	OAc	HO^+	Br^-	15	—	85	0·26	~15°
IVb'	OCH_3	HO^+	Br^-	—	—	100	0·31	~30°
IVc'	OAc	HO^+	Br^-	—	—	100	0·31	~30°
VIb'	OCH_3	HO^+	Br^-	91	—	9	0·26	~15°
VIc'	OAc	HO^+	Br^-	8	—	92	0·26	~15°
VIIIc'	OAc	HO^+	Br^-	92	—	8	0·25	~ 0°

[a] Data for ions *I'* (ref.[5,6]), *II'* (ref.[7]), *III'* (ref.[5,6,8]) and *IV'* (ref.[7,9]) are taken from our previous papers; [b] see Scheme 2; [c] for competition of external attack and 7(O)[π,n] see text and ref.[8,9]; [d] the distance between 19-O and the reaction center in 5(O)[n] participation; [e,f] the given figures do not include the accompanying reactions of the 5β,6β-bromonium ion representing 35% (*e*) (ref.[6]) and 10% (*f*) (ref.[8]) of the overall conversion.

ble IV only α-oriented bromonium ions are considered. The course of processes where both bromonium ions take part in the reaction (namely addition to *IIIb* and *IIIc*) was discussed in our earlier papers[5-9].

Table IV shows that all ions (except 5α,6α-ions *IIIc'* and *IVc'*) tend strongly to $5(O)^n$ participation in all investigated cases of $C_{(19)}$-substituents: OH, OCH_3, $OCOCH_3$. The $6(O)^{\pi,n}$ participation is only possible with 5α,6α-ions (*IIIc'* and *IVc'*) where it could compete with $5(O)^n$ participation. It has been found experimentally[8,9] in these ions, that $6(O)^{\pi,n}$ participation is an important reaction pathway and $5(O)^n$ participation is entirely suppressed. Table IV also demonstrates that 6,7-olefin *V* behave similarly as 2,3-olefins *I*; both are in sharp contrast with 5,6-olefins *III*. The same is true of corresponding epoxides *II*, *IV* and *VI*.

A characteristic feature of 6,7-ions *VII'* and *VIII'* is the annelation of the ring of the ion to the seven-membered B-ring. They are more prone to fission with $5(O)^n$ participation than analogous 6,7-ion *V'* and *VI'* with a six-membered B-ring. This may be attributed to the following facts: *1*) In B-homo derivatives, the 19-O lies practically in the plane of the three-membered ion ring. *2*) The external nucleophile attacking on $C_{(6)}$ in the B-homo series (in $C_{(9)}$-chair conformation of the B-ring) is more shielded by the 19-substituent than in the normal series.

If 2,3-ions *I'* and *II'* are compared with 6,7-ions *V'* and *VI'* it becomes clear that the dimension and conformations of the rings A and B and the distances of the 19-substituent from the reaction centers are the same. However, the epoxide or bromonium ion ring is flanked by only methylene groups in *I'* or *II'* whereas more highly substituted carbon atoms are present in analogous positions in *V'* and *VI'* (Fig. 2). The ratio between products of internal and external attack is about the same in 2,3- and 6,7-bromonium ions. On the other hand, more ready external attack

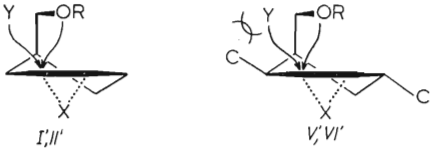
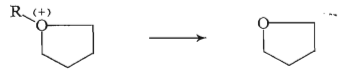


FIG. 2

Steric Interactions in the Cleavage of the Ions *I'*, *II'*, *V'* and *VI'* by an External or Internal Nucleophile Attack

was observed in 2α,3α- than in 6α,7α-epoxides. This may be due to relative steric accessibility and flexibility of the ring A but it is not clear why this applies for epoxides but not for bromonium ions (Table IV).

So far, all our observations are in conformity with the order of reactivity as proposed in our earlier papers[8,9]: $6(O)^{\pi,n} > 5(O)^{n} > 7(O)^{\pi,n} \geqq$ external attack by weak nucleophile. If a strong nucleophile (such as Br^-) is present, neighboring group participation may be suppressed depending on the distance and angle of approach of the neighboring group. No evidence was found for $7(O)^{n}$ participation. The problem of $6(O)^{n}$ participation is being investigated. Previously we demonstrated that $6(O)^{\pi,n}$ participation can reverse the regioselectivity of the cleavage of cyclic ions[8,9]. Similarly, results obtained in the present paper with seven-membered B-ring models demonstrate that $5(O)^{n}$ participation can also reverse the normal regioselectivity. If we compare the capability of the OH, OCH_3, and $OCOCH_3$ groups to participate in a $5(O)^{n}$ process, we observe the order OH > OCH_3 > OAc (Table IV). The hydroxyl group reacts most rapidly since the intermediary cyclic oxonium ion is most rapidly split to a stable cyclic ether if R = H (Scheme 3). On the other hand, if R = $COCH_3$, the cyclic oxonium is not readily formed due to decreased electron density at the ether oxygen by the carbonyl group effect.



R = H
R = CH_3
R = Ac

SCHEME 3

Syntheses

Addition of hypobromous acid (generated *in situ*) to the olefin[50] *XXI* furnished, *via* the intermediary bromonium ion *XXII*, the bromohydrin *XXIII* as a major product which gave the bromo epoxide *IX* on reaction with lead tetraacetate in the presence of iodine. The compound *IX* was reduced with zinc in acetic acid to give the 6,7-unsaturated 19-hydroxy derivative *Va* which on acetylation smoothly yielded the diacetate *Vc*. Attempts at preparing the 19-methyl ether *Ve* by methylation of *Va* were, in our hands, unsuccessful: Methylation of *Va* with methyl iodide in the presence of sodium hydride gave only a minute yield of *Ve* in a complex mixture. On attempted methylation with methyl iodide and silver oxide or with diazomethane

no reaction was observed. We circumvented these difficulties by preparing the dimethyl ether *Vb* as a model. We first saponified the monoacetate *Va* to the diol *Vd* which on treatment with methyl iodide and sodium hydride at elevated temperature and prolonged reaction time furnished the dimethyl ether *Vb*. Difficult methylation of $C_{(19)}$-hydroxyl is indicative of strong steric shielding in this position. Epoxidation of the olefin *Vb* with monoperoxyphthalic acid did not furnish the desired 6α,7α--epoxide *VIb* but gave directly the product of its intramolecular cleavage, *i.e.* the cyclic ether *XIb*. Reaction with *m*-chloroperoxybenzoic acid in the presence of potassium acetate led to a mixture in which the desired 6α,7α-epoxide *VIb* was present as major product accompanied by a smaller amount of *XIb* and a less polar compound which probably is isomeric 6β,7β-epoxide. Pure 6α,7α-epoxide was obtained from this mixture by preparative thin-layer chromatography on ammonia-pretreated plates. The epoxide *VIc* was prepared without difficulties on epoxidation of the olefin *Vc* with monoperoxyphthalic acid. α-Configuration of the epoxide ring in *VIb* and *VIc* follows from their reactions: Acid cleavage gives the cyclic ethers *IXb* or *IXc*, respectively. Formation of these compounds is possible only from epoxides with 6α,7α-configuration.

The known[49] bromohydrin *XXVI*, prepared by hypobromous acid addition to the olefin *XXIV* (*via* ion *XXV*), was treated with lead tetraacetate in the presence of iodine to give the cyclic ether *XXVII* which on reduction with zinc in acetic acid gave the 6,7-unsaturated 19-hydroxy derivative *VIIa*; acetylation of the latter furnished the diacetate *VIIc*. Methylation of the alcohol *VIIa* by methyl iodide–sodium hydride method led to a complex mixture of four products: *VIIb* (22%), *VIIc* (10%), *VIIe* (25%) and *VIIf* (39%). Low yield of 19-methoxy derivative *VIIe* or *VIIb* enforced preparation of the dimethyl ether *VIIb* in a different manner: The diacetate *VIIc* was converted to diol *VIId* on reduction with lithium aluminum hydride (saponification with potassium hydroxide in boiling methanol gives only the monoacetate *VIIg*) and the product was methylated using the sodium hydride–methyl iodide method. The resulting dimethyl ether *VIIb* was purified by chromatography. Attempts at preparing the epoxide *VIIIb* were unsuccessful since on epoxidation of the olefin *VIIb* only the cyclic hydroxy ether *XVb* was isolated. The 6α,7α-epoxide *VIIIc* was prepared from the unsaturated diacetate *VIIc* by monoperoxyphthalic acid epoxidation. The 6α,7α-configuration of this epoxide follows from the result of its treatment with perchloric acid which leads to formation of the cyclic ether *XVc*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°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 spectrometer in tetrachloromethane unless other wise stated. The ^{1}H-NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz) in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm.

Apparent coupling constants were obtained from the first order analysis. The mass spectra were recorded on a Jeol JMS D-100 spectrometer operating at 75 eV. The samples were introduced using a direct inlet at 140°C. The elemental composition of the ions were determined by accurate mass measurements. The decompositions of metastable ions in the 1st field-free region were monitored by using the accelerating voltage scan method. The identity of the 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. Usual work up 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*.

Addition of Hypobromous Acid to the Compounds *Va*—*Vc* and *VIIa*—*VIIc*

The unsaturated compound (0·5 mmol) was dissolved in dioxane (5 ml) and water (0·5 ml) and treated with 10% aqueous perchloric acid (0·4 ml) and N-bromoacetamide (80 mg, 0·6 mmol) for 30 min at room temperature. The mixture was diluted with water and the product extracted with ether. The ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, aqueous sodium thiosulfate solution, water, then dried with sodium sulfate and evaporated. The residue was chromatographed on four preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The zones were collected, eluted with ether, the filtrates were evaporated and the residue dried in a vacuum dessicator overnight. The products were crystallized from aqueous acetone or from a mixture of chloroform and methanol. The yields are given in Table I, the ^{1}H-NMR spectra, analytical and physical data of the isolated compounds are given in Tables III and V.

Cleavage of Epoxides *VIb*, *VIc* and *VIIIc*

The epoxide (200 mg) was dissolved in dioxane (6—8 ml), water (0·5 ml) was added and the mixture was treated with acid, *i.e.* 72% aqueous perchloric acid (0·3 ml) or 48% hydrobromic acid (0·5 ml) for 30 min. The mixture was diluted with ether and water, the organic layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried with sodium sulfate and the solvent was evaporated. The residue was chromatographed on four preparative silica gel plates using a mixture of light petroleum, ether and acetone (80 : 10 : 10) for development. Corresponding zones were collected, eluted with ether, the solvent was evaporated and the residue dried in a vacuum dessicator overnight. The products were crystallized from aqueous acetone or methanol. The yields of products are given in Table II. Their ^{1}H-NMR spectra, analytical and physical data are given in Tables III and V.

5α-Cholest-6-ene-3β,19-diol 3-Monoacetate (*Va*)

Powdered zinc (36 g) was added to a solution of the epoxide *IX* (7·2 g) in acetic acid (150 ml), the mixture was heated at 50°C for 20 min and at 100°C for 40 min. The mixture was cooled, the inorganic material was filtered off, the filtrate was poured into water, the product was extracted with ether, the ethereal solution was washed with water, 5% aqueous potassium hydrogen carbonate, water, dried and the solvent was evaporated. The residue (6·7 g) was chromatographed on a column of silica gel (500 g) with a mixture of light petroleum and ether (90 : 10). The corresponding fractions were collected and evaporated to yield the crude product (3·9 g) which on crystallization from a mixture of chloroform and methanol afforded *Va* (3·2 g), m.p. 102—103·5°C, $[\alpha]_D^{20}$ —91°

(*c* 1·9). IR spectrum: 708, 1028, 1246, 1641, 1735, 3055 cm^{-1}. ^{1}H-NMR spectrum: 0·73 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·83 (2 H, s, 19-H), 4·76 (1 H, m, W = 30 Hz, 3α-H), 5·23 and 5·54 (2 H, 2 d, J = 10 Hz, AB system of 6-H and 7-H). For $C_{29}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·60% C, 11·17% H.

TABLE V

Analytical and Physical Data of the Products of Hypobromous Acid Addition and the Epoxide Cleavage

Compound	Formula (m.w.)	Calculated/Found			M.p., °C $[\alpha]_D^{20}$
		% C	% H	% Br	
IXb	$C_{28}H_{47}BrO_2$	67·86	9·56	16·12	oil
	(495·6)	67·59	9·48	16·33	−59°
IXc	$C_{29}H_{47}BrO_3$	66·52	9·05	15·26	129—130
	(523·6)	66·39	8·96	15·41	−66°
Xb	$C_{29}H_{51}BrO_3$	66·01	9·74	15·14	oil
	(527·6)	65·84	9·63	15·29	−25°
Xc	$C_{31}H_{51}BrO_5$	63·79	8·81	13·69	oil
	(583·7)	63·55	8·62	13·87	−30°
XIb	$C_{28}H_{48}O_3$	77·73	11·18	—	foam
	(432·7)	77·52	11·09	—	−18°
XIc	$C_{29}H_{48}O_4$	75·61	10·50	—	158—159
	(460·7)	75·48	10·36	—	−22°
XIIb	$C_{29}H_{52}O_4$	74·95	11·28	—	oil
	(464·7)	74·80	11·17	—	−4°
XIIc	$C_{31}H_{52}O_6$	71·50	10·07	—	oil
	(520·8)	71·61	10·26	—	−6°
XIIIc	$C_{31}H_{51}BrO_5$	63·79	8·81	13·69	oil
	(583·7)	63·68	8·65	13·82	−20°
XIVb	$C_{30}H_{49}BrO_2$	69·08	9·47	15·32	oil
	(521·6)	68·87	9·31	15·60	−21°
XIVc	$C_{30}H_{49}BrO_3$	67·02	9·19	14·96	oil
	(537·6)	66·74	9·05	15·01	−21°
XVb	$C_{29}H_{50}O_3$	77·97	11·28	—	132—134°
	(446·7)	78·11	11·14	—	−2°
XVc	$C_{30}H_{50}O_4$	75·90	10·62	—	184—186°
	(474·7)	75·72	10·59	—	−8°
XVIc	$C_{32}H_{53}BrO_5$	64·31	8·94	13·37	145—147°
	(597·7)	64·10	8·73	13·61	+12°

3β,19-Dimethoxy-5α-cholest-6-ene (*Vb*)

The diol *Vd* (200 mg) in 1,2-dimethoxyethane (3 ml) was treated with sodium hydride (20 mg) and methyl iodide (0·2 ml). The mixture was stirred at 50°C for 10 h. The excess of hydride was decomposed with wet ether, the mixture was diluted with ether and worked up as usual. The residue was filtered through a column of alumina and the filtrate was evaporated. The residue was crystallized from a mixture of chloroform and methanol to yield *Vb* (88 mg), m.p. 108 to 109°C, $[\alpha]_D^{20}$ —113° (*c* 1·7). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·20 (1 H, m, $W = 30$ Hz, 3α-H), 3·24 (3 H, s, CH_3O), 3·32 (3 H, s, CH_3O), 3·45 (2 H, brd s, 19-H), 5·37 (2 H, m, $W =$ = 40 Hz, 6-H and 7-H). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·93% C, 11·59% H.

5α-Cholest-6-ene-3β,19-diol 3,19-Diacetate (*Vc*)

The alcohol *Va* (500 mg) was dissolved in pyridine (5 ml) and treated with acetic anhydride (1 ml) at room temperature overnight. The mixture was decomposed with ice, the product was taken up in ether and the ethereal solution was worked up as usual to yield the oily *Vc* (460 mg), $[\alpha]_D^{20}$ —84° (*c* 2·1). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 2·03 (3 H, s, CH_3CO_2), 4·11 (1 H, d, $J = 12$ Hz, 19-H), 4·70 (1 H, d, $J = 12$ Hz, 19-H), 4·70 (1 H, m, $W = 30$ Hz, 3α-H), 5·50 (2 H, m, $W = 60$ Hz, 6-H and 7-H). For $C_{31}H_{50}O_4$ (486·7) calculated: 76·50% C, 10·35% H; found: 76·34% C, 10·67% H.

5α-Cholest-6-ene-3β,19-diol (*Vd*)

A mixture of the acetate *Va* (400 mg) and potassium hydroxide (200 mg) in methanol (10 ml) was refluxed for 1 h. The solvent was distilled off under reduced pressure, the residue was treated with ether and water, the ethereal layer was washed with water, dried and evaporated. The residue was crystallized from aqueous methanol to yield the diol *Vd* (260 mg), m.p. 179—180°C, $[\alpha]_D^{20}$ +93° (*c* 1·7). ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 3·60 (1 H, m, $W = 30$ Hz, 3α-H), 3·84 (2 H, brd s, 19-H), 5·38 (2 H, m, $W = 40$ Hz, 6-H and 7-H). For $C_{27}H_{46}O_2$ (402·7) calculated: 80·54% C, 11·51% H; found: 80·27% C, 11·40% H.

19-Methoxy-5α-cholest-6-en-3β-ol 3-Acetate (*Ve*)

The alcohol *Va* (500 mg) in 1,2-dimethoxyethane (15 ml) was treated with sodium hydride (40 mg) and methyl iodide (0·5 ml) as given for *Vb*. The residue was chromatographed on a column of silica gel (50 g) using a mixture of light petroleum and ether (97 : 3) as eluent. Corresponding fractions were collected, evaporated and the residue was crystallized from a mixture of chloroform and methanol to yield *Ve* (90 mg), m.p. 117—119°C, $[\alpha]_D^{20}$ —106° (*c* 1·5). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·29 (3 H, s, CH_3O), 3·48 (2 H, brd s, 19-H), 4·75 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·30% C, 11·26% H.

3β,19-Dimethoxy-6α,7α-epoxy-5α-cholestane (*VIb*)

The olefin *Vb* was dissolved in chloroform (2 ml), potassium acetate (100 mg) was added and the mixture was treated with *m*-chloroperoxybenzoic acid (50 mg) at room temperature for 2 h. The mixture was diluted with ether and water, the ethereal layer was washed with water, a 5% aqueoues potassium hydrogen carbonate solution, water, dried and evaporated. The residue

was chromatographed on one preparative plate of silica gel (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) for development. Corresponding zone was separated, eluted with ether and the solution was evaporated to afford the oily epoxide *VIb* (44 mg), $[\alpha]_D^{20}$ +21°. For $C_{29}H_{50}O_3$ (446·7) calculated: 77·97% C, 11·28% H; found: 77·73% C, 11·22% H.

6α,7α-Epoxy-5α-cholestane-3β,19-diol 3,19-Diacetate (*VIc*)

The olefin *Vc* (450 mg) was dissolved in benzene (10 ml) and treated with a solution of monoperoxyphthalic acid in ether (5 ml, 90 mg/ml) at room temperature for 10 h. The mixture was diluted with ether and water, the ethereal solution was washed with water, 5% aqueous potassium hydrogen carbonate, an aqueous sodium thiosulfate solution, water, dried and the solvent was evaporated to yield the oily *VIc* (420 mg), $[\alpha]_D^{20}$ +23° (*c* 1·6). For $C_{31}H_{50}O_5$ (502·7) calculated: 74·06% C, 11·02% H; found: 73·87% C, 10·96% H.

B-Homo-5α-cholest-6-ene-3β,19-diol 3-Monoacetate (*VIIa*)

The epoxide *XXVII* (1·8 g) in acetic acid (40 ml) was treated with powdered zinc (9 g) at 100°C for 1 h. The mixture was cooled, inorganic material was filtered off, the filtrate was poured into water, the product was extracted with ether, the ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on a column of silica gel (100 g) with a mixture of light petroleum and ether (90 : 10). Corresponding fractions were collected and evaporated to yield the crude product (1·5 g), which on crystallization from methanol afforded *VIIa* (1·2 g), m.p. 105—107°C, $[\alpha]_D^{20}$ +48° (*c* 2·2). IR spectrum: 1033, 1247, 1736, 3025, 3640 cm^{-1}. ^{1}H-NMR spectrum: 0·69 (3 H, s, 18-H), 3·58 (1 H, d, J = 12 Hz, 19-H), 3·93 (1 H, d, J = 12 Hz, 19-H), 4·37 (1 H, m, W = 30 Hz, 3α-H), 5·33 (1 H, dd, J = 5·5 Hz, J' = 10 Hz, 6-H), 5·91 (1 H, m, W = 35 Hz, 7-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·12% C, 10·88% H.

3β,19-Dimethoxy-B-homo-5α-cholest-6-ene (*VIIb*)

The diol *VIId* (300 mg) in 1,2-dimethoxyethane (3 ml) was treated with sodium hydride (30 mg) and methyl iodide (0·1 ml) as given for *Vb*. The residue was chromatographed on a column of silica gel (30 g) using a mixture of light petroleum and benzene (60 : 40) as eluent. Corresponding fractions were collected and evaporated. The residue was crystallized from a mixture of chloroform and methanol to yield *VIIb* (180 mg), m.p. 89—90°C, $[\alpha]_D^{20}$ +25° (*c* 2·9). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 3·21 (3 H, s, CH_3O), 3·34 (6 H, s, 19-H and CH_3O), 3·00 (1 H, m, W = 30 Hz, 3α-H), 5·51 and 5·70 (2 H, m, W = 21 Hz and W = 25 Hz, 6-H and 7-H). For $C_{30}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 80·86% C, 11·53% H.

B-Homo-5α-cholest-6-ene-3β,19-diol 3,19-Diacetate (*VIIc*)

The alcohol *VIIa* (1 g) was dissolved in pyridine (10 ml) and treated with acetic anhydride (1 ml) at room temperature overnight. The mixture was decomposed with ice, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to afford *VIIc* (760 mg), m.p. 94—95°C, $[\alpha]_D^{20}$ +18° (*c* 4·3). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 1·99 (3 H, s, CH_3CO_2), 2·01 (3 H, s, CH_3CO_2), 4·17 (2 H, s, 19-H), 4·60 (1 H, m, W = 30 Hz, 3α-H), 5·20 (1 H, m, W = 22 Hz, 6-H), 5·70 (1 H, m, W = 30 Hz, 7-H). For $C_{32}H_{52}O_4$ (500·8) calculated: 76·75% C, 10·47% H; found: 76·41% C, 10·52% H.

B-Homo-5α-cholest-6-ene-3β,19-diol (*VIId*)

A solution of the diacetate *VIIc* (70 mg) in ether (5 ml) was treated with lithium aluminum hydride (20 mg) at room temperature overnight. The mixture was decomposed with water and the ethereal layer was worked up as usual. The residue was crystallized from aqueous methanol to give the diol *VIId* (36 mg), m.p. 185—186°C, $[\alpha]_D^{20}$ +21° (*c* 2·0). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·66% C, 11·94% H.

19-Methoxy-B-homo-5α-cholest-6-en-3β-ol 3-Acetate (*VIIe*)

The alcohol *VIIa* (200 mg) in 1,2-dimethoxyethane (5 ml) was treated with sodium hydride (20 mg) and methyl iodide (0·2 ml) as given for *Vb*. The residue was chromatographed on three preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (85 : 10 : 5) as eluent. The most lipophilic zone was separated, eluted with ether and the solvent was evaporated to yield the crude *VIIe* (51·4 mg) which on crystallization from a mixture of chloroform and methanol furnished *VIIe*, m.p. 143—145°C, $[\alpha]_D^{20}$ +28° (*c* 1·5). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 1·99 (3 H, s, CH_3CO_2), 3·22 (3 H, s, CH_3O), 3·35 (2 H, s, 19-H), 4·60 (1 H, m, W = 30 Hz, 3α-H), 5·20 (1 H, m, W = 22 Hz, 6-H), 5·70 (1 H, m, W = 32 Hz, 7-H). For $C_{31}H_{52}O_3$ (472·8) calculated: 78·76% C, 11·09% H; found: 78·55% C, 10·94% H. From the second zone, the dimethyl ether *VIIb* (42·7 mg) was isolated, m.p. 89—90°C. The third zone, after working up, afforded the diacetate *VIIc* (22·6 mg), m.p. 94—95°C. Elution of the fourth zone afforded the oily *VIIf* (80 mg).

3β-Methoxy-B-homo-5α-cholest-6-en-19-ol 19-Acetate (*VIIf*)

Elution of the fourth zone from the chromatography of the products of methylation of the alcohol *VIIa* and evaporation furnished the oily *VIIf* (80 mg), $[\alpha]_D^{20}$ +16° (*c* 5·1). ^{1}H-NMR spectrum: 0·64 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·10 (1 H, m, W = 30 Hz, 3α-H), 3·30 (3 H, s, CH_3O), 4·17 (2 H, s, 19-H), 5·25 (1 H, m, W = 22 Hz, 6-H), 5·65 (1 H, m, W = 32 Hz, 7-H). For $C_{31}H_{52}O_3$ (472·8) calculated: 78·76% C, 11·09% H; found: 78·50% C, 11·24% H.

B-Homo-5α-cholest-6-ene-3β,19-diol 19-Monoacetate (*VIIg*)

A mixture of the acetate *VIIc* (700 mg) and potassium hydroxide (200 mg) in methanol (15 ml) was refluxed for 30 min. The solvent was distilled off under reduced pressure, the residue was treated with ether and water, the ethereal solution was washed with water, dried and evaporated. The residue was crystallized from aqueous methanol to give the alcohol *VIIg* (590 mg), m.p. 105 to 107°C, $[\alpha]_D^{20}$ +23°. ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·50 (1 H, m, W = 30 Hz, 3α-H), 4·16 (2 H, brd s, 19-H), 5·22 (1 H, m, W = 22 Hz, 6-H), 5·80 (1 H, m, W = 30 Hz, 7-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·39% C, 10·86% H.

6α,7α-Epoxy-B-homo-5α-cholestane-3β,19-diol 3,19-Diacetate (*VIIIc*)

The olefin *VIIc* (500 mg) in benzene (10 ml) was treated with monoperoxyperphthalic acid in ether (5 ml, 90 mg/ml) at room temperature for 5 h. The mixture was diluted with ether, the ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was crystallized from aqueous methanol to yield *VIIIc* (440 mg), m.p. 149—150°C, $[\alpha]_D^{20}$ +24° (*c* 1·9). For $C_{32}H_{52}O_5$ calculated: 74·38% C, 10·14% H; found: 74·19% C, 10·07% H.

6β,19-Epoxy-7α-bromo-5α-cholestan-3β-ol 3-Acetate (*IXc*)

A mixture of lead tetraacetate (7 g) and calcium carbonate (3·5 g) in benzene was refluxed for 1 h. The bromohydrin *XXIII* (3·5 g) and iodine (3·5 g) were added and the mixture was refluxed for 40 min. The inorganic material was filtered off, the filtrate was diluted with ethyl acetate and water, the organic layer was washed with water, a 10% aqueous sodium thiosulfate solution, dried and the solvent was evaporated. The residue (2·1 g) was crystallized from a mixture of acetone, methanol and water to yield *IXc* (1·9 g), m.p. 129—130°C, $[\alpha]_D^{20}$ —66° (*c* 2·7). IR spectrum: 1038, 1246, 1737 cm^{-1}. ^{1}H-NMR spectrum: 0·73 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 3·77 and 4·05 (two m, 6α-H, 7β-H and 19-H), 4·70 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{29}H_{47}BrO_3$ (523·6) calculated: 66·52% C, 9·05% H, 15·26% Br; found: 66·39% C, 8·81% H, 15·47% Br.

3β,19-Diacetoxy-6β-bromo-B-homo-5α-cholestan-7-one (*XVII*)

The bromohydrin *XVIc* (10 mg) was dissolved in acetone (3 ml) and treated with Jones' reagent at room temperature for 3 min. The excess of reagent was decomposed with methanol, the mixture was diluted with ether and water, the ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and the solvent was evaporated. The residue was chromatographed on one silica gel plate (7 × 10 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zone was separated, washed with ether and the filtrate was evaporated to yield the oily *XVII* (8 mg), $[\alpha]_D^{20}$ —11° (*c* 0·7).

3β,19-Diacetoxy-B-homo-5α-cholestan-7-one (*XVIII*)

The bromo ketone *XVII* (6 mg) was dissolved in a mixture of ether (2 ml) and acetic acid (0·2 ml), powdered zinc (20 mg) was added and the mixture was stirred at room temperature for 10 h. The inorganic material was filtered off, washed with ether and the filtrate was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and the solvent was evaporated. The residue was chromatographed on a silica gel plate (7 × 10 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zone was collected, eluted with ether and evaporated to yield the oily *XVIII* (4 mg).

7α-Bromo-5α-cholestane-3β,6β-diol 3-Monoacetate (*XXIII*)

The olefin[50] *XXI* (17 g) was dissolved in dioxane (1·7 l), water (27 ml) was added and the mixture was treated with 9% perchloric acid (15·3 ml) and N-bromoacetamide (6·38 g). The mixture was stirred at room temperature for 2 h, then diluted with water, the product was taken up in ether, the ethereal solution was washed with water, saturated aqueous potassium hydrogen carbonate solution, water, dried and the solvent was evaporated. The residue was chromatographed on a column of silica gel (200 g) using a mixture of light petroleum and ether (2 : 1). Corresponding fractions were collected and evaporated. The residue was crystallized from methanol to yield *XXIII* (8·42 g), m.p. 183—185°C, $[\alpha]_D^{20}$ —24° (*c* 1·2). IR spectrum: 1030, 1245, 1266, 1714 sh, 1721 sh, 1738, 3625 cm^{-1}. ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 1·03 (3 H, s, 19-H), 1·99 (3 H, s, CH_3CO_2), 3·91 (1 H, m, $W = 14$ Hz, 6α-H), 4·17 (1 H, dd, $J = 2·5$ Hz, $J' = 2·5$ Hz, 7β-H), 4·76 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{29}H_{49}BrO_3$ (525·6) calculated: 66·27% C, 9·40% H, 15·20% Br; found: 65·98% C, 9·38% H, 15·49% Br.

6α-Bromo-7β,19-epoxy-B-homo-5α-cholestan-3β-ol 3-Acetate (*XXVII*)

A mixture of lead tetraacetate (7·7 g) and calcium carbonate (3·85 g) in benzene (110 ml) was refluxed for 80 min. A solution of the bromohydrin[49] *XXVI* (3·85 g) in benzene (400 ml) and crystalline iodine (3·85 g) were added and the mixture was then refluxed for 90 min. The inorganic material was filtered off, the filtrate was diluted with water, the product was extracted with benzene, the organic layer was washed with water, a 10% aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was chromatographed on a column of silica gel (150 g) using a mixture of light petroleum and ether (90 : 10) as eluent. Corresponding fractions were collected and evaporated to yield the oily *XXVII*, $[\alpha]_D^{20}$ +3° (*c* 1·3). IR spectrum: 1025, 1036, 1071, 1245, 1742 cm^{-1}. ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 3·66 (2 H, m, 19-H), 4·02 (2 H, m, 6β-H and 7α-H), 4·88 (1 H, m, W = 30 Hz, 3α-H). For $C_{30}H_{49}BrO_3$ (537·6) calculated: 67·02% C, 9·19% H, 14·86% Br; found: 67·14% C, 9·18% H, 15·02% Br.

The analyses were carried out in the Analytical Laboratory of this Institute (under the direction of dr J. Horáček). The IR spectra were recorded by Mrs K. Matoušková and Mr P. Formánek and interpreted by Dr S. Vašíčková. ^{1}*H-NMR spectra were recorded by Mrs J. Jelínková and Mrs M. M. Snopková and interpreted by Dr M. Synáčková. The mass spectra were recorded and interpreted by Dr F. Tureček, J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Prague.*

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