NEIGHBORING GROUP PARTICIPATION IN HYPOBROMOUS ACID ADDITION TO 19-SUBSTITUTED 5α-CHOLEST-1-ENES AND IN ACID CLEAVAGE OF THEIR EPOXY ANALOGS*

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Reactions of the title compounds (bearing an OH, OCH_3 or $OCOCH_3$ group at $C_{(19)}$) involve $5(O)^n$, $7(O)^{\pi,n}$-participation by the 19-substituent or attack by an external nucleophile. The $6(O)^{\pi,n}$-participation does not occur. The behavior of 1,2-unsaturated (or epoxidated) compounds has been compared with the earlier described 2,3-unsaturated or epoxidated analogs. The 1,2-type is generally less prone to participation. The reasons for this behavior are discussed.

As part of an investigation concerned with neighboring group participation in 19-substituted steroids we previously studied[1-3] the behavior of 2,3-unsaturated steroids of this type in the course of hypobromous acid additions. Reactions of the intermediary 2α,3α-bromonium ion with a competing internal or external nucleophile were found to be analogous to those of 2α,3α-epoxides which we investigated in a separate study[4].

In the present paper we report such reactions of 19-substituted 1,2-unsaturated steroids *Ia*–*Ic* and corresponding 1α,2α-epoxides *IIa*–*IIc* and compare them with the earlier results. This comparison was though to bring useful information for the following reasons. First, the 1,2- and 2,3-isomers show differences in the shape of the A-ring and in distances between the potential reaction centers and the 19-substituent. Second, certain reaction mechanisms are principally possible in only one structural type. Thus, for instance, intramolecular attack by the carbonyl oxygen of the 19-acetoxy group under formation of a six-membered cyclic intermediate, *i.e.* a $6(O)^{\pi,n}$-participation (for notation see ref.[3]), can only be considered for 1α,2α-bromonium ions or 1α,2α-epoxides, not for their 2α,3α-analogs. It was of interest how these different factors would be reflected in the reaction mechanism.

The compounds used in this investigation were unsaturated substances *Ia*–*Ic* and the related 1α,2α-epoxides *IIa*–*IIc*. The compound *Ia* (ref.[5]) served for preparation of all these models. The methyl ether *Ib* was prepared from *Ia* by methylation with methyl iodide in the presence of sodium hydride, the acetyl derivative *Ic* by the acetic anhydride–pyridine method. Epoxidation of the 19-acetoxy derivative *Ic*

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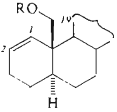
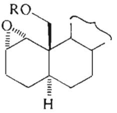
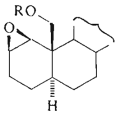
proceeds stereospecifically to give the 1α,2α-epoxide *IIc*. Its alkaline hydrolysis furnished the 19-hydroxy-1α,2α-epoxide *IIa* possessing no intramolecular hydrogen bridge (IR-spectrum). On the other hand, epoxidation of the free hydroxy derivative *Ia* yields mainly the β-epoxide *IIIa*. In its IR-spectrum are present two bands (at 3 611 and 3 543 cm^{-1}) corresponding to two possible conformations of the 19-hydroxyl bonded by the hydrogen bridge to the epoxide oxygen. Acetylation of *IIIa* gives the compound *IIIc*. Epoxidation of the methyl ether *Ib* yields predominantly the 1α,2α-epoxide *IIb*.



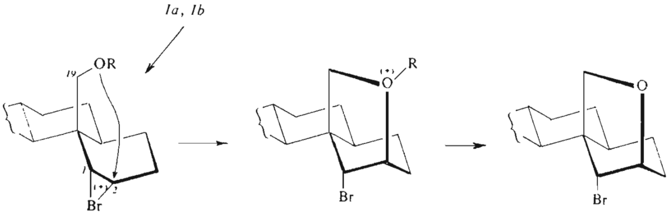
Ia, R = H
Ib, R = CH_3
Ic, R = Ac



IIa, R = H
IIb, R = CH_3
IIc, R = Ac



IIIa, R = H
IIIb, R = CH_3
IIIc, R = Ac



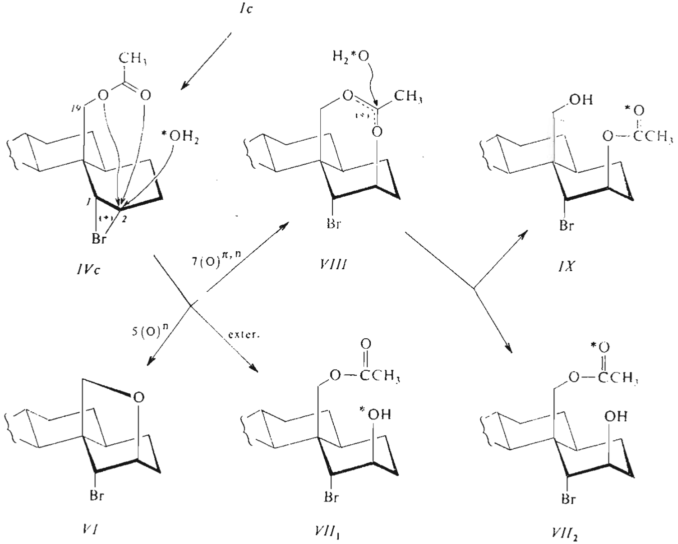
IVa, R = H
IVb, R = CH_3

Va, R = H
Vb, R = CH_3

VI

Reaction of *Ia* with hypobromous acid gives the known[5] bromo epoxide *VI* in practically quantitative yield. Similarly, on treatment with hypobromous acid, the methyl ether *Ib* yields the same 2β,19-epoxy derivative *VI* as the sole product.

The acetyl derivative *Ic* reacts with hypobromous acid to form three products. One of them is identical with the compound *VI*. The remaining two substances (*VII* and *IX*) are positionally isomeric acetyl derivatives of the same bromohydrin since acetylation converts them to the diacetyl derivative *XVI*. Position 2 of the secondary hydroxyl in the compound *VII* follows from the IR-spectrum of its oxidation product *XVII* showing the presence of one methylene group flanked to a keto group. The axial conformation of the two A-ring substituents in the product *VII* is obvious from the width of signals associated with $C_{(1)}$ and $C_{(2)}$-protons (Table I). Further confirmation of the structure is the preparation of compound *VII* by cleavage of the 1β,2β-epoxide *IIIc* with hydrobromic acid. The structure of *IX* follows from the above evidence and from ^1H NMR spectral properties proving the presence of a hydroxyl group in position 19. Due to coupling with the OH proton, the signal of the 19-protons appears as a multiplet convertible into two characteristic doublets on treatment with trichloroacetyl isocyanate (Table I).



Reaction of the hydroxy epoxide *IIa* with perchloric acid results in the preponderant formation of a cyclic ether *X* along with a small amount of the triol *XIa*. The structure of *X* is based on spectral data. Thus, the IR-spectrum demonstrates the presence of both hydroxyl and epoxide functions (3 635, 1 111, 1 090, 1 031, 1 016, 978, 965, 902, 890 cm^{-1}) while the ^1H NMR spectrum is also in conformity with the structural and steric features of the formula *X* (Table I).

The methoxy epoxide *IIb* reacts with perchloric acid to give preponderantly the cyclic ether *X*. The minor product is the diol *XIb*. Spectral evidence proves in *XIb* the presence of functional groups. Thus, the IR-spectrum shows characteristic bands

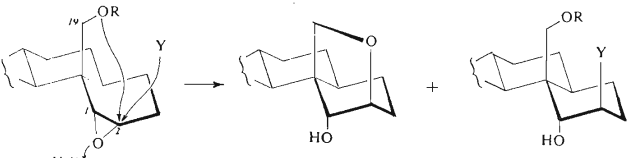
TABLE I

^{1}H NMR data of the products of hypobromous acid addition to the olefins *Ia*–*Ic* and of cleavage products of the epoxides *IIa*–*IIc*

Compound	19-H (J_{gem})[a]	1-H (W or J)[a]	2-H (W)	Other
VII	4·47 d, 4·68 d, J = 12	4·72 m, W = 9	4·39 m, W = 12	2·08 s ($OCOCH_3$)
	4·30 d, 4·79 d, J = 12[b]	4·70 bs, W = 8	5·35 m, W = 11	2·05 s ($OCOCH_3$)
IX	3·99 bd, W = 17	4·83 bs	5·28 m, W = 14	2·06 s ($OCOCH_3$)
	4·51 d, 4·84 d, J = 19[b]	4·85 bd	5·28 m, W = 14	1·95 s ($OCOCH_3$)
X	3·75 d, 3·92 d, J = 9	4·13 m, W = 22		
	3·80 d, 3·97 d, J = 9[b]	5·25 d, $J_{1,2}$ = 6	4·35 m, W = 14	
XIb	3·48 d, 3·80 d, J = 10	4·07 m, W = 8	4·23 m, W = 10	3·32 s (OCH_3)
	3·53 d, 3·83 d, J = 9[b]	5·75 d, $J_{1,2}$ = 4	5·10 m, W = 13	3·22 s (OCH_3)
XIc	4·48 d, 4·59 d, J = 11·8[c]	4·14 dd, $J_{1,2}$ = 3·2 $J_{1,OH}$ = 5·2	4·01 m, W ~ 10	2·07 s ($OCOCH_3$)
	4·19 d, 5·05 d, J = 11·8[b,c]	5·37 d, $J_{1,2}$ = 3·2	5·06 m, W = 8·5	2·12 s ($OCOCH_3$)
XIIb	3·65 d, 3·87 d, J = 10	4·38 m, W = 16		3·23 s (OCH_3)
	3·80 bs,[b]	5·65 d, $J_{1,2}$ = 3	4·38 m, W = 10	3·27 s (OCH_3)
XIIc	4·42 d, 4·67 d, J = 12	4·37 m		2·06 s ($OCOCH_3$)
	4·57 bs[b]	5·60 d, $J_{1,2}$ ~ 2·5	4·36 m, W = 12	2·10 s ($OCOCH_3$)
XIV	3·96 m[c]	4·26 dd, $J_{1,2}$ = 3·2 $J_{1,OH}$ = 5·2	4·97 m, W = 8·8	2·08 s ($OCOCH_3$)
	4·63 d, 4·68 d, J = 11·8[b,c]	5·48 d, $J_{1,2}$ = 3·2	5·03 m, W = 8·5	2·00 s ($OCOCH_3$)

[a] Values in Hz; [b] values obtained with trichloroacetyl isocyanate; [c] measured on Varian XL 200.

of hydroxy and methoxy groups (3 635, 1 031, 956 cm^{-1} (OH); 2 820, 1 105, 1 096 cm^{-1} (OCH_3)). The location and axial conformation of the hydroxy groups at $C_{(1)}$ and $C_{(2)}$ follows, after treatment with trichloroacetyl isocyanate, from the characteristic doublet of 1β-H and a multiplet of 2α-H in ^1H NMR spectrum (Table I).



IIa, R = H
IIb, R = CH_3

X

XIa, R = H, Y = OH
XIb, R = CH_3, Y = OH
XIIb, R = CH_3, Y = Br

Reaction of the 19-acetoxy epoxide *IIc* with aqueous perchloric acid yields three compounds (Table II), two of them being triol monoacetates, the third being a triol (*XIa*, *XIc*, *XIV*). The IR spectrum reveals the presence of an intramolecular hydrogen bridge along with a free hydroxyl (3 548, 3 634 cm^{-1}) in the triol *XIa*. All three products give identical triacetyl derivative *XV* on acetylation. Distinction between the monoacetates makes possible their ^1H NMR spectra. Characteristic shifts of the signals of 1-H and 2-H after reaction with trichloroacetyl isocyanate show that both hydroxyls in the substance *XIc* are secondary. The axial character of the hydroxyl

TABLE II

Yields of products of cleavage of epoxides *IIa*—*IIc*

Starting compound	Neighboring group	Reagent	Mode of reaction, % of the total yield			Total yield, %
			$5(O)^n$	external	other	
IIa	OH	$HClO_4$	81 (*X*)	13 (*XIa*)	~ 6[a]	70
IIb	OCH_3	$HClO_4$	70 (*X*)	30 (*XIb*)		99
IIb	OCH_3	HBr	—	100 (*XIIb*)		86
IIc	$OCOCH_3$	$HClO_4$	—	9 (*XIa*)[b] 77 (*XIc*)[b]	15 (*XIV*)	91
IIc	$OCOCH_3$	HBr	—	100 (*XIIc*)		98

[a] Unidentified; [b] the $7(O)^{\pi,n}$-mechanism is also possible.

groups is shown by the low value of the coupling constant (for 1-H) or of the signal width (for 2-H). The acetoxy group is thus present in position 19, this being in accord with the presence of two doublets for the 19-protons with $J = 11{\cdot}8$ Hz (Table I). In *XIV* the axial hydroxyl is in position 1 as evident from the value of the coupling constant and from a characteristic shift toward the low field after treatment with trichloroacetyl isocyanate. The presence of an axial acetoxy group at position 2 is demonstrated by the width of the multiplet of 2-H and by the practically unchanged position of this signal after the reaction with trichloroacetyl isocyanate. Therefore, the remaining hydroxyl has to be located in position 19. Accordingly, the signal of the 19-protons appears as a mutiplet owing to coupling with the proton of the 19-hydroxyl. As expected, after treatment with trichloroacetyl isocyanate this multiplet is converted into two doublets with a characteristic coupling constant (Table I).

Reaction of the epoxide *IIb* with hydrobromic acid provides the bromohydrin *XIIb* quantitatively. Its structure is corroborated by spectroscopic evidence (IR-spectrum: 3 628 cm^{-1} (OH); 2 815, 1 117 cm^{-1} (OCH_3) and ^1H NMR spectrum (Table I).

Reaction of the epoxide *IIc* with hydrobromic acid gives the bromohydrin *XIIc* in which the axial conformation of both functional groups in the A-ring is demonstrated by the ^1H NMR spectrum (Table I). Oxidation by Jones' reagent converts *XIIc* to the bromo ketone *XVIII* in which the ^1H NMR spectrum shows the presence of the CHBr multiplet ($W \sim 7$) in accord with the 2-position of the bromine atom. The structure *XVIII* is corroborated by the IR spectrum since the substance does not contain a $COCH_2$ group. The axial conformation of the bromine atom in *XVIII* is proved by both the IR ($\nu(CO) = 1\,710\ cm^{-1}$) and CD-spectrum ($\Delta\varepsilon_{312} = -4{\cdot}69$). For comparison, we converted *XVIII* into 1-ketone *XIX* which exhibits a CD-spectrum ($\Delta\varepsilon_{304} = -0{\cdot}32$) practically identical with that of 5α-cholestan-1-one ($\Delta\varepsilon_{300} = -0{\cdot}39$)[6] thus showing that the presence of the acetoxy group does not affect the value of CD.

The results of hypobromous acid treatment of olefins *Ia*–*Ic* show that all products are derived from the 1α,2α-bromonium ions while no product of the 1β,2β-diastereoisomer can be found. This is a close analogy to the behavior of 2,3-unsaturated compounds[1-3].

The extent of neighboring group participation is dependent on the substituents in the order established earlier[3,7]: OH > OCH_3 > $OCOCH_3$ (Table III). The $5(O)^n$-participation is quantitative for *Ia* and nearly so for *Ib*; in the latter case a trace amount of a side product indicates the possibility of negligible external attack. For *Ia* and *Ib*, 19-group participation can only proceed by the $5(O)^n$-mechanism (we do not consider the $4(O)^n$-pathway). For *Ic* with its less reactive, ambident acetoxy group, both $5(O)^n$ and $7(O)^{\pi,n}$-mechanisms may be considered. The product analysis shows that the respective products *VI* and *IX* are indeed formed; the $5(O)^n$-route prevails. The possibility of acetoxyl migration in *VII* to form *IX* was ruled out by a blank experiment showing that the compound *VII* remains unchanged on treatment for 30 min with 10% perchloric acid in dioxane solution.

The presence of *VII* may be due either to an external attack of the bromonium ion *IVc* by water or to $7(O)^{\pi,n}$-participation involving conversion of the intermediate *VIII* not to *IX* but to *VII*. Which of these alternative routes is responsible for the formation of *VII* can be decided by means of tracer experiments. If participation by the 19-acetoxy group were the reaction route, the intermediary cation *VIII* would be attacked by a water molecule to form either *IX* or *VII* with the oxygen atom from water being incorporated into the acetoxy group (VII_2). If the compound *VII* were formed from the bromonium ion *IVc* by the external attack of water, the oxygen atom from water would be incorporated into the 2β-hydroxyl group (VII_1). The reaction of *Ic* with hypobromous acid in the presence of $H_2{}^{18}O$ was followed by mass spectrometric analysis of the product *VII*. The mass spectrum contains the following ions (m/z): 524–526 ($M^{+\bullet}$), 506–508 ($M-H_2O$), 493–495 ($M-CH_2OH$), 464–466 ($M-AcOH$), 427 ($M-Br-H_2O$), 384 ($M-AcOH-HBr$), 367 ($M-H_2O-AcOH-Br$), 355 and lower m/z. The content of ^{18}O was determined in the ions ($M-H_2O$), ($M-AcOH$) and $M^{+\bullet}$. The content of the label in $M^{+\bullet}$ does not change in the course of evaporation and amounts to 18·2 ± 1·0% of ^{18}O. The content in the ions ($M-H_2O$) rises from 4·0 ± 0·3% of ^{18}O at the start to 10·1 ± 0·1% of ^{18}O at the end of evaporation. The content in the ions ($M-AcOH$) drops from 6·7 ± 0·1% to 5·9 ± 0·1% of ^{18}O. As regards the content of ^{18}O, the ions $M-H_2O$) and ($M-AcOH$) are complementary so that the unduly large loss must be due to transesterification. The transesterification is both intra- and intermolecular since ions corresponding to diacetate (m/z 566–568 and diol (m/z 482–484) are both present

TABLE III

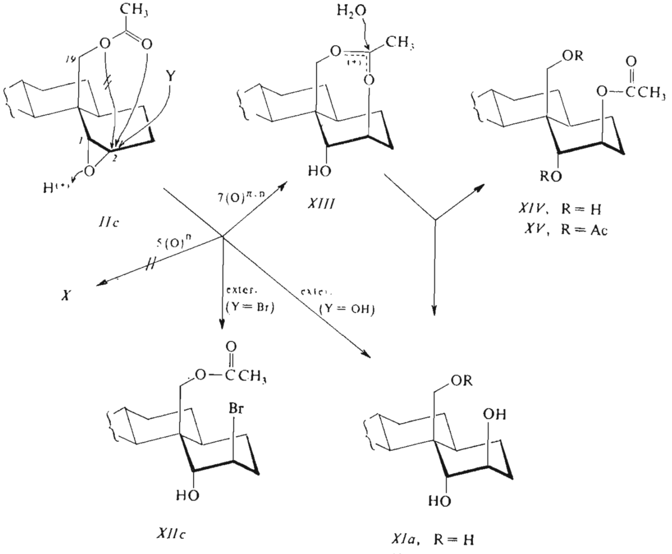
Yields of products of hypobromous acid addition to the olefins *Ia*–*Ic*

Starting compound	Neighboring group	Mode of reaction, % of the total			Total yield, %
		$5(O)^n$	external	$7(O)^{\pi,n}$	
Ia	OH	99 (*VI*)	–	–	91
Ib	OCH_3	97 (*VI*)	3[a] (?)	–	94
Ic	$OCOCH_3$	42 (*VI*)	43 (*VII*)[b]	15 (*IX*)	86

[a] Unidentified; [b] formed mainly by external attack ($\geqq 33\%$; the rest of $\leqq 10\%$ is due to $7(O)^{\pi,n}$-participation).

in the spectrum. The transesterification is incomplete at the beginning (58·9% retention of the label) and in the course of evaporation more of the second isomer is formed (88·5% of the label)). In view of different (and unknown) loss of water and acetic acid from the monoacetates, the mutual proportion of which is also unknown, exact distribution of the label between acetyl and hydroxyl cannot be established. Under the assumption that the label in the hydroxyl does not migrate, the values measured at the beginning of the evaporation permit the conclusion that at least 78% of ^{18}O is contained in the hydroxyl group. This value represents the lower limit and the real figure depends on the contribution of the rearranged isomer to the total intensity of the ions $(M - H_2O)$. Thus, most of the product *VII* is formed by external attack.

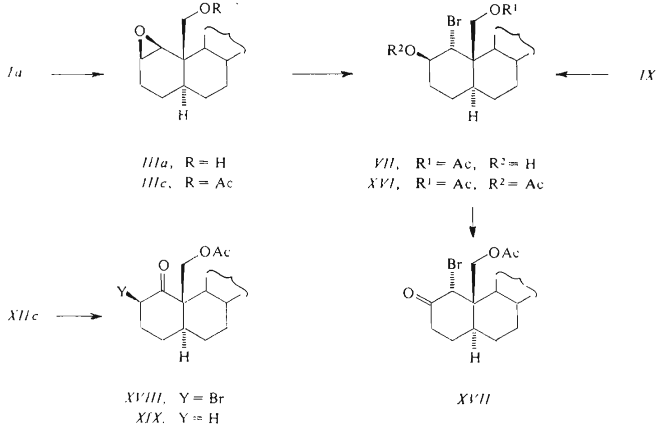
Following our earlier[4] approach, we investigated the behavior of the epoxides *IIa*, *IIb* and *IIc* towards strong acids represented by perchloric (weak nucleophile) and hydrobromic acid (strong nucleophile). Depending on the functional group, the tendency to participate decreases in the above mentioned order. It is obvious from Table II that with perchloric acid, participation by the 19-substituent largely predominates in *IIa* and *IIb*; the only possible participation mechanism for these



compounds is the $5(O)^n$-process. In *IIc*, the $5(O)^n$-mechanism does not work at all and only formation of *XIV* is unequivocally attributable to a specific mechanism *i.e.* $7(O)^{\pi,n}$-participation. Formation of *XIa* and *XIc* (major product of the reaction) may be due both to external attack by water or to $7(O)^{\pi,n}$-participation. It is extremely likely from the analogy to unsaturated compounds that formation of *XIa* and particularly of *XIc* is largely due to an external attack.

Finally, reaction of hydrobromic acid was applied to *IIb* and *IIc*. Attack by an external nucleophile was the only reaction occurring under these conditions; the bromohydrins *XIIb,c* are thus formed.

The 1,2-unsaturated compounds and 1,2-epoxy derivatives are less prone to neighboring group participation than their 2,3-counterparts. For understanding this difference it has to be realized that both $5(O)^n$- and $7(O)^{\pi,n}$-participations are involved, the first being quantitatively more important while the second is operative to a lesser extent; both these mechanisms should be considered separately. Generally, the conditions for $5(O)^n$-participation are more favorable for 2,3-derivatives. This is due to a smaller distance of the attacking oxygen from the reaction center in 2,3- than in 1,2-compounds. The Dreiding models show for the half-chair conformation of the A-ring that this distance is *c.* 2·5 and 3·0 . 10^{-10} m for 2,3- and for 1,2-compounds, respectively. Moreover, the angle of approach in 2,3-compounds is smaller (~15°) than in 1,2-isomers (~30°). Our observations are completely in accord



Ia → *IIIa*, R = H; *IIIc*, R = Ac → *VII*, R^1 = Ac, R^2 = H; *XVI*, R^1 = Ac, R^2 = Ac ← *IX*

VII → *XVII*

XIIc → *XVIII*, Y = Br; *XIX*, Y = H

with this reasoning. Due to the ambident character of the acetoxy group, either $5(O)^{n}$ or $7(O)^{\pi,n}$-participation is principally possible in 19-acetoxy derivatives. For $7(O)^{\pi,n}$-participation by the acetoxy group the Dreiding models show that the carbonyl oxygen can adopt a position favorable for an attack at the reaction center at $C_{(2)}$ equally well in both the 1,2- and 2,3-unsaturated (or epoxidated) compounds due to the flexibility of the entire 19-substituent. In spite of this equality the contribution of $7(O)^{\pi,n}$-participation relative to the external attack is considerably lower for the 1,2-unsaturated 19-acetoxy derivative *Ic* than for its 2,3-isomer. In the case of *Ic* the relation ($7(O)^{\pi,n}$-participation: external attack) is *c*. 25 : 33 (Table I) whereas in the 2,3-unsaturated isomer it is 10 : 2 (ref.[7]). This behavior is conceivable since in the 1,2-olefin the $C_{(2)}$-reaction center is more accessible to attack by an external nucleophile from the β-side than in the 2,3-unsaturated analog; this is due to the suitably shaped A-ring in the compound *Ic* where the approaching external nucleophile is subject to lesser steric hindrance by the 19-substituent than in the 2,3-olefin.

Still another aspect emerges from the comparison of 1,2- with 2,3-unsaturated or epoxidated compounds. Whereas for the latter compounds, studied earlier[1-4] in this laboratory, the $6(O)^{\pi}$-^{n}participation by the 19-acetoxy group is not possible for structural reasons, it may be taken into consideration for the 1,2-unsaturated compound *Ic* (or 1,2-epoxide *IIc*). In the cases investigated earlier, the $6(O)^{\pi,n}$-participation appeared as a route preferred to $5(O)^{n}$ or $7(O)^{\pi,n}$ mechanisms when alternative pathways were possible[8]. With *Ic* or *IIc* the $6(O)^{\pi,n}$-participation should lead to diequatorial cleavage of the oxirane or bromonium ion ring. Such a reaction course would violate the Fürst–Plattner rule (without being supported by any other influence) and we did not observe any indication of it.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 40—60°C/26 Pa (0·2 Torr). Optical activity 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 stated otherwise. 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 CD spectra were recorded on a Dichrographe II (Jouan–Roussel) in dioxane. Mass spectra were measured on a Jeol JMS-100 apparatus at 75 eV. The samples were introduced by direct inlet at 150—160°C from an open glass capillary tube. The ^{18}O content of the compounds was determined by mass spectrometry. The intensities of ion species were recorded at a constant total ion current and scan rate of 60 min/mass decade. The intensity values were corrected for a natural abundance of ^{13}C, ^{2}H and ^{18}O isotopes. The correcting factors were taken from the mass spectra of the corresponding unlabeled compounds. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography (TLC) and by infrared spectra. Usual workup of a 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 *Ia*, *Ib* and *Ic*

The unsaturated compound (200 mg) 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) for 45 min at room temperature. The mixture was diluted with water and the product extracted with ether. The solution was washed with water several times, with a 5% aqueous potassium hydrogen carbonate solution, aqueous sodium thiosulfate solution, water, then dried with sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on four preparative silica gel plates (20 × 20 cm) using a mixture of heptane–ether (4 : 1). Corresponding fractions were collected, eluted with ether and the solvent was evaporated ***in vacuo***. The yields of the products are given in Tables II and III, their analytical and physical data in Table IV. ^{1}H NMR data in Table I.

TABLE IV

Analytical and physical data of products

Compound	Formula (m.w.)	Calculated/Found			M.p., °C $[\alpha]_D^{20}$ (CHCl$_3$)
		% C	% H	% Br	
VI	$C_{27}H_{45}BrO$	69·65	9·74	17·16	97–98·5[a]
	(465·5)	69·75	9·54	17·68	+70°
VII	$C_{29}H_{49}BrO_3$	66·26	9·39	15·20	94–99; 129–131[b]
	(525·6)	66·69	9·54		+44°
IX	$C_{29}H_{49}BrO_3$	66·26	9·39	15·20	119–121[c]
	(525·6)	66·61	9·42		+16°
X	$C_{27}H_{46}O_2$	80·54	11·52	—	164–164·5[b]
	(402·6)	80·68	11·36	—	+42°
XIa	$C_{27}H_{48}O_3$	77·09	11·50	—	188–189[d]
	(420·6)	76·69	11·30	—	
XIb	$C_{28}H_{50}O_3$	77·36	11·59	—	124–125[a]
	(434·7)	77·17	11·47	—	+22°
XIc	$C_{29}H_{50}O_4$	75·28	10·89	—	79–82[c]
	(462·7)	75·19	10·88	—	+22°
XIIb	$C_{28}H_{49}BrO_2$	67·58	9·92	16·06	137–138[c]
	(497·6)	67·90	9·96	16·66	+20°
XIIc	$C_{29}H_{49}BrO_3$	66·26	9·39	15·20	163–164·5[e]
	(525·6)	66·42	9·16	15·50	+14°
XIV	$C_{33}H_{54}O_6$	72·48	9·96	—	186–187[c]
	(546·8)	72·31	9·88	—	+11°

[a] Acetone; [b] heptane; [c] aqueous acetone; [d] acetone–light petroleum; [e] chloroform–heptane.

Addition of Labeled Hypobromous Acid to the Compound *Ic*

The unsaturated compound *Ic* (100 mg) was dissolved in dioxane (2 ml), water (0·2 ml) containing 22% of $H_2{}^{18}O$ was added and the mixture was treated with 70% aqueous perchloric acid (*c.* 0·01 ml) and N-bromoacetamide (40 mg) at room temperature for 30 min. The mixture was diluted with ether and water, the ethereal phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, 5% aqueous sodium thiosulfate, water, dried and the solvent was evaporated. The residue was chromatographed on two preparative silica gel plates (20 × 20 cm) with a mixture of light petroleum, ether and acetone (90 : 5 : 5) as given for unlabelled compounds above.

Cleavage of Epoxides *IIa*, *IIb* and *IIc*

The epoxide (200 mg) was dissolved in dioxane (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% aqueous hydrobromic acid (0·5 ml) at room temperature for 30 min. The mixture was diluted with ether, the solution washed several times with water, sodium hydrogen carbonate and water, dried with sodium sulfate and the solvent was removed *in vacuo*. The residue was chromatographed on four preparative silica gel plates (20 × 20 cm) using a mixture of benzene and ether (1 : 1) for development. Corresponding fractions were collected, eluted with ether and the solvent was evaporated *in vacuo*. The yields of products are given in Table II, their analytical and physical data in Table IV, ^1H NMR data in Table I.

19-Methoxy-5α-cholest-1-ene (*Ib*)

The hydroxy derivative *Ia* (400 mg) was dried azeotropically with benzene, dissolved in tetrahydrofuran (10 ml) (distilled over $LiAlH_4$) and a suspension of sodium hydride (200 mg) in light petroleum was added under argon. The mixture was stirred with a magnetic stirrer, methyl iodide (2 ml) was added dropwise and the mixture was stirred at 60°C for 2 h. An additional 2 ml of methyl iodide was added and stirring continued for a further 2 h. After standing overnight, the mixture was diluted with moist ether and the solution washed with water, 5% hydrochloric acid, sodium hydrogen carbonate, sodium thiosulfate solution and water. Evaporation provided an oily residue which was purified by chromatography on a column of silica gel. Light petroleum eluted the methyl ether *Ib* (340 mg) which was crystallized from acetone to give the pure product (290 mg), m.p. 87—88°C, $[\alpha]_D$ −21°C (*c* 1·4). ^1H NMR spectrum: 3·27 (3 H, s, OCH_3), 3·33 (1 H, d, $J = 10$ Hz, 19-H), 3·55 (1 H, d, $J = 10$ Hz, 19-H), 5·80 (2 H, m, $W = 10$ Hz, 1 H and 2 H). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·08% H; found: 83·53% C, 12·08% H.

5α-Cholest-1-en-19-ol 19-Acetate (*Ic*)

5α-Cholest-1-en-19-ol[5] (*Ia*, 410 mg) was acetylated with acetic anhydride (1 ml) in pyridine (3 ml) by standing overnight at room temperature. Usual working up gave the acetate *Ic* (430 mg, oil), $[\alpha]_D$ −28° (*c* 1·1). For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·28% H; found: 80·94% C, 11·41% H.

1α,2α-Epoxy-5α-cholestan-19-ol (*IIa*)

The epoxide *IIc* (60 mg) was dissolved in a mixture of methanol (8 ml) and benzene (0·2 ml), a solution of potassium hydroxide (100 mg) in methanol (1 ml) and water (0·1 ml) was added and the course of hydrolysis was monitored by TLC. After 1 h, when most of the starting compound was converted to the more polar hydroxy derivative but the amount of the (less and more polar) by-products was increasing, the mixture was poured into water and the product extracted with ether. After washing with water and removal of the solvent, the residue was purified by TLC on one silica gel plate using a mixture of benzene and ether (4 : 1) for development. The product (25 mg) was repeatedly crystallized from n-heptane to yield the hydroxy derivative *IIa* (23 mg), m.p. 108—110°C, $[\alpha]_D$ +7° (*c* 1·1). IR spectrum: 1 040, 3 639 cm^{-1} (CH_2OH). No hydrogen bridge is present. For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·56% C, 11·65% H.

1α,2α-Epoxy-19-methoxy-5α-cholestane (*IIb*)

The methoxy derivative *Ib* (330 mg) and *m*-chloroperoxybenzoic acid (170 mg) in chloroform (6 ml) were kept at 5°C for 24 h. The mixture was then diluted with ether, washed with sodium thiosulfates, sodium hydrogen carbonate and water. Evaporation of the solvent yielded the mixture of products which was chromatographed on a silica gel (15 g) column. Light petroleum–benzene (9 : 1) separated the less polar component (190 mg) which was crystallized from acetone to give the epoxide *IIb* (160 mg), m.p. 70—71°C, $[\alpha]_D$ —6° (*c* 1·4). ^1H NMR spectrum: 0·70 (3 H, s, 18-H), 3·27 (2 H, m, 1β-H and 2β-H), 3·33 (3 H, s, OCH_3), 3·61 (2 H, bs, 1-H). For $C_{28}H_{48}.O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·53% C, 11·61% H.

1α,2α-Epoxy-5α-cholestan-19-ol Acetate (*IIc*)

The acetyl derivative *Ic* (135 mg) was treated with *m*-chloroperoxybenzoic acid (70 mg) in chloroform (2 ml) at 5°C. After 3 h the mixture was diluted with ether, washed with potassium carbonate, water, and the solvent removed *in vacuo*. The residue (120 mg) was crystallized from methanol to yield the product *IIc* (102 mg), m.p. 81—82°C. Recrystallization from the same solvent provided the analytical sample, m.p. 82—82·5°C, $[\alpha]_D$ —12° (*c* 1·5). IR spectrum: 1 745, 1 237, 1 039 cm^{-1} ($OCOCH_3$). ^1H NMR spectrum: 0·67 (3 H, s, 18-H), 2·05 (3 H, s, $OCOCH_3$), 3·20 (2 H, m, 1β-H and 2β-H), 4·36 (2 H, s, 19-H). For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·06% C, 10·51% H.

1β,2β-Epoxy-5α-cholestan-19-ol (*IIIa*)

The unsaturated compound *Ia* (110 mg) and *m*-chloroperoxybenzoic acid (60 mg) in chloroform (3 ml) were kept at +5°C for 4 h. Dilution with ether, washing with water, drying and evaporation yielded the crude product which was purified on one preparative silica gel plate (20 × 20 cm; benzene–ether 4 : 1) and crystallized from aqueous acetone to yield the epoxide *IIIa* (70 mg), m.p. 93—95°C, $[\alpha]_D$ +28° (*c* 1·2). IR spectrum: 3 611, 3 543 cm^{-1} at $4 . 10^{-4}$M in CCl_4 (OH, intramolecular hydrogen bond). For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·61% C, 11·42% H.

1β,2β-Epoxy-19-methoxy-5α-cholestane (*IIIb*)

The more polar fraction (126 mg) after separation of *IIb* was crystallized from acetone to yield the isomeric epoxide *IIIb* (92 mg), m.p. 88—90°C, $[\alpha]_D$ +14° (*c* 1·3). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 81·56% C, 11·53% H.

1α-Bromo-5α-cholestan-2β,19-diol 19-Monoacetate (*VII*)

The epoxy alcohol *IIIa* (64 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (1 ml) at room temperature overnight. The homogeneous (TLC) product was checked by its IR spectrum: 1 741, 1 240, 1 041 cm^{-1} ($OCOCH_3$), 852 cm^{-1} (epoxide). The crude acetate *IIIc* was dissolved in dioxane (3·5 ml), water (0·2 ml) and 48% hydrobromic acid (0·2 ml) were added and the mixture was kept at room temperature for 45 min, diluted with water, taken up in ether, washed with water, sodium hydrogen carbonate solution, water, dried and the solvent evaporated. TLC shows the presence of two compounds which were separated on one silica gel plate (20 × 20 cm; benzene–ether 7 : 3). The more polar major product *VII* (53 mg) was crystallized repeatedly from aqueous acetone (32 mg), m.p. 81—90°C and 129—131°C undepressed on admixture of *VII* obtained from *Ic* on treatment with hypobromous acid. $[\alpha]_D$ +47° (*c* 1·6). IR spectrum: identical with that of *VII* obtained from *Ic*.

5α-Cholestan-1α,2β,19-triol Triacetate (*XV*)

a) The monoacetate *XIV* (30 mg) was treated with pyridine (1 ml) and acetic anhydride (0·5 ml) at room temperature for 3 days. The usual workup gave the oily product *XV* (30 mg). IR spectrum (KBr:) 1 741, 1 252, 1 232, 1 212, 1 039 cm^{-1} ($OCOCH_3$). For $C_{33}H_{54}O_6$ (546·8) calculated: 72·48% C, 9·96% H; found: 72·31% C, 9·88% H.

b) Products with identical IR spectra (KBr) were obtained from *XIa* and *XIc* by acetylation.

1α-Bromo-5α-cholestan-2β,19-diol Diacetate (*XVI*)

a) The hydroxy derivative *VII* (60 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (2 ml) at room temperature for 12 h. After the usual workup the product was crystallized from aqueous acetone–methanol to give the diacetate *XVI* (26 mg), m.p. 101—103°C, undepressed upon admixture of the sample obtained from *IX*. IR spectrum: 1 744, 1 244, 1 029 cm^{-1} ($OCOCH_3$). Identical with that of the diacetate from *IX*. For $C_{31}H_{51}BrO_4$ (567·6) calculated: 65·58% C, 9·06% H; found: 65·67% C, 8·93% H.

b) A sample of *IX* (60 mg) was treated with acetic anhydride (0·5 ml) in pyridine (2 ml) at room temperature for 48 h. The usual workup and crystallization from aqueous acetone–methanol gave the product *XVI* (51 mg), m.p. 103—104°C, $[\alpha]_D$ +22° (*c* 1·2), identical with the diacetate obtained from *VII*. For $C_{31}H_{51}BrO_4$ (567·6) calculated: 65·58% C, 9·06% H; found: 65·28% C, 8·89% H.

19-Acetoxy-1α-bromo-5α-cholestan-2-one (*XVII*)

The hydroxy derivative *VII* (70 mg) was dissolved in acetone (4 ml) and treated dropwise with Jones' reagent until the presence of excess reagent was manifested by persistent red color of the solution. After several minutes the solution was poured into water and the product taken up in ether. The ethereal solution was washed with water, sodium sulfite solution, sodium carbonate, water and dried. Evaporation under reduced pressure gave the oily residue (68 mg) which was crystallized from methanol to give the product *XVII* (37 mg), m.p. 74—76°C, $[\alpha]_D$ −13° (*c* 1·1). IR spectrum: 1 752, 1 228, 1 041 cm^{-1} ($OCOCH_3$), 1 723 cm^{-1} (CO), 1 420 cm^{-1} (CH_2 flanked to CO). CD: $\Delta\varepsilon_{311}$ −2·63. For $C_{29}H_{47}BrO_3$ (523·6) calculated: 66·51% C, 9·04% H; found: 66·33% C, 8·90% H.

19-Acetoxy-2β-bromo-5α-cholestan-1-one (*XVIII*)

The epoxide *IIc* (60 mg) was cleaved with hydrobromic acid as given above, the crude product was dissolved in acetone and Jones' reagent (2·6 g CrO_3 in 12 ml H_2O and 2·3 ml H_2SO_4) was added dropwise until a permanent red color was achieved; the temperature was maintained at 20°C by external cooling. After 4 min the mixture was poured into water, extracted with ether and the solution washed with water, sodium hydrogen carbonate, sodium sulfite and water. Evaporation yielded a homogeneous (TLC) product *XVIII* (oil, 65 mg) which after crystallization from methanol melted at 60—61°C, $[\alpha]_D$ $-54°$ (c 1·4); CD: $\Delta\varepsilon_{312} = -4·69$. IR spectrum: 1 746, 1 242 cm^{-1} ($OCOCH_3$); 1 710 cm^{-1} (CO). ^{1}H NMR spectrum: 0·64 (3 H, s, 18-H), 2·00 (3 H, s, $OCOCH_3$), 4·43 (1 H, d, $J = 12$ Hz, 19-H), 4·45 (1 H, m, $W \sim 7$ Hz, 2α-H), 4·70 (1 H, d, $J = 12$ Hz, 19-H). For $C_{29}H_{47}BrO_3$ (523·6) calculated: 66·51% C, 9·04% H; found: 66·98% C, 9·03% H.

19-Acetoxy-5α-cholestan-1-one (*XIX*)

The bromo ketone *XVIII* (115 mg) was dissolved in dioxane (10 ml), acetic acid (3 ml), methanol (3 ml) and zinc powder (300 mg) were added and the mixture was stirred at room temperature for 1 h. After this time the reaction was complete (TLC) and the mixture was filtered, the filtrate diluted with water and the product taken up in ether. The solution was washed with water, dilute hydrochloric acid, water, sodium hydrogen carbonate and water, dried and the solvent evaporated. The residue was crystallized from methanol to give the product *XIX* (55 mg), m.p. 64—66°C, $[\alpha]_D$ $+105°$ (c 1·4), CD: $\Delta\varepsilon_{304} = -0·32$. For $C_{29}H_{48}O_3$ (444·7) calculated: 78·33% C, 10·88% H; found: 78·16% C, 10·89% H.

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