COMPETITION OF TWO PARTICIPATING GROUPS IN HYPOBROMOUS ACID ADDITION TO SOME 4-CHOLESTENE DERIVATIVES*

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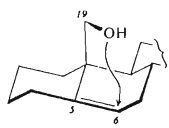
Hypobromous acid addition to the 4,5-unsaturated hydroxy acetate *VIII* results in formation of the cyclic bromo ether *XXIXa* as a product of $5(O)^n$ participation. $5(O)^n$. Participation by hydroxy group is thus preferred over $5(O)^{\pi,n}$ process by acetoxyl. Under the same conditions the 4,5-unsaturated diacetate *IX* afforded the diaxial bromohydrin *XXXI* arising from 4α,5α-bromonium ion with $5(O)^{\pi,n}$ participation by the 3β-acetoxyl whereas an alternative $6(O)^{\pi,n}$ participation by the 19-acetoxyl is not operative. The 3-epimeric diacetate *XV* reacts with hypobromous acid in a more complex way: the molecule is attacked by the electrophile from both α- and β-sites to give two diastereoisomeric bromonium ions *XXXII* and *XXXIII*. The former is simply cleaved with water as an external nucleophile to afford the diaxial bromohydrin *XXXIV*. The latter undergoes fission both with $5(O)^{\pi,n}$ and $6(O)^{\pi,n}$ participation: The first route leads to the *trans*-bromohydrin *XXXVI*. In the second pathway the acyloxonium ion *XXXVII* postulated as an inter mediate is further cleaved with $6(O)^{\pi,n}$ participation by 19-acetoxyl to give the acyloxonium ion *XXXVIII*, which is trapped by water to yield an unusual *cis*-bromohydrin *XXXIX*. The differences in the reaction course are discussed.

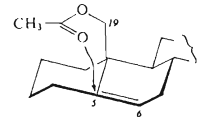
In a series of preceding papers[1-13], we have shown how striking can be the influence of neighboring group participation on reaction course of electrophilic additions, particularly from the point of view of their regio- and stereoselectivity. We demonstrated that under certain conditions the addition accompanied by participation can proceed with violation of Markovnikov of Fürst–Plattner rule. Thus, *e.g.* the unsaturated alcohol *I* (Scheme 1) reacts with hypobromous acid to yield exclusively a cyclic ether[1] (the related 5α,6α-bromonium ion is cleaved diaxially, in accord with Fürst–Plattner but in contradiction to Markovnikov rule). On the other hand, its acetate *II* reacts with hypobromous acid with participation by the acetate carbonyl to cleave the corresponding 5α,6α-bromonium ion under formation of a diequatorial bromohydrin[2,4], *i.e.* in contradiction to Fürst–Plattner rule and in accord with Markovnikov rule. The $5(O)^n$ participation (for notation *cf.* ref.[2]), though possible on the basis of structural reasons, does not proceed. In the both cases the olefin molecule is attacked by the electrophile from the more accessible α-face and in the same manner

* Part CCXCVIII in the series On Steroids. Part CCXCVII: This Journal *48*, 3629 (1983).

as in 5,6-unsaturated steroids lacking the 19-participating group[14]. With the derivative *II* we only observed the change in regioselectivity[4,6].



I



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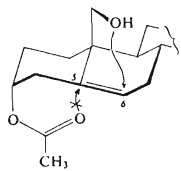
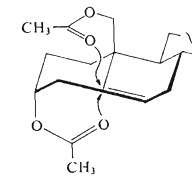


III



IV

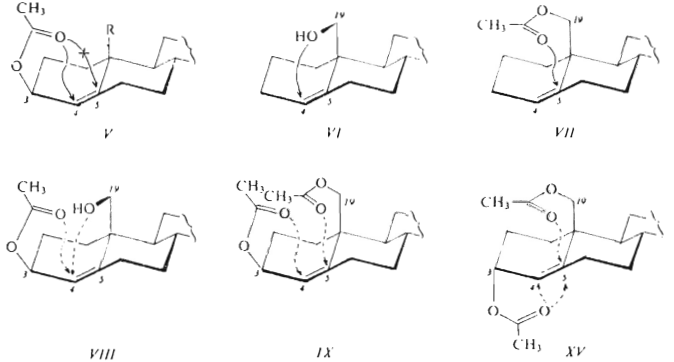
SCHEME 1

It now appears of interest to investigate the behavior of compounds containing two or more functional groups that could compete in participation; equally interesting seems to be the behavior of compounds in which the functional groups capable of S_N2-like participation are located in such a manner that participation of the first group would require attack of the electrophile from one site, and participation of the second group would only occur if the electrophile attacked from the other site.

In one of our recent papers[13] we studied the derivatives *III* and *IV* and demonstrated that in the compound *III* solely hydroxyl participates (as in *I*) while in the compound *IV* the 3α-acetoxy group competes in participation with the 19-acetoxyl. In this case (in contrast to *II*) the 5β,6β-bromonium ion takes an important part in the reaction and as a result, stereoselectivity of the reaction is changed considerably.

In the cited paper[13] structural reasons permitted only competitions between $5(O)^n$ and $6(O)^{\pi,n}$ (in the hydroxy acetate *III*) and between two $6(O)^{\pi,n}$ participations (in the diacetate *IV*). It therefore appeared desirable to prepare such models in which also a $5(O)^{\pi,n}$ participation would be possible. With a 19-acetoxyl is this not feasible but the literature reports[15–19] that, *e.g.* 3β-acetoxy-4-cholesten (*V*; Scheme 2) reacts with hypobromous acid with exclusive $5(O)^{\pi,n}$ participation by the allyl acetoxyl

to give the corresponding diaxial bromohydrin. No competition of the $6(O)^{\pi,n}$ process was observed. Participation by functional groups located in position 19 in the course of electrophilic additions to 4,5-double bond was studied in this laboratory earlier (*cf.* compounds *VI* and *VII*)[5]. This investigation demonstrated similarity to the isomers *I* and *II* and it is evident that the 4,5-unsaturated derivatives *VIII*, *IX* and *XV* are suitable as models in which all above mentioned types of competition can be expected to occur (Scheme 2). Reaction of hypobromous acid with the hydroxy derivative *VIII* is likely to involve competition of $5(O)^n$ and $5(O)^{\pi,n}$ processes in clea-



V *VI* *VII*

VIII *IX* *XV*

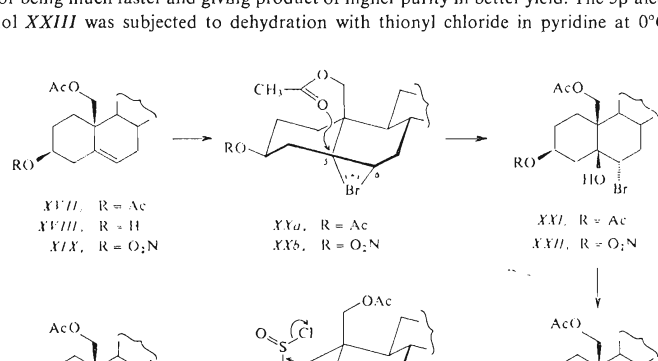
SCHEME 2

VIII, R^1 = Ac,	R^2 = H	*XV*, R = Ac
IX, R^1 = Ac,	R^2 = Ac	*XVI*, R = H
X, R^1 = H,	R^2 = Ac	
XI, R^1 = H,	R^2 = H	
XII, R^1 = CF_3CO,	R^2 = Ac	
XIII, R^1 = O_2N,	R^2 = Ac	
XIV, R^1 = CH_3OCH_2,	R^2 = Ac	

SCHEME 3

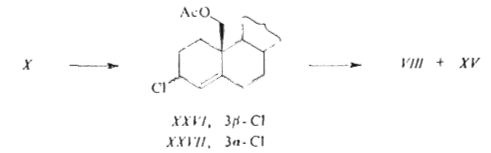
vage of the same bromonium ion; with the diacetate *IX* competition between $5(O)^{\pi,n}$ and $6(O)^{\pi,n}$ participations can be expected, again in the cleavage of the same bromonium ion. By contrast, the S_N2-like participation in *XV* can be expected to involve both α- and β-oriented bromonium ions, competition of $5(O)^{\pi,n}$ with $6(O)^{\pi,n}$ process and, moreover, interplay of antagonistic effects of Fürst–Plattner and Markovnikov rules.

According to our method[20] of transposition of a double bond from 5,6 to 4,5-position, we prepared the model compounds *VIII* and *IX* in the following manner (Schemes 3 and 4). The bromohydrin *XXI* (*cf.* ref.[2]) was prepared by addition of hypobromous acid to the diacetate *XVII* and reduced with tri-n-butyltin hydride to *XXIII*. This method is superior to earlier described reduction with Raney nickel[2,6,20] for being much faster and giving product of higher purity in better yield. The 5β-alcohol *XXIII* was subjected to dehydration with thionyl chloride in pyridine at 0°C.



SCHEME 4

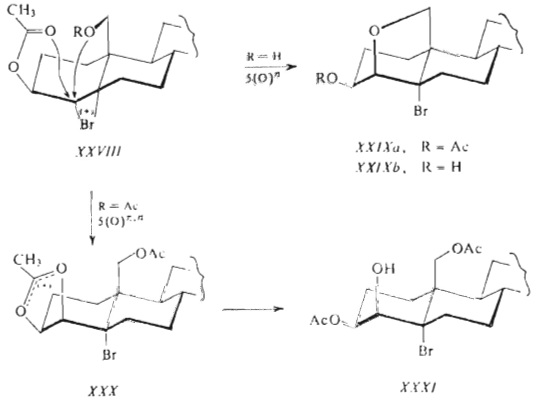
In the intermediate *XXV* of this reaction, only the 4α-hydrogen assumes the desired antiperiplanar orientation with respect to leaving group. As in the case of analogous 3-deoxy derivative[20], the reaction provides very pure 4,5-olefin *IX*. An attempt at selective hydrolysis of the diacetate *IX* with potassium hydrogen carbonate in methanol at 45°C gave a mixture of four compounds, the hydroxy acetate *VIII* (6%), the unreacted *IX* (27%), *X* (54%), and *XI* (9%).



SCHEME 5

Inversion of configuration at $C_{(3)}$ was conducted as follows (Scheme 5). The hydroxy acetate *X* was treated with thionyl chloride in ether at 0°C to yield a mixture of unstable epimeric allyl chlorides *XXVI* and *XXVII* which on acetolysis at room temperature gave a non-separable mixture of 3-epimeric diacetates *VIII* and *XV* in which the ^{1}H NMR-spectrum proves the 3α-epimer as predominating component. The crude mixture was reduced with lithium aluminum hydride to a mixture of diols *XI* and *XVI* which could be easily separated by chromatography. Acetylation of the diol *XVI* provided then the pure diacetate *XV*.

The hydroxy acetate *VIII* was treated with hypobromous acid generated *in situ* from N-bromoacetamide and perchloric acid in aqueous dioxane. The reaction



SCHEME 6

gave a sole product, the known bromo epoxide *XXXIXa* (Scheme 6), arising by $5(O)^n$ participation of the 19-hydroxyl under diaxial cleavage of the 4α,5α-bromonium ion *XXVIII* (R = H). Thus, the acetoxy group in position 3 does not intervene. Analogously, the diol *XI* yields the bromo epoxide *XXIXb* characterized as acetate *XXIXa*. Also, the diacetate *IX* reacts with hypobromous acid in a uniform way: The preferentially formed 4α,5α-bromonium ion *XXVIII* (R = Ac) is cleaved at $C_{(4)}$ in accord with Fürst–Plattner rule to give the diaxial bromohydrin *XXXI*. Its exclusive formation can be attributed to $(5O)^{\pi,n}$ participation by 3β-acetoxyl *via* the acyloxonium ion *XXX* hydrated to the bromohydrin *XXXI*. The same compound should also be formed on cleavage of the bromonium ion *XXVIII* (R = Ac) by water as external nuclepohile. However, this possibility can be excluded from the following reasons: *1*) It has been established[14–19] that during the addition to the acetate *V* the $5(O)^{\pi,n}$ participation takes precedence over external attack; *2*) if for some reasons the $5(O)^{\pi,n}$ participation did not occur in *IX*, the reactivity of the acetate *VII* would analogously require participation of the 19-acetoxyl[5] which would provide another product. The structure of the bromohydrin *XXXI* is inferred from ^{1}H NMR spectra showing preservation of the acetoxy groups in their original positions and proving the presence of an axial hydroxyl in the position 4. The half-width of the 3α-H multiplet points to *trans*-annellation of A and B rings with α-configuration of the bromine atom in position 5. We have thus established that from the two acetoxy groups in the diacetate *IX* competing for participation the acetoxyl in 3β-position is preferred.

As we demonstrated[6–8,22] the $6(O)^{\pi,n}$ participation by 19-acetoxyl in 5,6-unsaturated steroids is of synthetic interest as a method for simple introduction of 5β--hydroxyl into the molecule[6,20] (*cf.* also Scheme 4, *XVII*→*XXIII*). In the 4,5-unsaturated derivative *IX* is the introduction of 5β-hydroxyl rendered impossible by a competitive process due to the presence of 3β-acetoxy group. Consequently, we attempted to find a group the presence of which in the 3β-position would not impair the $6(O)^{\pi,n}$ participation by the 19-hydroxyl. The possibility of such a participation in this structural type we could demonstrate on the 3-deoxy derivative[5] *VII*.

The simplest possibility seemed to be a reaction of hypobromous acid with the 3β-hydroxy derivative *X* where the complication with the competitive participation should be excluded. Unfortunately, the hydroxy acetate *X*, when treated with hypobromous acid, gave a mixture of several unstable compounds which we did not study further. This failure is likely to be due to oxidation of the allylic hydroxyl followed by other reactions. We therefore decided to protect the 3β-hydroxyl by a group which should not interefere with participating 19-acetoxyl. One possibility appeared to be blocking by trifluoroacetylation since this group cannot undergo $6(O)^{\pi,n}$ participation[23]. From the latter fact we assumed that the capability of this group to participate by a $5(O)^{\pi,n}$ process would be – at least – impaired which would give the 19-acetoxy group a chance. We prepared the trifluoro acetate *XII*

XII as a rather unstable compound which we could characterize only by its ^{1}H NMR spectrum. However, reaction with hypobromous acid results in a complex mixture of unstable lipophilic products which we did not deal with any more.

Another possibility appeared to be the nitrate group. In an attempt to prepare the nitrate *XIII* by a direct nitration of the alcohol *X* we only obtained an intractable mixture of many compounds. Therefore, we had to try another route for the preparation of the nitrate *XIII*,to avoid esterification of the allylicc alcohol with acetyl nitrate by introducing the nitrate group into the molecule in some preceding, and the allylic double bond in the final step (Scheme 4). Selective saponification of the diacetate *XVII* with potassium hydrogen carbonate in methanol at 60°C afforded the 3β-alcohol *XVIII* in very good yield.In this case, selective hydrolysis of 3β-acetoxyl is much more successful than with the isomer *IX*. As shown by Dreiding models, this is evidently due to greater steric hindrance of the 19-acetoxyl in *XVII* than in *IX*. Reaction of the alcohol *XVIII* with acetyl nitrate at −30°C gave smoothly the nitrate *XIX* which on treatment with hypobromous acid gave the corresponding bromohydrin *XXII* by way of the bromonium ion *XXb*. Reduction of this compound with tri-n-butyltin hydride provided the alcohol *XXIV* which, in contrast to the diacetate *XXIII* gave a complex mixture of lipophilic compounds on attempted elimination of the 5β-hydroxyl. Our effort to prepare the nitrate *XIII* by the both routes thus failed.

The last approach was based on protection of the 3β-hydroxyl as a methoxymethyl ether. A relatively smooth reaction of the alcohol *X* with chloromethyl methyl ether in benzene solution in the presence of dimethylaniline afforded the corresponding methoxymethoxy derivative *XIV* but again, treatment of the latter with hypobromous acid furnished a mixture of several unstable products which we were unable to separate.

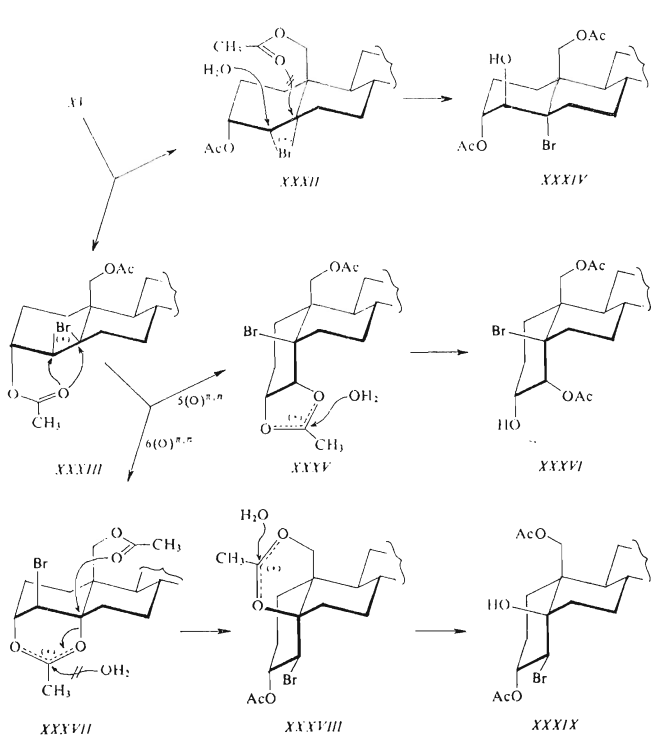
TABLE I

Yields and ratios of products of hypobromous acid addition to compounds *VIII*, *IX* and *XV*

Starting compound	Relative yield in % (product)			Total yield (%)
	participation	external attack	others	
VIII	~100 (*XXIX*)	—	—	92
IX	~100 (*XXXI*)	—	—	94
XV	29 (*XXXVI*)	28 (*XXXIV*)	43 (*XXXIX*)[a]	81

[a] Product of double participation (see Scheme 7 and the text).

After these unsuccessful experiments we draw our attention to the diacetate *XV*. The change of configuration at $C_{(3)}$ in the model compound resulted in essential changes in the course of hypobromous acid addition. The diacetate *XV* gave three main products (Scheme 7), *XXXIV*, *XXXVI* and *XXXIX* (Table I) the structure



SCHEME 7

of which was proved by means of ^{1}H NMR and IR spectra. ^{1}H NMR spectrum of the bromohydrin *XXXIV* shows that both the acetoxy groups remained unaffected in their original location (Table II). The sum of coupling constants of the 3β-H

multiplet demonstates *trans*-junction of A and B rings and the coupling constant of the $C_{(4)}$-proton reveals the axial character of the substituent at $C_{(4)}$. This reduces the number of possible structures to two, namely 4β-OH-5α-Br and 4β-Br-5α-OH. Treatment of this compound with trichloroacetyl isocyanate results in a marked shift of the proton at $C_{(4)}$ by more than 1·4 ppm (Table II). This result leads to the conclusion that the hydroxyl group must be located in the 4β-position (*XXXIV*); the alternate structure is thus ruled out. A comparison of the ^{1}H NMR spectrum of the second bromohydrin (*XXXVI*) with the spectrum after reaction with trichloroacetyl isocyanate revealed that the bromohydrin *XXXVI* is a product of acetoxy group migration from the 3- into the 4-position. It follows from the sum of the coupling constants of 3β-H that annellation of the rings A and B must be *cis*. As expected, the coupling constant of 4-H characterizes the 3-acetoxy group as axial and the structure *XXXVI* is beyond doubt.

The ^{1}H NMR spectrum of the bromohydrin *XXXIX* points to retention of the both acetoxy groups in their original positions and the coupling constants of 3β-H indicate *cis*-annellation of the A and B rings. Treatment with trichloroacetyl isocyanate results in no significant change of the spectrum which leads to the conclusion that the hydroxyl group must be tertiary, *i.e.* in $C_{(5)}$ position and with regard to *cis*-annellation of the A and B rings must be 5β. Accordingly, the bromine atom is located in position 4; as indicated by the coupling constant of 4-H, its conformation is equatorial. The possibility of a conformational change of the A-ring conformation into a boat or twist boat would imply the 4α-configuration of the bromine atom. However, this is out of the question since it would not be in accord with the value of $J_{3,4}$. The last possibility for the *trans*-bromohydrin could be 4β-Br-5α-OH ar-

TABLE II

^{1}H NMR Data of the products of hypobromous acid addition

Compound	18-H	19-H (*J*)[a]	3- (*W*)[a]	4-H (*J*)[a]
XXIXa	0·77	4·15 d + 4·55 d (6)	5·27 m (22)	4·25 d (5·0)
XXXI	0·67	4·21 d + 4·36 d (11)	5·12 m (20)	3·09 d (2·9)
XXXIV	0·66	4·30 d + 4·40 d (12)	5·21 m (14)	4·16 d (3·8)
XXXIV[b]		4·35 d + 4·51 d	5·42 m	5·59 d
XXXVI	0·65	4·30 d + 4·46 d (12)	4·52 m (20)	5·68 d (3·4)
XXXVI[b]		4·33 d + 4·48 d	5·71 n	5·84 d
XXXIX	0·65	4·38 d + 4·50 d (12)	5·29 ddd[c]	4·70 d (10·5)
XXXIX[b]		4·38 d + 4·50 d	5·26 ddd	4·70 d

[a] Values given in Hz; [b] values obtained after treatment with trichloroacetyl isocyanate; [c] $J_{3\beta,2\alpha} = 10{\cdot}9$ Hz, $J_{3\beta,2\beta} = 5{\cdot}3$ Hz, $J_{3\beta,4\alpha} = 10{\cdot}5$ Hz.

rangement in a twist-boat conformation of the ring A; this would accommodate the coupling constants of 3-H and 4-H. This alternative, however, can be ruled out on the basis of a strong intramolecular hydrogen bond (IR, ν(OH) = 3 572 cm^{-1}) which is incompatible with a twist boat with 5α-hydroxyl. All these facts leave only the structure *XXXIX* with *cis* arrangement of the bromine atom and hydroxyl group which has to be considered proved.

The bromohydrin *XXXIV* is formed by cleavage of the 4α,5α-bromonium ion *XXXII* by water as external nucleophile. Though the 7(O)$^{\pi,n}$ participation by the 19-acetoxy group could also be taken into consideration, the compounds of this type are known to undergo this participation only to a small extent[24,25]. The bromohydrins *XXXVI* and *XXXIX* are evidently formed by way of the 4β,5β-bromonium ion *XXXIII*. This ion is cleaved by 3α-acetoxy group in a 5(O)$^{\pi,n}$ process to give-against Markovnikov rule – the acyloxonium ion *XXXV* hydrated to the diaxial bromohydrin *XXXVI*.

Formation of the *cis*-bromohydrin *XXXIX* is more complicated: We assume splitting of the 4β,5β-bromonium ion *XXXIII* by the 3α-acetoxyl as in the preceding case but with 6(O)$^{\pi,n}$ participation in accord with both Fürst–Plattner and Markovnikov rule to afford the acyloxonium ion *XXXVII*. This ion instead of the usual hydration on the electron-deficient carbonyl carbon atom[14,26–29] is assumed to be cleaved under $C_{(5)}$—O bond breaking with 6(O)$^{\pi,n}$ participation by the 19-acetoxyl. This process leads to the acyloxonium ion *XXXVIII* which is hydrated to yield the *cis* bromohydrin *XXXIX* as a result of a double invesrion of configuration at $C_{(5)}$. An alternate explanation by formation of this bromohydrin from the 4α,5α-bromonium ion *XXXII* with the assumption of a subsequent isomerization of the axial 4α-bromine to equatorial 4β-Br is unlikely on the basis of our previous experiments.

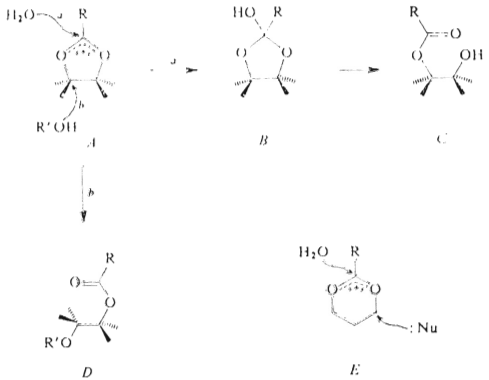
General Considerations

Following conclusions result from our experiments. The 5(O)^n participation by a hydroxyl group proceeds in precendence to participation by an acetoxyl group, irrespective of its possible (5(O)$^{\pi,n}$ or 6(O)$^{\pi,n}$) mechanism. If the molecule contains two acetoxy groups capable of participation during addition to the same double bond, the 5(O)$^{\pi,n}$ process takes precedence over the 6(O)$^{\pi,n}$ participation.

The cleavage of individual bromonium ions is of particular interest from the point of view of Fürst–Plattner and Markovnikov rules. The 4α,5α-bromonium ion is always cleaved in accord with Fürst–Plattner rule whether it occurs with participation by hydroxyl (*VI, VIII*) or 3β-acetoxyl (*V, IX*) or without participation, by external attack. In competition of 5(O)$^{\pi,n}$ and 6(O)$^{\pi,n}$ processes (*IX*), the first one is favored: it proceeds in accord with Fürst–Plattner but violates Markovnikov rule. The 6(O)$^{\pi,n}$ participation, which would proceed in opposite sense in accord with Markovnikov, does not take part in this competition. More complicated situation is observed

with 4β,5β-bromonium ion *XXXIII*. The cleavage of this ion by 3α-acetoxyl always obeys Fürst–Plattner rule (the diaxial product can be always formed due to possible distortion of the A-ring, *XXXV* and *XXXVII*) without regard whether the cleavage proceeds with $5(O)^{n,n}$ (at $C_{(4)}$) or with $C(O)^{n,n}$ (at $C_{(5)}$) participation. However, the latter process, in contrast to the former, proceeds in accord with Markovnikov rule which is an additional favoring factor. Evidently, this is the reason why the $6(O)^{n,n}$ participation is slightly favored over the $5(O)^{n,n}$ process in this case.

Finally, behavior of acyloxonium ions deserves some comment. It is well known[29] that acyloxonium ions are usually hydrated in an aqueous medium at electron-deficient carbonyl carbon atom (*cf.* Scheme 8, route *a*) as for instance in Woodward



SCHEME 8

addition[29]. On the other hand, in non-aqueous medium they can undergo an S_N2 attack with breaking of the C—O bond (*e.g.* Prévost addition[28,30]; *cf.* Scheme 8, route *b*). The case of the acyloxonium ion *XXXVII* is notable: This ion, though in aqueous medium, is not hydrated but undergoes an S_N2 attack by the 19-acetoxy group in a second $6(O)^{n,n}$ process and only the acyloxonium ion *XXXVIII* is hydrated by water present in the reaction mixture. In this case, this unusual S_N2 reaction is presumably made possible because of its intramolecular character and, most likely, also by the tertiary nature of the $C_{(5)}$—O bond (*cf.* also refs[30–33]). Thus the route *b* (*cf.* Scheme 8, formula *E*) can obviously take part even in aqueous medium if the geometric disposition permits a nucleophilic attack by a suitable neighboring group.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). Optical rotations were measured in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H NMR spectra were recorded on a Varian XL-200 apparatus and 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 14–75 eV. The samples were introduced using a direct inlet at lowest temperature enabling evaporation. The elemental composition of ions was determined by accurate mass measurements. 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 Model Compounds

The unsaturated compound (0·5 mmol) was was dissolved in dioxane (5 ml) and treated with 10% perchloric acid (0·5 ml) and N-bromoacetamide (80 mg, 0·6 mmol) at room temperature for 30 min. The mixture was diluted with ether and water, a 5% auqoeus potassium hydrogen carbonate solution, a 5% aqueous sodium thiosulfate solution, water, dried with sodium sulfate and evaporated.The residue was chromatographed on three preparative silica gel plates using a mixture of light petroleum, ether and acetone (85 : 10 : 5) or (90 : 10 : 10) as eluent. Zones containing products were collected, washed with ether and the eluate was evaporated. The yields are given in Table I. ^{1}H NMR data in the Table II and physical and analytical data in Table III.

TABLE III

Analytical and physical data of products of hypobromous acid addition

Compound	Formula (m.w.)	Calculated/Found			M.p., °C $[\alpha]_D^{20}$
		% C	% H	% Br	
XXIXa	$C_{29}H_{47}BrO_3$	66·52	9·05	15·26	118–120
	(523·6)	63·31	9·18	15·47	+23°
XXXI	$C_{31}H_{51}BrO_5$	63·79	8·81	13·69	oil
	(583·7)	63·57	8·59	13·82	+5°
XXXIV	$C_{31}H_{51}BrO_5$	63·79	8·81	13·69	oil
	(583·7)	63·60	8·87	13·85	+7°
XXXVI	$C_{31}H_{51}BrO_5$	63·79	8·81	13·69	oil
	(583·7)	63·72	8·99	13·84	−10°

4-Cholestene-3β,19-diol 3-Monoacetate (*VIII*)

Isolated from the mixture of products of saponification of *IX*; m.p. 111–113°C (lit.[10] gives 116°C). $[\alpha]_D^{20}$ +13° (*c* 4·3). ^{1}H NMR spectrum: 0·65 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·62 (1 H, d, J = 11 Hz, 19-H), 4·00 (1 H, d, J = 11 Hz, 19-H), 5·22 (1 H, m, W = 20 Hz, 3α-H), 5·62 (1 H, m, W = 7 Hz, 4-H).

4-Cholestene-3β,19-diol 3,19-Diacetate (*IX*)

The alcohol *XXIII* (1·4 g) was dissolved in pyridine (20 ml) and treated with thionyl chloride (1 ml) at 0°C for 30 min. The mixture was decomposed with ice and water, the product was extracted with ether and the ethereal solution was worked up as usual. The residue was crystallized from aqueous acetone to afford the olefin *IX* (860 mg), m.p. 86–87°C, $[\alpha]_D^{20}$ +33° (*c* 1·6) (literature[36] gives m.p. 88–89°C, $[\alpha]_D^{20}$ +31°). ^{1}H NMR spectrum: 0·64 (3 H, s, 18-H), 2·02 (6 H, s, 2 × CH_3CO_2), 4·08 (1 H, d, J = 12 Hz, 19-H), 4·50 (1 H, d, J = 12 Hz, 19-H), 5·22 (1 H, m, W = 22 Hz, 3α-H), 5·45 (1 H, m, W = 7 Hz, 4-H).

4-Cholestene-3β,19-diol 19-Monoacetate (*X*)

The diacetate *IX* (4·0 g) was dissolved in a mixture of benzene (120 ml) and methanol (200 ml) and treated with a solution of potassium hydrogen carbonate (4 g) in a mixture of water (80 ml) and methanol (200 ml) at 45°C for 30 h. The mixture was concentrated by evaporation *in vacuo* to about 1/5, treated with ether and water and the ethereal layer was worked up as usual. The residue was chromatographed on a column of silica gel using a mixture of light petroleum and ether (90 : 10) which eluted the unreacted *IX* (1·08 g), and then a mixture of light petroleum, ether and acetone (89 : 10 : 1) which eluted impurities (*c.* 50 mg). Elution with a mixture of the same solvents (88 : 10 : 2) gave the 19-hydroxy derivative *VIII* (215 mg). Elution with a mixture of the same solvents (86 : 10 : 4) furnished the 3β-hydroxy derivative *X* (1·96 g), m.p. 113–114°C (the literature[36] gives 114–116°C). ^{1}H NMR spectrum: 0·65 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 4·10 (1 H, d, J = 12 Hz, 19-H), 4·13 (1 H, m, W = 22 Hz, 3α-H), 4·48 (1 H, d, J = 12 Hz, 19-H), 5·53 (1 H, m, W = 8 Hz, 4-H). Finally, using a mixture of the same mixture of solvents (80 : 10 : 10) led to elution of the diol *XI* (306 mg).

4-Cholestene-3β,19-diol (*XI*)

Isolated from the previous experiment. M.p. 147–148°C. For $C_{27}H_{46}O_2$ (402·7) calculated: 80·54% C, 11·51% H; found: 80·33H C, 12·78% H.

4-Cholestene-3β,19-diol 3-Trifluoroacetate 19-Acetate (*XII*)

The alcohol *X* (200 mg) was dissolved in pyridine (2 ml) and treated with trifluoroacetic anhydride (0·2 ml) at −20°C for 2 h. The mixture was decomposed with ice and water, the product was extracted with ether and the ethereal phase was worked up as usual to yield the unstable ester *XII* (oil, *c.* 190 mg), which was immediately used for further operation. ^{1}H NMR spectrum: 0·67 (3 H, s, 18-H), 2·03 (3 H, s, CH_3CO_2), 4·05 (1 H, d, J = 11 Hz, 19-H), 4·55 (1 H, d, J = 11 Hz, 19-H), 5·40 (1 H, m, W = 25 Hz, 3α-H), 5·50 (1 H, m, W = 6 Hz, 4-H).

3β-Methoxymethoxy-4-cholesten-19-ol 19-Acetate (*XIV*)

The alcohol *X* (200mg) in benzene (7 ml)was stirred with dimethylaniline (0·24 ml) and chloromethyl methyl ether (0·14 ml) at room temperature for 3 days. The mixture was diluted with ether

and water and the ethereal solution was worked up as usual. The residue was dissolved in a mixture of benzene and light petroleum (1 : 10) and filtered through a column of aluminum oxide. The eluate was evaporated to yield the oily ether *XIV* (179 mg). $[\alpha]_D^{20}$ +60° (*c* 1·6). ^{1}H NMR spectrum: 0·66 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 3·55 (3 H, s, CH_3O), 3·83 (1 H, m, W = 18-Hz, 3α-H), 4·12 (1 H, d, J = 12 Hz, 19-H), 4·50 (1 H, d, J = 12 Hz, 19-Hz, 4·72 (2 H, s, O—CH_2—O), 5·53 (1 H, m, W = 7 Hz, 4-H). For $C_{31}H_{52}O_4$ 488·8) calculated: 76·18% C, 10·72H H; found: 75·94% C, 10·86% H.

4-Cholesten-3α,19-diol 3,19-Diacetate (*XV*)

The diol *XVI* (240 mg) was dissolved in pyridine (6 ml) and treated with acetic anhydride (2 ml) at room temperature for 2 days. The mixture was decomposed with ice and water, the product was taken up into ether and the ethereal solution was worked up as usual. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated to afford the oily diacetate *XV* (215 mg), $[\alpha]_D^{20}$ +171° (*c* 2·4) (the literature[36] gives +185°), ^{1}H NMR spectrum: 0·68 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 2·03 (3 H, s, CH_2CO_2), 4·03 (1 H, d, J = 11 Hz, 19-H), 4·48 (1 H, J = 11 Hz, 19-H), 5·17 (1 H, m, W = 11 Hz, 3β-H), 5·58 (1 H, m, W = 4 Hz, 4-H).

4-Cholestene-3α,19-diol (*XVI*)

The crude mixture of 3-chloro derivatives *XXVI* and *XXVII* (*c.* 400 mg) was dissolved in acetic acid (14 ml) containing anhydrous potassium acetate (200 mg) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with ether and water, the ethereal layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried with sodium sulfate and evaporated to yield the mixture of *IX* and *XV* (in *c.* 1 : 2 ratio as follows from ^{1}H NMR spectrum of the mixture). The crude product (*c.* 400 mg) was dissolved in ether (20 ml) and stirred with lithium aluminum hydride (100 mg) at room temperature for 4 h. The excess of reagent was decomposed with water, the mixture was diluted with ether and 5H hydrochloric acid and the ethereal phase was worked up as usual. The residue was chromatographed on a column of silica gel (50 g) using a mixture of light petroleum, ether and acetone (85 : 10 : 5) as eluent which eluted lipophilic impurities. Elution with a mixture of the same solvents (80 : : 10 : 10) afforded the diol *XVI* (220 mg), m.p. 130—131°C (acetone–n-heptane mixture), $[\alpha]_D^{20}$ +95° (*c* 1·7). ^{1}H NMR spectrum: 0·65 (3 H, s, 18-H), 3·52 (1 H, d, J = 10 Hz, 19-H), 3·95 (1 H, d, J = 10 Hz, 19-H), 4·13 (1 H, m, W = 12 Hz, 3β-H), 5·77 (1 H, d, J = 3 Hz, 4-H). For $C_{27}H_{46}O_2$ (402·7) calculated: 80·54% C, 11·51% H; found: 80·29% C, 11·57% H. Continued elution with the same mixture furnished the diol *XI* (154 mg).

5-Cholestene-3β,19-diol 19-Monoacetate (*XVIII*)

The diacetate[34] *XVII* (12 g) was dissolved in a mixture of benzene (400 ml) and methanol (100 ml) and treated with a solution of potassium hydrogen carbonate (10 g) in a mixture of water (200 ml) and methanol (1 000 ml) at 60°C for 3 days. The mixture was concentrated *in vacuo* to about 1/5, diluted with water and the product was extracted with ether. The ethereal layer was washed with water, dried with sodium sulfate and evaporated to give the monoacetate *XVIII* (9·3 g) of sufficient purity for further preparations. A sample was crystallized from acetone to afford the pure *XVIII*, m.p. 103—105°C (literature[35,36] gives 103·5—104·5°C).

5-Cholestene-3β,19-diol 3-Nitate 19-Acetate = *XIX*)

A solution of the alcohol *XVIII* (2 g) in chloroform (50 ml) was introduced over a period of 30 min

into a reagent prepared from acetic anhydride (12 ml) and 65% nitric acid (2·8 ml) at −30°, the mixture was stirred for an additional 2 h at −30 to −20°C for 2 h, then poured onto ice and aqueous ammonia and stirred for 1·5 h. The product was extracted with ether and the ethereal solution was worked up as usual. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The eluate was evaporated to yield the nitrate *XIX* (1·5 g). A sample was crystallized from a mixture of acetone, methanol and water to give the pure *XIX*, m.p. 67–69°C (dec.), $[\alpha]_D^{20}$ −56 (*c* 2·3). ^{1}H NMR spectrum: 0·68 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 3·93 (1 H, d, *J* 12 Hz, 19-H), 4·45 (1 H, *J* 12 Hz, 19-H), 4·85 (1 H, m, *W* = = 30 Hz, 3α-H), 5·70 (1 H, m, *W* 13 Hz, 5-H). For $C_{29}H_{47}NO_5$ (489·7) calculated: 71·13% C, 9·67% H; found: 71·04% C, 9·72% H.

6α-Bromo-5β-cholestane-3β,5,19-triol 3-Nitrate 19-Acetate (*XXII*)

The olefin *XIX* (1 g) was dissolved in dioxane (50 ml) and treated with 10% aqueous perchloric acid (5 ml) and N-bromoacetamide (400 mg) at room temperature for 1 h. The mixture was then diluted with ether and water, the ethereal phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, a 5% aqueous sodium thiosulfate solution, water, dried with sodium sulfate and evaporated. The residue was chromatographed on a column of silica gel (70 g) using a mixture of light petroleum and ether (90 : 10) as eluent. This mixture eluted some impurities. Elution with a mixture of light petroleum, ether and acetone (89·5 : 10 : 0·5) furnished the oily bromohydrin *XXII* (427 mg), $[\alpha]_D^{20}$: 28° (*c* 1·9). ^{1}H NMR spectrum: 0·62 (3 H, s, 18-H), 2·08 (3 H, s, CH_3CO_2), 4·35 (2 H, s, 19-H), 4·70 (1 H, q, *J* 6 Hz and 12 Hz, 6β-H), 5·35 (1 H, m, *W* = 12 Hz, 3α-H). For $C_{29}H_{48}BrNO_6$ (586·6) calculated: 59·38% C, 8·25% H, 13·62% Br; found: 59·20% C, 8·31% H, 13·55% Br.

5β-Cholestane-3β,5,19-triol 3,19-Diacetate (*XXIII*)

The bromohydrin[2] *XXI* (2 g) in benzene (50 ml) was refluxed with a 1 mol l^{-1} benzene solution of tri-n-butyltin hydride (4 ml) and a catalytic amount of 2,2′-bis(azo-2-methyl-propionitrile) for 30 min. The solvent was evaporated, the residue was chromatographed on a silica gel column (50 g) using a mixture of light petroleum and ether (90 : 10) as eluent. This mixture eluted impurities. Continued elution with a mixture of light petroleum, ether and acetone (87 : 10 : 3) furnished the pure oily *XXIII* (1·6 g), $[\alpha]_D^{20}$ + 41°, identical with an authentic sample[2].

5β-Cholestane-3β,5,19-triol 3-Nitrate 19-Acetate (*XXIV*)

The bromohydrin *XXII* (300 mg) in benzene (10 ml) was refluxed with a 1 mol l^{-1} benzene solution of tri-n-butyltin hydride (0·8 ml) in the presence of catalytic amount of 2,2′-bis(azo-2-methyl-propionitrile) for 2 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel (20 g) using a mixture of light petroleum and ether (90 : 10) as eluent to give the oily unstable *XXIV* (165 mg), $[\alpha]_D^{20}$ + 24° (*c* 1·4). ^{1}H NMR spectrum: 0·65 (3 H, s, 18-H), 2·05 (3 H, s, CH_3CO_2), 4·38 (2 H, s, 19-H), 5·30 (1 H, m, *W* = 13 Hz, 3α-H). For $C_{29}H_{49}NO_5$ (507·7) calculated: For $C_{29}H_{49}NO_5$ (507·7) calculated: 68·61% C, 9·73H H; found: 68·43H C, 9·78% H.

3ξ-Chloro-4-cholesten-19-ol 19-Acetate (*XXVI* and *XXVII*)

The alcohol *X* (400 mg) was dissolved in dry ether (20 ml), a solution of thionyl chloride (0·45 ml) in ether (4 ml) was added at 0°C with stirring in the course of 5 min, the mixture was stirred at 0°C for 20 min, then evaporated *in vacuo* at room temperature to yield the crude mixture

of unstable epimeric chlorides *XXVI* and *XXVII* (*c* 450 mg) which was immediately used in preparation of *XVI*. ^{1}H NMR spectrum of the mixture of *XXVI* and *XXVII*: 0·68 (3 H, s, 18-H), 1·99 (s, CH_3CO_2 of the major component), 2·01 (CH_3CO_2 of the minor component), 4·03 (2 H, d, J = 11 Hz, 19-H), 4·48 (1 H, d, J = 11 Hz, 19-H), 4·60 (1 H, m, W = 20 Hz, 3ξ-H), 5·65 (1 H, m, W = 13 Hz, 4-H).

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EEFEEENCES

1. Kočovský P., Černý V.: This Journal *43*, 327 (1978).
2. Kočovský P., Černý V., Synáčková M.: This Journal *44*, 1483 (1979).
3. Kočovský P., Kohout L., Černý V.: This Journal *45*, 559 (1980).
4. Kočovský P., Černý V.: This Journal *45*, 3023 (1980).
5. Kočovský P., Černý V.: This Journal *45*, 3030 (1980).
6. Kočovský P.: This Journal *44*, 2156 (1979).
7. Kočovský P., Černý V.: This Journal *45*, 921 (1980).
8. Kočovský P.: Tetrahedron Lett. *21*, 555 (1980).
9. Kočovský P., Tureček F.: Tetrahedron Lett. *22*, 2699 (1981).
10. Kočovský P., Starý I., Tureček F., Hanuš V.: This Journal *48*, in press.
11. Kočovský P.: This Journal *48*, in press.
12. Kočovský P.: This Journal *48*, in press.
13. Kočovský P., This Journal *48*, in press.
14. Kirk D. N., Hartshorn M. P.: *Steroid Reaction Mechanisms*. Elsevier, Amsterdam 1968.
15. Julia S., Fürer B.: Bull. Soc. Chim. Fr. *1966*, 1114.
16. Julia S., Lorne R.: C. R., Acad. Sci., Ser C. *268*, 1617 (1969).
17. Lorne R., Julia S.: Bull. Soc. Chim. Fr. *1973*, 1357.
18. Morand P., Polakova-Paquet A.: Can. J. Chem. *51*, 4098 (1973).
19. Covey D. F., Parikh V. D.: Steroids *36*, 451 (1980).
20. Kočovský P.: This Journal *45*, 3008 (1980).
21. Young W. G., Ireland R. E., Erigley T. I., Shoppee C. W., Dagashe B., Summers G. H. R.: J. Amer. Chem. Soc. *81*, 1451 (1959).
22. Kočovský P.: This Journal *45*, 2998 (1980).
23. Kočovský P.: This Journal *48*, in press.
24. Kočovský P., Tureček F., Černý V.: This Journal *47*, 117 (1982).
25. Kočovský P., Tureček F., Černý V.: This Journal *47*, 124 (1982).
26. De la Mare P. B. D., Bolton P.: *Electrophilic Additions to Unsaturated Systems*. Elsevier, Amsterdam 1982.
27. Capon B., McManus S. P.: *Neighboring Croup Participation*, Vol. 1. Plenum Press, New York 1976.
28. Wilson C. V.: Org. Reactions *9*, 350 (1957).
29. Woodward R. B., Brutcher F. V.: J. Amer. Chem. Soc. *80*, 209 (1958).
30. Cambie R. C., Potter G. J., Rutledge P. S., Woodgate P. D.: J. Chem. Soc., Perkin Trans. 1, *1977*, 530.
31. Cambie R. C., Chambers D., Rutledge P. S., Woodgate P. D.: J. Chem. Soc., Perkin Trans. 1, *1977*, 2231.

32. Yoshino T., Inaba S., Komura H., Ishido Y.: J. Chem. Soc., Perkin Trans. 1, *1977*, 1266.
33. Paulsen H.: Pure Appl. Chem. *41*, 69 (1975).
34. Morand P., Kaufman M.: Can. J. Chem. *49*, 3185 (1971).
35. Moriarty R. M., Paaren H. E.: J. Org. Chem. *46*, 970 (1981).
36. Joska J., Fajkoš J.: This Journal *45*, 1850 (1980).

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