PARTICIPATION OF 19-SUBSTITUENTS IN HYPOBROMOUS ACID ADDITION TO 3,4- AND 4,5-UNSATURATED STEROIDS*

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Participation of a 19-substituent (hydroxyl, methoxyl, acetoxyl) in hypobromous acid addition to 3- and 4-cholestenes was investigated. All three 3,4-unsaturated compounds *Ia—Ic* yielded exclusively the cyclic ether *VI* as a product of $5(O)^n$ participation. Contrasting with this behavior, the isomeric 4-cholestenes react differently depending on the substituent at $C_{(19)}$: Either exclusively (*IIa*→*XI*) or predominantly (*IIb*→*XI*) with $5(O)^n$ participation or with $6(O)^{\pi,n}$ participation (*IIc*→*XIVc*). These results are compared with those of 19-substituted 6- and 5-cholestenes *III* and *IV*.

Previously, we studied electrophilic additions, particularly additions of hypobromous acid, to 19-substituted steroids[1–11] with a double bond located in positions 2,3-, 5,6- and 6,7. In these reactions, the participating groups were hydroxyl, methoxyl and acetoxyl. The results were informative of the steric factors controlling the participation processes[8]. In an effort to obtain a deeper insight into these reactions, we are now extending the investigation to further model compounds[10], namely 19-substituted steroids, with a double bond located in positions 3,4- and 4,5 (*Ia–Ic*, *IIa–IIc*). These types are "symmetrical" analogs of 6,7- and 5,6-unsaturated steroids *IIIa–IIIc* and *IVa–IVc* studied in this laboratory earlier[3,8]. Thus, it is also of interest to compare the behavior of these two classes.

All three 3,4-unsaturated model compounds[10] *Ia–Ic* react with hypobromous acid smoothly to give the cyclic ether *VI* as the sole product (Table I). The 4,5-unsaturated steroids *IIa–IIc* gave different results depending on the nature of the 19-substituent: The alcohol *IIa* gave exlusively the cyclic ether *XI*. The methoxy derivative *IIb* yielded the ether *XI* accompanied by the diastereoisomeric epoxides *XIIIb* and *XIVb* as minor products (Table I). The 19-acetoxy derivative *IIc* afforded the 4β,5β-epoxide *XIVc*, again as the sole product.

All the products are known compounds[10] except for *XI*, the structure of which is derived from its elemental analysis, mode of formation both from the alcohol *IIa*

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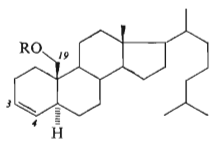
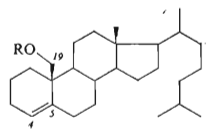
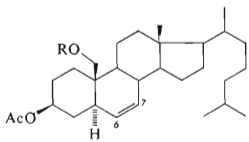
and methyl ether *IIb*, its conversion to the alcohol *IIa* on reduction with zinc in acetic acid and spectral evidence including mass determination. Absence of a hydroxy group was demonstrated by the IR spectrum and axial conformation of the oxygen bridge was proved by the ^{1}H-NMR spectrum (Table II).



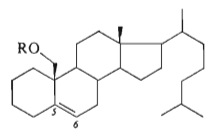
Ia, R = H
Ib, R = CH_3
Ic, R = Ac



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

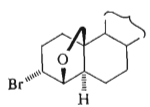


IIIa, R = H
IIIb, R = CH_3
IIIc, R = Ac



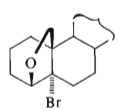
IVa, R = H
IVb, R = CH_3
IVc, R = Ac

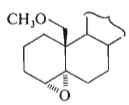
Ia – Ic →

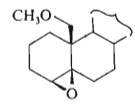


VI

IIa, IIb →

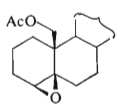


XI + 

XIIIb + 

XIVb

IIc →



XIVc

Formation of the cyclic ether *VI* from the 3,4-unsaturated compounds *Ia–Ic* is due to $5(O)^n$ participation in the cleavage of the 3α,4α-bromonium ions *Va–Vc* (for notation ref.[3]). In all these cases, no attack by an external nucleophile was observed.

The three products (*XI*, *XIIIb* and *XIVb*) arising from the 4,5-unsaturated 19-methoxy derivative *IIb* are associated with the intermediary formation of the two diastereoisomeric bromonium ions *VIIb* and *VIIIb*. The predominant reaction

Va, R = H
Vb, R = CH_3
Vc, R = Ac

VI

SCHEME 1

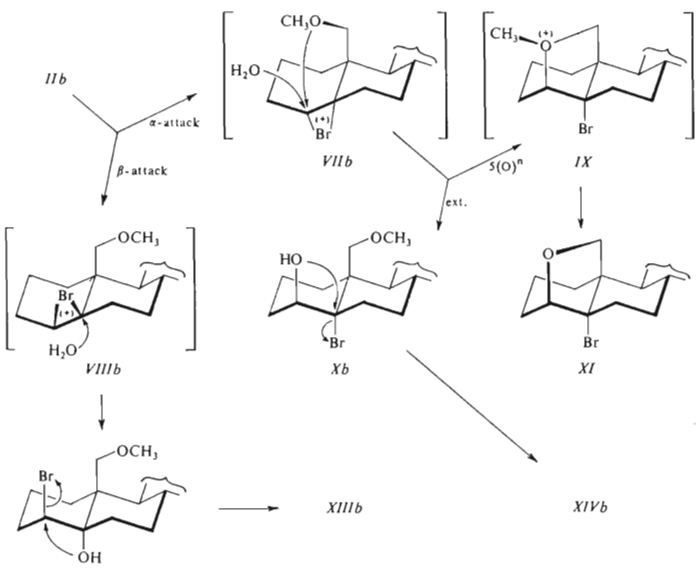
TABLE I

Yields and Ratios of Products of Hypobromous Acid Addition to the Olefins *I—IV*

Starting compound	Neighboring group	Mode of reaction, % of the total yield				Total yield %	Ref.
		$5(O)^n$	$6(O)^{\pi,n}$	Ext.[a]	β-ion[b]		
Ia	OH	100 (*VI*)	—	—	—	94	—
Ib	OCH_3	100 (*VI*)	—	—	—	95	—
Ic	OAc	100 (*VI*)	—	—	—	91	—
IIa	OH	100 (*XI*)	—	—	—	93	—
IIb	OCH_3	86 (*XI*)	—	6 (*XIVb*)	8 (*XIIIb*)	96	—
IIc	OAc	—	100 (*XIVc*)	—	—	92	—
IIIa	OH	100	—	—	—	96	8
IIIb	OCH_3	93	—	7	—	89	8
IIIc	OAc	92	—	8	—	94	8
IVa	OH	99	—	—	—	93	11
IVb	OCH_3	92	—	—	8	95	11
IVc	OAc	—	100	—	—	92	11

[a] Attack of external nucleophile; [b] products of reaction of the β-bromonium ion.

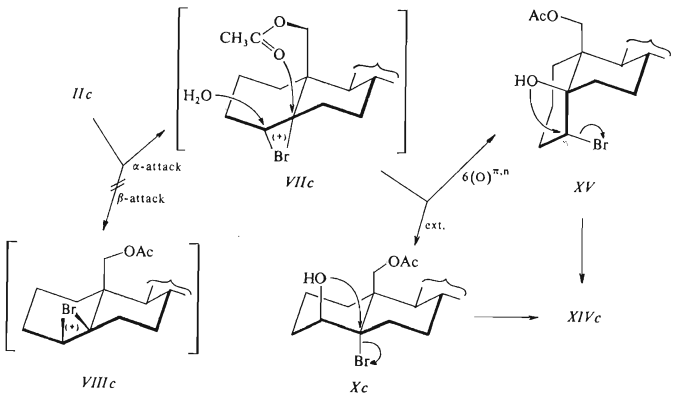
is cleavage of the 4α,5α-bromonium ion *VIIb* at $C_{(4)}$ by the 19-methoxyl oxygen in a $5(O)^n$ process to give (*via* the ion *IX*) the cyclic ether *XI*. Formation of the epoxide *XIVb* proceeds *via* the diaxial bromohydrin *Xb* and is due to competing external attack at $C_{(4)}$ by water. Alternative attack of water at $C_{(5)}$ which would lead to the



SCHEME 2

intermediary 4α-bromo-5β-hydroxy derivative may be excluded on the basis of our earlier results[3,11]. Similar opening of the 4β,5β-bromonium ion *VIIIb* results in the formation of the diaxial bromohydrin *XII* spontaneously cyclizing to the 4α,5α-epoxide *XIIIb*. Alternatively, the 4β,5β-bromonium ion *VIIIb* could be cleaved by a molecule of water at $C_{(4)}$ to give the diaxial 4α-hydroxy-5β-bromo derivative. This isomeric bromohydrin would cyclize to the same 4α,5α-epoxide *XIIIb*. However,

this route is less probable from analogy with perchloric acid fission of the 4β,5β-epoxide *XIVb* which is cleaved solely at $C_{(5)}$ to give the corresponding 4β,5α-diol[12]. It has been demonstrated that the cleavage of bromonium ions and protonated epoxides by nucleophiles shows close analogy[8,13].



SCHEME 3

TABLE II

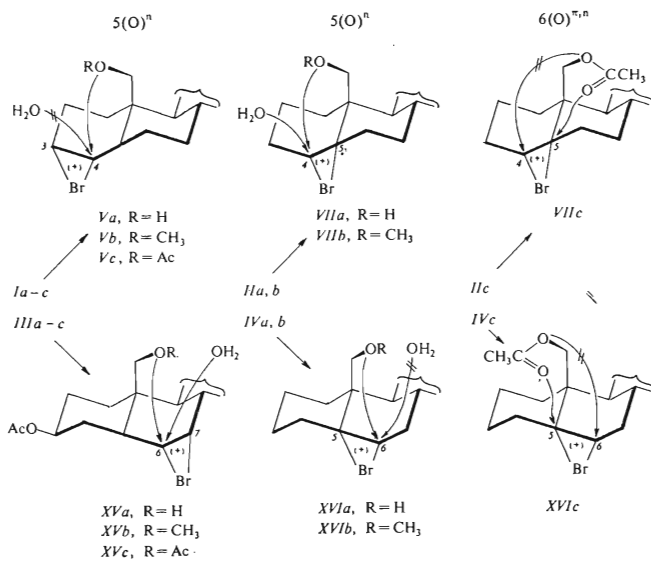
^{1}H-NMR Data of the Products of Hypobromous Acid Addition

Compound	18-H	19-H[a]	CH—O (*W* in Hz)	CH—Br (*W* in Hz)
VI	0·65	3·42	3·15 m (10)	4·24 m (20)
XI	0·65	3·88	4·00 m (11)	—
XIIIb	0·68	3·56	2·95 m (8)	—
XIVb	0·67	3·47	2·88 m (11)	—
XIVc	0·67	4·25	2·79 m (10)	—

[a] Center of AB system.

When considering the reaction of the 4,5-unsaturated 19-acetoxy derivative *IIc*, it is obvious that only the 4α,5α-bromonium ion *VIIc* can be the intermediate in the formation of the sole product of the reaction, the 4β,5β-epoxide *XIVc*. The latter compound may arise from *VIIc* with $6(O)^{\pi,n}$ participation by the 19-acetoxyl (*via* diaxial bromohydrin *XV*) or by external attack by water at $C_{(4)}$ (*via* diaxial bromohydrin *Xc*). This route is less probable since *a*) acid cleavage of the analogous 4α,5α--epoxide proceeds largely with $6(O)^{\pi,n}$ participation[12] and *b*) the 5α,6α-bromonium ion, being a "symmetrical" analog of the 4α,5α-ion *VIIc*, is cleaved solely with $6(O)^{\pi,n}$ participation[11]. Alternative attack of water as external nucleophile at $C_{(5)}$ which would lead to *XV* may be excluded on the basis of our earlier results[3,11].

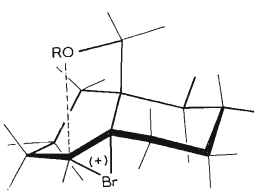
Based on studies performed to date[1-11] on selected model compounds, the behavior of 19-substituted steroids with a double bond situated in the ring A or B (2,3-, 3,4-, 5,6- and 6,7-positions) may be characterized as follows: The 19-alcohols and



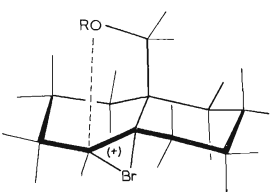
SCHEME 4

methyl ethers react in the same manner undergoing $5(O)^n$ participation in all cases so far investigated. The differences in the quantity of minor reaction products are small and are due to competitive side reactions involving interaction with an external nucleophile. In this context, comparison of 4α,5α- (*VIIb*) with 5α,6α-bromonium ion (*XVIb*) deserves comment. The 4α,5α-bromonium ion *VIIb* reacts predominantly with $5(O)^n$ participation accompanied by some external attack while 5α,6α-bromonium ion *XVIb* was shown[11] to react with $5(O)^n$ participation exclusively. Presumably, this difference may be due to the location of the double bond in the rigid B-ring in the one case and in the flexible A-ring in the second case. The A-ring of the 4α,5α-ion -ion *VIIb* may assume either the conformation A_1 favorable for $5(O)^n$ participation or the unfavorable conformation A_2 (ref.[14–19]) in which the distance of 19-oxygen from the reaction center at $C_{(4)}$ is considerably larger (Fig. 1). A similar unfavorable conformation cannot be adopted by the rigid B-ring.

Contrasting with the behavior of 19-hydroxy and 19-methoxy compounds, differences in the reactivity of various 19-acetoxy derivatives are of qualitative character. These differences are associated with the ambident nature of the acetoxy group and are largely dependent on the structure. Accordingly, the 19-acetoxy olefins may be divided into two groups. The first constitutes compounds with the double bond situated in positions 2,3- (ref.[3]), 3,4- and 6,7- (ref.[8]) which react with $5(O)^n$ participation; external attack is either not operative or only to a limited extent ($\leqq 15\%$). In these compounds, the distance of the reaction center from the oxygen of the ester function is approximately the same (0·26 nm) and the angle of approach[8] of the 19-oxygen to the plane of the three-membered bromonium ion ring is also about the same ($\leqq 15°$), as shown by Dreiding models.



VII (A_1)



VII (A_2)

FIG. 1
Conformations of the 4α,5α-Bromonium Ion *VII*

Comparison of the 6α,7α-bromonium ion *XVc* (ref.[8]) with the 3α,4α-bromonium ion *Vc* reveals an interesting difference. While the latter ion reacts quantitatively to give the product of $5(O)^n$ participation (*VI*), the 6α,7α-bromonium ion undergoes some external attack by water (Table I). This fact cannot be explained in terms of accessibility of the external nucleophile which should be about the same in both cases. The difference may be attributed to greater flexibility of the A-ring of the ion *Vc*. Thus the A-ring may adopt a conformation in which the reaction center may approach the 19-oxygen more closely.

The second group of 19-acetoxy derivatives (*IIc* and *IVc*) contains a double bond in 4,5- or 5,6-position. Here, the $6(O)^{\pi,n}$ participation is possible. We have previously shown[3,11,20] that $6(O)^{\pi,n}$ participation takes precedence over the $5(O)^n$ process in 5,6-unsaturated steroids. It is not surprising that the same applies to 4,5-unsaturated analogs.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). 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 otherwise 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 CD spectra were recorded on a Dichrographe II (Jouan–Roussel) in dioxane. 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 compositions of ions were determined by accurate mass measurements. The identity of the samples prepared by different routes was checked by mixture melting points 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 *Ia—Ic* and *IIa—IIc*

The unsaturated compound (0·5 mmol) was dissolved in dioxane (5—7 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 was extracted with ether. The ethereal solution was washed with water, 5% aqueous potassium hydrogen carbonate solution, 10% aqueous potassium thiosulfate solution, water, then dried with sodium sulfate and evaporated. The residue was chromatographed (if necessary) on four preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10 or 85 : 10 : 5) as eluent. The zones were collected, eluted with ether, the filtrates were evaporated and the residue dried in a vacuum desiccator 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 in the Table II, and the physical and analytical data of new compounds are given below.

4-Cholesten-19-ol (*IIa*)

The bromo epoxide *XI* (55 mg) in dioxane (1 ml) and acetic acid (2 ml) was reduced with zinc (200 mg) as given in the previous paper[11] to afford the alcohol *IIa* (28 mg), m.p. 84—85°C. $[\alpha]_D^{20}$ +57° (*c* 2·0), identical with an authentic sample[10].

5-Bromo-4β,19-epoxy-5α-cholestane (*VI*)

The compound was prepared by hypobromous acid addition to the olefin *Ia* or *Ib*. M.p. 119—120°C $[\alpha]_D^{20}$ +12° (*c* 2·1). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 3·72 (1 H, d, J = 8 Hz, 19-H), 4·03 (1 H, d, J = 8 Hz, 19-H), 4·00 (1 H, m, W = 11 Hz, 4α-H). For $C_{27}H_{45}BrO$ (465·6) calculated: 69·66% C, 9·74% H, 17·16% Br; found: 69·43% C, 9·71% H, 17·29% Br.

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

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