PARTICIPATION OF 19-SUBSTITUENTS IN ELECTROPHILIC ADDITIONS. INFLUENCE OF 3β-SUBSTITUTION ON HYPOBROMOUS ACID ADDITION TO 5,6-UNSATURATED STEROIDS*

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Reactions of 19-hydroxy-, methoxy- and acetoxy-5-cholestenes *Ia*, *IIa*, *IIIa* were studied and compared with those previously obtained with analogous 3β-acetoxy-19-substituted 5-cholestenes *Ib*, *IIb*, *IIIc*. A marked difference was found in 19-acetoxy derivatives where the 3-unsubstituted compound *IIIa* yields exclusively the bromohydrin *XVIa* as a product of $6(O)^{n,n}$ participation while the 3β-acetoxy derivative *IIIb* gives, apart from the analogous bromohydrin *XVIb*, also products of competing reactions: The epoxide *XIIb* and the bromohydrin *XIIIb*.

In our earlier papers[1-9] we dealt with the participation of 19-hydroxy, methoxy and acetoxy groups in hypobromous acid addition to 5,6-unsaturated steroids. All the compounds we investigated (*Ib*, *IIb*, *IIIb*) contained an acetoxy group at the 3β-position. In all cases participation by the 19-substituent predominated over the competing attack of an external nucleophile, the course of the reaction being strongly dependent on the nature of the participating group. It may be anticipated that the inductive and/or steric effect of the 3β-acetoxy group should also be reflected in the reaction[10-18] and it is the aim of the present paper to investigate the influence of this substitution.

We subjected these model compounds[19] *Ia*, *IIa* and *IIIa* to treatment with hypobromous acid (generated *in situ* from N-bromoacetamide and aqueous perchloric acid) in aqueous dioxane, and used product analysis for evaluation of the reaction mixture. The 19-alcohol *Ia* yielded solely the cyclic ether *VIa*. The 19-methoxy derivative *IIa* afforded the same product *VIa* accompanied by a small proportion of the known[19] epoxide *VIIIa* (Table I). The 19-acetoxy derivative *IIIa* yielded solely the known[19] bromohydrin *XVIa*.

The structure proof of the cyclic ether *VIa* is based on its elemental analysis, mode of formation both from the alcohol *Ia* and the methyl ether *IIa*, its conversion to the alcohol *Ia* on reduction with zinc and acetic acid, and spectral evidence including

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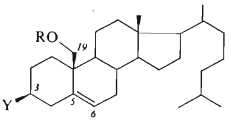
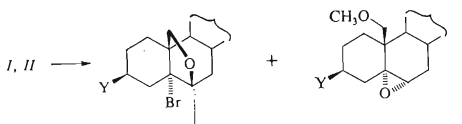
mass determination. The absence of a hydroxyl group was shown by the IR spectrum and axial conformation of the oxygen bridge was demonstrated by ^{1}H-NMR measurement.



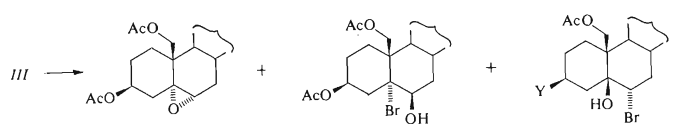
Ia, R = H, Y = H
Ib, R = H, Y = AcO
IIa, R = CH_3, Y = H
IIb, R = CH_3, Y = AcO
IIIa, R = Ac, Y = H
IIIb, R = Ac, Y = AcO

The course of the reaction of the alcohol *Ia* with hypobromous acid is identical with that of the 3β-acetoxy analog *Ib* (ref.[1]). In both cases solely cyclic ethers *VI* as products of 5(O)^n participation in 5α,6α-bromonium ion cleavage are formed (for notation cf ref.[3]). In the case of the methoxy derivative *IIa* we isolated products of both 5α,6α- and 5β,6β-bromonium ions *IVa*, *Va*. The 5α,6α-ion *IVa* is cleaved



VIa, Y = H
VIb, Y = AcO

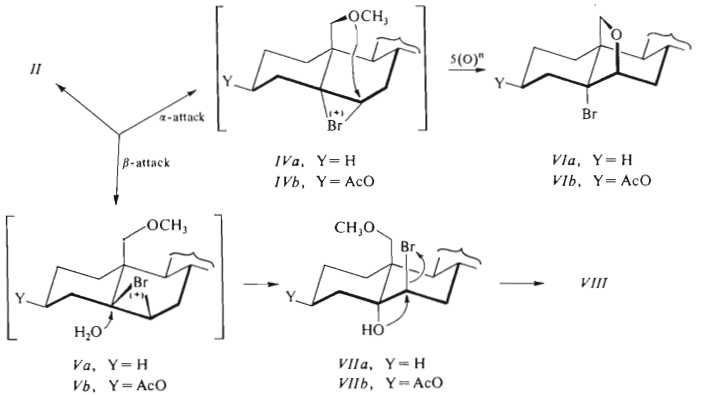
VIIIa, Y = H
VIIIb, Y = AcO



XIIb

XIIIb

XVIa, Y = H
XVIb, Y = AcO



SCHEME 1

exclusively with $5(O)^n$ participation by the 19-methoxyl to give the cyclic ether *VIa*. The diastereoisomeric bromonium ion *Va* gives the 5α,6α-epoxide *VIIIa via* the unstable and non-isolated bromohydrin *VIIa*. When the behavior of the 5,6-unsaturated methyl ether *IIa* is compared with that of its 3β-acetoxy analog *IIb* (ref.[2]),

TABLE I

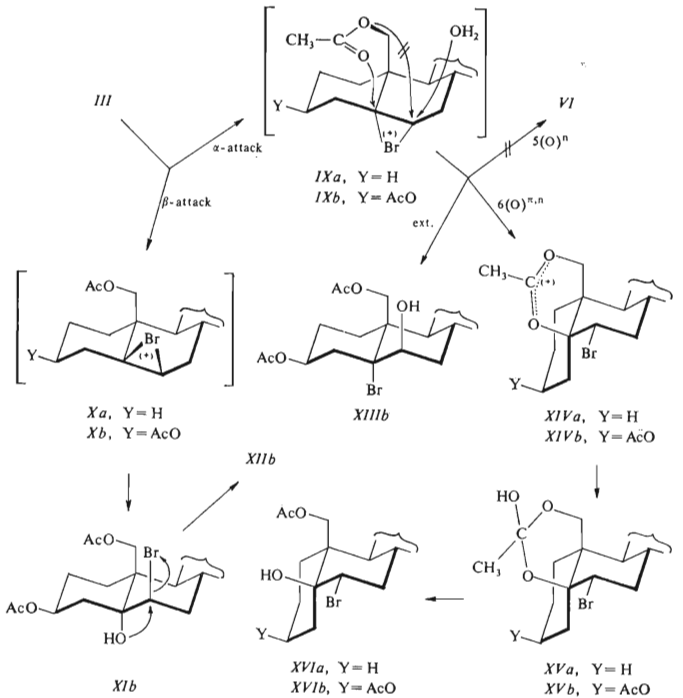
Yields and Ratios of Products of Hypobromous Acid Addition to the Olefins *I*—*III*

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	>99 (*VIa*)	—	—	—	93	—
Ib	OH	>99 (*VIb*)	—	—	—	97	1
IIa	OCH_3	92 (*VIa*)	—	—	8 (*VIIIa*)	95	—
IIb	OCH_3	75 (*VIb*)	—	—	25 (*VIIIb*)	88	2
IIIa	OAc	—	100 (*XVIa*)	—	—	92	—
IIIb	OAc	—	78 (*XVIb*)	12 (*XIIIb*)	10 (*XIIb*)	86	3

[a] Product of external nucleophile attack; [b] product of reaction of the 5β,5β-bromonium ion.

the only slight difference is in the relative proportion of the analogous products *VI* and *VIII* (Table I).

The acetoxy derivative *IIIa* gives in practically quantitative yield the diequatorial bromohydrin *XVIa*. Its formation is due to regio- and stereospecific cleavage of the intermediary 5α,6α-bromonium ion *IXa* with $6(O)^{\pi,n}$ participation by the 19-acetoxy group (*IXa* → *XIVa* → *XVa* → *XVIa*). Alternative $5(O)^n$ participation or external attack at $C_{(6)}$ are not operative[19]. Although external attack



SCHEME 2

by water at $C_{(5)}$ could also lead to opening of the 5α,6α-bromonium ion *IXa* to give *XVIa*, we consider this possibility as ruled out for following reasons: *1*) Formation of a diequatorial bromohydrin by this mechanism would be unusual (Fürst–Plattner rule). *2*) Operation of $6(O)^{\pi,n}$ participation was directly proved in an analogous case 3β-acetoxy series[3]. Recently, Rodewald and Siciński[20] reported addition of hypobromous acid to 19-acetoxy-5,6-unsaturated compounds of androstane series and attributed formation of 5β-hydroxy-6α-bromo derivative to inductive effect of electron-withdrawing acetoxy group at $C_{(19)}$. However, our earlier[3] and present results demonstrate that $6(O)^{\pi,n}$ participation accounts for this reaction.

As we demonstrated earlier[3], the 3β-acetoxy analog *IIIb* reacts in a more complicated manner since it gives rise *1*) predominantly to a product of $6(O)^{\pi,n}$ participation (*XVIb*) in the cleavage of the 5α,6α-bromonium ion *IXb*, *2*) to the diaxial bromohydrin *XIIIb* arising from the same bromonium ion *IXb* by the external attack of water[3], and *3*) epoxide *XIIb*. Formation of the latter product[3] is due to cleavage of the intermediary 5β,6β-bromonium ion *Xb* by water to provide the unstable diaxial bromohydrin *XIb* which spontaneously cyclizes to *XIIb*.

The remarkable difference in the behavior of 3-unsubstituted *vs* 3-substituted 19-acetoxy derivatives *IIIa* and *IIIb* confirmed the assumption that a 3β-acyloxy group should modify the reactivity of the 5,6-double bond with hypobromous acid. Decreased reactivity of the 5α,6α-bromonium ion *IXb* at $C_{(5)}$, due to the electron withdrawing effect of the 3β-acetoxy group, should be reflected in some suppression of the $6(O)^{\pi,n}$ participation in favor of competing reactions. To some extent, the $6(O)^{\pi,n}$ participation reaction could also be unfavorably influenced by converting the equatorial 3β-acetoxy group in the starting olefin *IIIb* into an axial one[21] in *XIVb* → *XVIb*.

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 point determination, by thin-layer chromatography (TLC) and by infrared and ^{1}H-NMR spectra. Usual work-up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

Addition of Hypobromous Acid to the Unsaturated Compounds *Ia—Ic*

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 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 the solvent was 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) as eluent. The corresponding zones were collected, eluted with ether, the filtrates were evaporated and the residue dried in a vacuum dessicator overnight. The products were crystallized from aqueous acetone or from a mixture of chloroform and methanol. The yields are given in Table I.

5-Cholesten-19-ol (*Ia*)

The bromo epoxide *VIa* (60 mg) was dissolved in a hot mixture of dioxane (1 ml) and acetic acid (2 ml) and refluxed with zinc powder (200 mg in four portions) for 5 min. The inorganic material was removed by filtration and washed with a hot mixture of acetic acid and dioxane. The filtrate was diluted with water and the product was extracted with ether. The ethereal solution was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, then dried and evaporated. The residue was chromatographed on one preparative plate of silica gel (20 × 20 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zone was collected, eluted with ether and the filtrate was evaporated to give the alcohol *Ia* (26 mg) which on crystallization gave the pure *Ia*, m.p. 86—87°C. $[\alpha]_D^{20}$ —34° (*c* 2·0), identical with an authentic sample[19].

5-Bromo-6β,19-epoxy-5α-cholestane (*VIa*)

The compound was prepared by hypobromous acid addition to the olefin *Ia* or *IIa*. M.p. 75 to 76°C, $[\alpha]_D^{20}$ +3° (*c* 2·2). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·65 (1 H, d, J = 8 Hz, 19-H), 4·00 (1 H, d, J = 8 Hz, 19-H), 4·03 (1 H, m, W = 8 Hz, 6-H). For $C_{27}H_{45}BrO$ (465·6) calculated: 69·66% C, 9·74% H, 17·16% Br; found: 69·48% C, 9·65% H, 17·32% 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 Mr P. Formánek and interpreted by Dr S. Vašíčková.* ^{1}H-NMR *spectra were recorded by Mrs J. Jelínková, M. Snopková and Dr J. Šaman. Mass spectra were recorded and interpreted by Dr F. Tureček.*

REFERENCES

1. Kočovský P., Černý V.: This Journal *43*, 327 (1978).
2. Kočovský P., Černý V.: This Journal *43*, 1924 (1978).
3. Kočovský P., Černý V., Synáčková M.: This Journal *44*, 1483 (1979).
4. Kočovský P.: This Journal *44*, 2156 (1979).
5. Kočovský P.: Tetrahedron Lett. *21*, 555 (1980).
6. Kočovský P.: This Journal *45*, 2998 (1980).
7. Kočovský P., Černý V.: This Journal *45*, 921 (1980).
8. Kočovský P., Kohout L., Černý V.: This Journal *45*, 559 (1980).
9. Tureček F., Kočovský P.: This Journal *45*, 274 (1980).

10. Schwarz V., Heřmánek S., Trojánek J.: This Journal *26*, 1438 (1961).
11. Schwarz V., Heřmánek S., Trojánek J.: This Journal *27*, 2778 (1962).
12. Schwarz V., Heřmánek S.: Tetrahedron Lett. *1962*, 809.
13. de la Mare P. B. D., Wilson R. D.: J. Chem. Soc. Perkin Trans. 1, *1977*, 2048.
14. de la Mare P. B. D., Wilson R. D.: J. Chem. Soc. Perkin Trans. 1, *1977*, 2055.
15. de la Mare P. B. D., Wilson R. D.: J. Chem. Soc. Perkin Trans. 1, *1977*, 2062.
16. Kasal A.: J. Chem. Soc. Perkin Trans. 1, *1979*, 1642.
17. Peterson P. E.: Tetrahedron Lett. *1963*, 181.
18. Kirk D. N., Hartshorn M. P.: *Steroid Reaction Mechanisms.* Elsevier, Amsterdam 1968.
19. Kočovský P.: This Journal *45*, 3008 (1980).
20. Rodewald W. J., Siciński R. R.: Polish J. Chem. *63*, 131 (1979).
21. Janot M.M., Devissauget C., Pais M., Khuong-Huu Q., Jarreau F. X., Goutarel R.: Bull. Soc. Chim. Fr. *1968*, 4323.

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