PARTICIPATION OF THE METHOXYL GROUP IN THE CLEAVAGE OF SOME 19-SUBSTITUTED STEROID EPOXIDES. A CASE OF COMPETITION BETWEEN INTERNAL AND EXTERNAL NUCLEOPHILE ATTACK*

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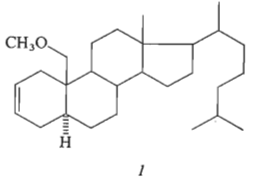
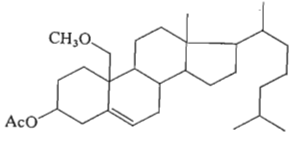
Acid cleavage of two steroid epoxides *III* and *IV*, bearing a methoxy group in position 19, with aqueous perchloric acid or hydrobromic acid gives two types of products, *i.e.* diols or bromohydrins *VI*, *VII*, *IX* and *X* as products of the normal reaction course and cyclic ethers *V* and *VIII* formed by participation of the 19-methoxy group. Discussed is the similarity of these reactions with electrophilic additions to the related 19-methoxy olefins *I* and *II*, the mechanism, and the difference in behavior of both epoxides *III* and *IV*. Also discussed is the dependence of product ratios on the nucleophility of the attacking species.

In our previous papers[1,2] we reported on the participation of the 19-methoxyl group in hypobromous acid addition to isomeric steroid olefins *I* and *II*. With regard to the similarity in the opening of the cyclic halonium ion[3-17] and the epoxide ring[18-24] it appeared of interest to investigate the behavior of the analogous epoxides *III* and *IV* in acid catalyzed cleavage, particularly whether or not participation of the 19-methoxyl will also be operative and if so, whether or not such a process will be accompanied by competitive attack of external nucleophile.

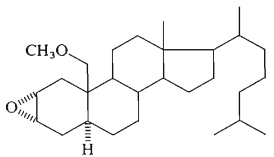


I

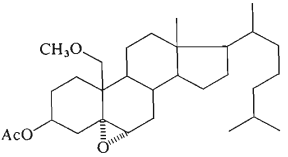


II

* Part CCXII in the series On Steroids; Part CCXI: This Journal *44*, 128 (1979).

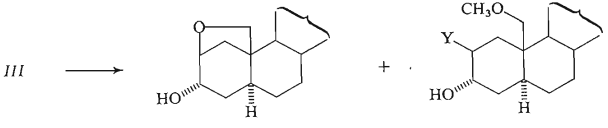


III

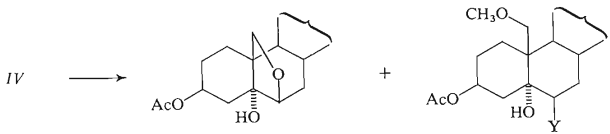


IV

On reaction with perchloric acid in aqueous dioxane, the 2α,3α-epoxide *III* yielded a mixture of the cyclic ether *V*, as a product of methoxyl group participation, and the diol *VI*, arising by normal diaxial opening of the epoxide ring by water as external nucleophile. Cleavage of *III* by hydrobromic acid in the same solvent led to a similar result (Table I). Reaction of the 5α,6α-epoxide *IV* with perchloric acid afforded also a mixture of two products *VIII* and *IX* with the latter compound prevailing. However, reaction of *IV* with hydrobromic acid gave only the bromohydrin *X* as a product of normal epoxide ring cleavage by bromide anion attack at $C_{(6)}$ (Table I).



V *VI*, Y = OH; *VII*, Y = Br



VIII *IX*, Y = OH; *X*, Y = Br

The compounds *V* and *X* are identical with the substances prepared earlier by other methods[2]. Structure of the diol *VI* follows mainly from the ^{1}H-NMR spectrum. The position of the 19-H signal (Table II) and a singlet at 3·36 ppm proves the presence of the methoxyl group in the 19-position. The presence of two axial secondary

hydroxyl groups was derived from the corresponding signals of 2α- and 3β-protons both in the free diol *VI* and its bis-trichloroacetylcarbamoyl derivative (Table II).

The structure of the bromohydrin *VII* was established in a similar manner: The ^{1}H-NMR spectrum demonstrates the presence of the 19-methoxyl and of two axial substituents in positions 2 and 3. In view of the configuration of the epoxide *III* the hydroxyl in the bromohydrin must have the α-configuration and only position 3 is in accord with its axial conformation. In alkaline medium the bromohydrin *VII* is

TABLE I

Yields and Ratios of Epoxide Cleavage Products

Starting compound	Reagent	Ratio of products	Total yield %
		Participation : Normal	
III	$HClO_4/H_2O$	68 (*V*) : 32 (*VI*)	91
III	HBr/H_2O	48 (*V*) : 52 (*VII*)	90
IV	$HClO_4/H_2O$	27 (*VIII*) : 73 (*IX*)	87
IV	HBr/H_2O	0 (*VIII*) : 100 (*X*)	94

TABLE II

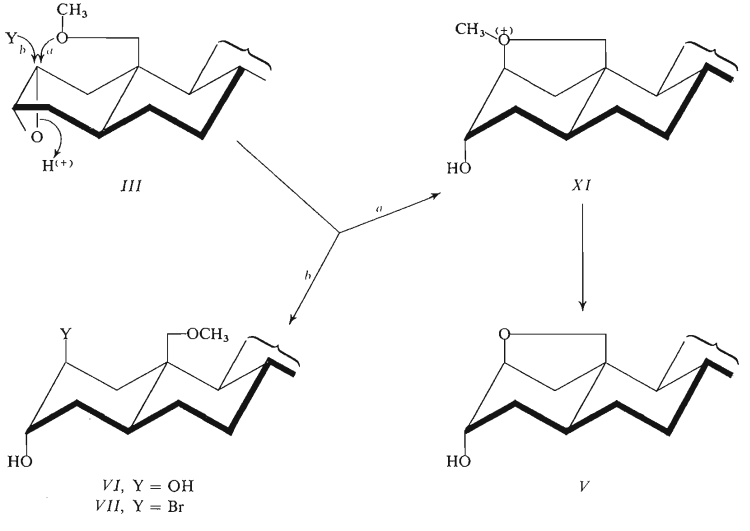
^{1}H-NMR Data of Epoxide Cleavage Products

Compound	18-H	19-H[a]	2α-H ($W_{1/2}$)	3-H ($W_{1/2}$)	6α-H ($W_{1/2}$)
V	0·65	3·77	4·15 m (9)	3·92 m (8)	—
VI	0·67	3·51	3·88 m (7)	3·73 m (7)	—
VII	0·67	3·53	4·40 m (8)	4·05 m (9)	—
			4·45 m (7)[b]	5·22 m (8)[b]	—
VIII	0·70	3·82	—	5·10 m (30)	3·70 m
			—	—	4·55 d (J = 4)[b]
IX	0·68	3·71	—	5·23 m (30)	4·64 m (7)
			—	—	6·03 m (7)[b]
X	0·73	3·86	—	5·12 m (30)	[c]
			—	—	5·24 m (8)[b]

[a] Center of AB system. [b] The values obtained after treatment with trichloroacetyl isocyanate. [c] Overlapped by other signals.

converted into the epoxide *III*. The structure proof of the cyclic ether *VIII* is also based mainly on the ^{1}H-NMR spectrum in which the methoxyl signal is absent and the presence of one tertiary hydroxyl can be demonstrated by acylation with trichloroacetyl isocyanate. This acylation results in a characteristic shift of the 6α-proton expected of the HO—C—CH—O— grouping. This fact coupled with the shape of the 6α-proton signal proves the structure *VIII*.

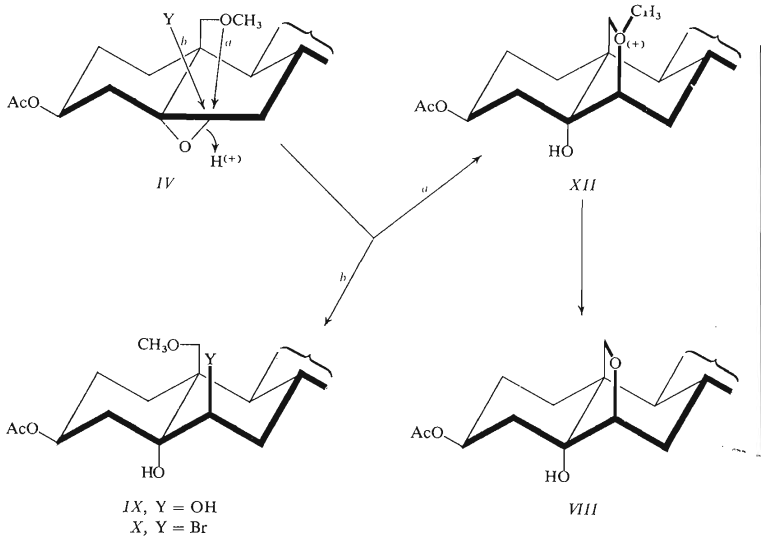
The ^{1}H-NMR spectrum of the diol *IX* is characterized by the signals of the CH_2—OCH_3 protons (Table II) and by the signal of the CH—OH proton. The spectrum of the bis-trichloroacetylcarbamoyl derivative shows the presence of one tertiary and one secondary hydroxyl in *IX*. The α-configuration of the tertiary 5α-hydroxyl is based on the width of the 3α-proton signal. The secondary hydroxyl at $C_{(6)}$ is axial as revealed by the shape of the 6-proton signal.



SCHEME 1

Acidic cleavage of the 2α,3α-epoxide *III* (Scheme 1) commences by protonation of the epoxide oxygen atom, the epoxide ring is then opened either by intramolecular

attack by the methoxyl group giving rise to the intermediary ion *XI* (path *a*) or by an external nucleophile, *i.e.* H_2O or Br^- (path *b*) leading to the compounds *VI* or *VII*, respectively. The cleavage mechanism of the 5α,6α-epoxide *IV* (Scheme 2) is analogous.



SCHEME 2

Table I shows the difference in the mutual proportion of participation products and products of simple cleavage. This difference depends both on the attacking nucleophile and on the position of the epoxide ring. The epoxide *III* is cleaved by aqueous perchloric acid to give a mixture of a participation product and of a normal cleavage product in about a 2 : 1 ratio. Thus, the 19-methoxyl competes succesfully with water as external nucleophile. However, when hydrobromic acid is used, the higher nucleophility of the bromide anion is reflected in a decrease in the proportion of the product of participation and the ratio of the alternative products is approximately 1 : 1. Similarly, treatment of the epoxide *IV* with aqueous perchloric acid gives both the products of normal cleavage (*IX*) and the product of participation *VIII*.

Contrasting with the behavior of the epoxide *III*, normal cleavage (path *b*) predominates. This tendency is even more markedly expressed in the reaction with hydrobromic acid where the formation of the participation product is completely suppressed. This difference in the behavior of both epoxides can be related to the differences in the spatial arrangement of both molecules. Inspection of Dreiding models shows that in the epoxide *III* the methoxyl oxygen (in the corresponding conformation) is in close proximity to the reaction center at $C_{(2)}$ (2·6 Å), whereas the smallest distance between the methoxyl oxygen and $C_{(6)}$ in the epoxide *IV* is larger (3·1 Å). This makes the intramolecular reaction in *IV* less favorable (Fig. 1). Moreover, in the epoxide *IV* the 19-methoxyl must overcome nonbonded interactions with axial hydrogens either in the 11β and 8β or 2β and 4β positions when it rotates to assume the conformation required for the intramolecular attack[1]. No such hindrance is present in the epoxide *III*.

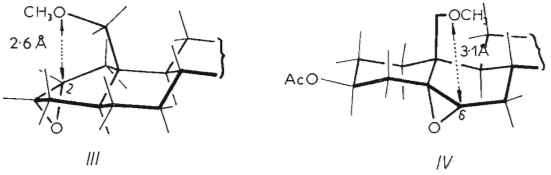


FIG. 1
Conformation of Participating 19-Methoxyl Group in Epoxides *III* and *IV*

This situation is similar to the recently reported[2] 19-methoxyl group participation in the course of hypobromous acid addition to olefins *I* and *II*. In the latter case both the 2α,3α- and 5α,6α-bromonium ions reacted solely with participation[1,2]. Therefore it is of interest that, in spite of structural similarity, in the case of epoxides competitive external nucleophilic attack is operative. This difference is presumably due to the higher activation energy required for protonated epoxide ring cleavage. The entropy factor[25] should be of about the same magnitude for both intramolecular reactions and is therefore relatively more important in the case of bromonium ions.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/0·2 Torr (26 Pa). Optical measurements were carried out in chloroform with an error of ±3°. The IR spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H-NMR spectra were recorded on a Varian HA-100 instrument (100 MHz) in deuteriochloroform at 30°C with tetramethyl silane as internal reference. Chemical shifts are given in ppm. Apparent coupling

constants were obtained from first order analysis. The identity of 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.

Cleavage of Epoxides *III* and *IV*

The epoxide (200 mg) was dissolved in dioxane (5—8 ml), water (0·5 ml) was added and the mixture was treated with acid, *i.e.* 72% perchloric (0·3 ml) or 48% hydrobromic (0·5 ml) for 1—2 h. The mixture was diluted with ether and water, the organic layer was washed ten times with water, dried with sodium sulfate and the solvent was evaporated. The residue was chromatographed on 4 preparative silica gel plates using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zones were collected, eluted with ether, the solvent was evaporated and the residue dried in a vacuum dessicator overnight. The yields of products are given in Table I. Their ^{1}H-NMR spectra, analytical data and physical constants are given in Tables II and III.

2α,3α-Epoxy-19-methoxy-5α-cholestane (*III*)

a) *From* 19-*methoxy*-5α-*cholest*-2-*ene* (I): The olefin[1] *I* (300 mg) was dissolved in chloroform (10 ml) and treated with *m*-chloroperoxybenzoic acid (200 mg) at room temperature for 3 h. The mixture was diluted with ether, the solution was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried with sodium sulfate and the solvent was evaporated. The residue was chromatographed on 4 preparative silica gel plates using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. The corresponding zones were collected

TABLE III

Analytical and Physical Data of Epoxide Cleavage Products

Compound	Formula (m.w.)	Calculated/Found % C	% H	% Br	M.p., °C $[\alpha]_D^{20}$
V	$C_{27}H_{46}O_2$	80·54	11·51	—	191—192[a]
	(402·7)	80·31	11·54	—	+33°
VI	$C_{28}H_{50}O_3$	77·36	11·59	—	oil
	(434·7)	77·21	11·46	—	+28°
VII	$C_{28}H_{49}BrO_2$	67·59	9·93	16·06	105—107
	(497·6)	67·30	9·91	15·87	+45°
VIII	$C_{29}H_{48}O_4$	75·61	10·50	—	162—163
	(460·7)	75·36	10·28	—	+ 9°
IX	$C_{30}H_{52}O_5$	73·13	10·64	—	oil
	(492·7)	73·41	10·59	—	−13°
X	$C_{30}H_{51}BrO_4$	64·85	9·25	14·38	oil
	(555·7)	64·61	9·12	14·56	+ 8°

[a] In accordance with literature[24].

and eluted with ether to yield crude *III* (210 mg), which on crystallization from a mixture of acetone, methanol and water gave the epoxide *III* (137 mg), m.p. 96—97°C, $[\alpha]_D^{20}$ +33° (*c* 2·5). For $C_{28}H_{48}O_2$ (416·7). calculated: 80·71% C, 11·61% H; found: 80·59% C, 11·62% H. Elution of the zones containing the polar compounds gave V (83 mg).

b) *From* 19-*methoxy*-2β-*bromo*-5α-*cholestan*-3α-*ol* (VII): The mixture of the bromohydrin *VII* (20 mg), potassium carbonate (20 mg) and water (0·5 ml) was refluxed in methanol (5 ml) for 5 min. The solvent was evaporated *in vacuo*, the residue was treated with ether and water, the ethereal layer was washed with water, dried with sodium sulfate and the solvent was evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield *VII* (6 mg), m.p. 94—95°C.

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

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