AN UNUSUAL REARRANGEMENT IN HYPOBROMOUS ACID ADDITION TO 10β-VINYL CHOLESTANE DERIVATIVES*

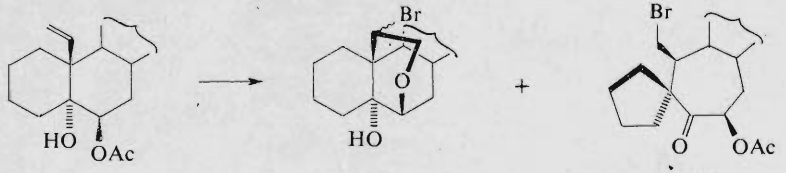
Pavel Kočovský[a] and František Tureček[b]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6 and*
[b] *The J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, 121 38 Prague 2*

Received April 2nd, 1981

On treatment with hypobromous acid, 19-nor-10β-vinyl-5α-cholestan-5-ol (*VIIa*) rearranges to the spirocyclic ketone *X*. The rearrangement is postulated to proceed *via* the intermediate (19*R*)-bromonium ion *VIIIa*. The same reaction was observed with the methyl ether *VIIb*. The mechanism of the rearrangement was elucidated by ^{18}O-labeling and product analysis.

In our previous paper[1], we reported the reaction of the 10β-vinyl derivative *I* with hypobromous acid. In addition to the expected product of 6(O)[n] participation (*II*), we isolated the spirocyclic ketone *III* which was formed by a skeletal rearrangement. We proposed an explanation of the mechanism of both competing reactions. We assume that two epimeric bromonium ions are formed in the first step. The (19*S*)-bromonium ion is further cleaved by 6(O)[n] participation of the 6β-acetoxy group to afford the (19*S*)-epimer *II*. By contrast, the epimeric (19*R*)-bromonium ion gave only a trace amount of the coresponding cyclic ether, while the major product was the spirocyclic ketone *III*.



I *II* *III*

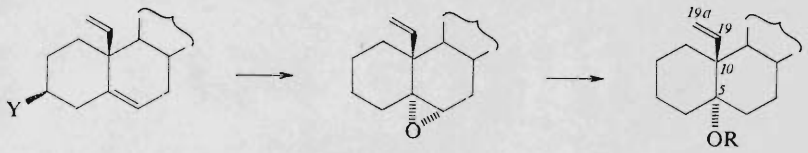
The mechanism of the rearrangement posed some questions as to what is the role of the oxygen-containing substituents at $C_{(5)}$ and $C_{(6)}$ in the starting compound. In order to get a deeper insight, we prepared the 10β-vinyl-5α-hydroxy and 10β-vinyl-5α-methoxy derivatives *VIIa* and *VIIb*, respectively. Both *VIIa* and *VIIb* lack the

* Part CCLIV in the series On Steroids; Part CCLIII This Journal *46*, 2872 (1981).

substituent at $C_{(6)}$ and, presumably, the hydroxyl and the methoxy group could show a different propensity for conversion to the carbonyl group.

The alcohol *VIIa* was prepared from the mesylate[2] *IV* in three steps. Methylation of *VIIa* (methyl iodide, sodium hydride) afforded the methoxy derivative *VIIb*. When treated with hypobromous acid (generated *in situ* from N-bromoacetamide and perchloric acid in aqueous dioxane), the unsaturated alcohol *VIIa* furnished the spirocyclic ketone *X* as a single product. Hypobromous acid addition to the methyl ether *VIIb* proceeded quite analogously furnishing the ketone *X* in high yield. It has to be noted that numbering of carbon atoms in the rearranged skeleton is not genetically related to that in the starting 10β-vinyl derivative, *e.g.* $C_{(10)}$ in *X* corresponds to $C_{(19)}$ in *VII*, $C_{(19)}$ in *X* corresponds to $C_{(19a)}$ in *VII*, *etc.* (ref.[1]).

The structure of *X* was deduced from the spectral data. The mass spectrum of *X* shows the molecular ion *m/z* 478–480 ($C_{28}H_{47}BrO$) and fragments *m/z* 437–439 $(M-C_3H_5)^+$, 419–421 $(M-C_3H_5-H_2O)^+$ 399 $(M-Br)^+$, and 381 $(M-Br-H_2O)^+$. The loss of a C_3H_5 radical from the molecular ion has been observed with the ketone *III* as well[1]. The ^{1}H-NMR spectrum of *X* exhibits two doublets of doublets (δ = 3·56 and δ = 3·29) which were assigned to the protons of the



IV, Y = MesO
V, Y = H

VI

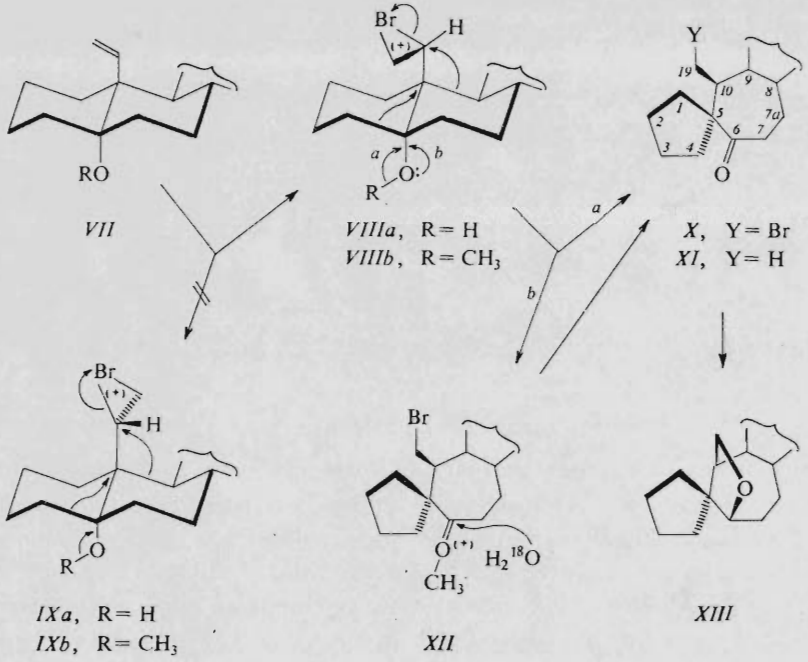
VIIa, R = H
VIIb, R = CH_3

bromomethyl group. The distinct signal of 7α-H appears as a doublet of doublets of doublets at δ = 2·87. By irradiation of the 7α-H, the 7β-proton was located at δ = 2·35 as a multiplet overlapped by the signals of two other skeletal protons. The ^{13}C-NMR spectrum proved that the ketone *X* did not contain any C=C double bond so that the AB part of the molecule must be composed of two rings. The overall similarity of the mass, ^{1}H- and ^{13}C-NMR spectra of *X* with those of the known ketone *III* (ref.[1]) strongly supports the proposed structure. Reduction of *X* with lithium aluminum hydride was accompanied by intramolecular displacement of the 19-bromine, yielding the cyclic ether *XIII*. This intramolecular cyclization made it possible to determine the configuration of the bromomethyl group in *X*. The ^{1}H-NMR spectrum of *XIII* shows three distinct signals: δ = 4·18 dd (J = 8·0 and 8·0 Hz), δ = 3·70 d (J = 8·0 Hz) and δ = 3·80 d (J = 5·2 Hz). The multiplicity of the last signal, assigned to 6α-H, shows that the vicinal torsion angle to the $C_{(6)}$—H and $C_{(7)}$—H bonds must be close to 90°. Inspection of models confirmed that the proper the geometry is attainable only in the β-configuration of the substituents

at $C_{(6)}$ and $C_{(10)}$. Reduction of the bromo ketone *X* with tri-n-butyltin hydride yielded the ketone *XI*.

The stereoselective formation of the 10β-bromomethyl ketone *X* can be explained in the following manner: In the first step, the attack of hypobromous acid upon the 10β-vinyl group leads to the (19*R*)-bromonium ion *VIII* which is subsequently cleaved with concomitant shifts of the $C_{(19)}$—Br, $C_{(9)}$—$C_{(10)}$ and $C_{(4)}$—$C_{(5)}$ bonds. The antiperiplanarity of the migrating bonds is probably crucial for the rearrangement to take place. The non-involvement of the epimeric (19*S*)-bromonium ion *IX* is peculiar and it cannot be safely deduced from simple stereochemical considerations.

In the last phase of the rearrangement, the hydroxyl (or methoxyl) group is converted to the $C_{(6)}$-keto group. This conversion can be regarded either as a solvent assisted cleavage of the O—R bond, or as proceeding via the "oxonium" ion *XII*



which is finally quenched by water to produce a transient hemiketal of the ketone *X*. The two routes can be distinguished by a labelling experiment. If water in the reaction medium is exchanged for $H_2{}^{18}O$, only the hemiketal route will result in incorporation of the label into *X*. A blank experiment proved that the acid-catalyzed exchange of the carbonyl oxygen for ^{18}O is very slow in *X* under the reaction conditions (hypobromous acid and $H_2{}^{18}O$ in dioxane). The total exchange (corrected for the ^{18}O content in the $H_2{}^{18}O$) did not exceed 8%. The addition of ^{18}O-labeled hypobromous acid to the methoxy derivative *VIIb* resulted in 53% incorporation

of the label into the ketone *X*. This means that the rearrangement mechanism displays a dichotomy in the last phase. Provided that isotope effects can be neglected, both the mechanistic routes outlined above are operative with a comparable probability.

In a summary, the rearrangement to spirocyclic ketones is the main reaction path of 5α-hydroxy and 5α-alkoxy cholestanes with electron-deficient center created at $C_{(19)}$. Further investigation of this unusual rearrangement is in progress in this laboratory.

EXPERIMENTAL

Melting points were determined on a Koffer block. Analytical samples were dried at 50°C/26 Pa or at 20°C/26 Pa. Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR-20 or on a Perkin–Elmer spectrometers in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were measured on a Varian XL-200 apparatus (200·05 MHz, FT-mode) and on a Tesla B 476 (60 MHz) instrument at 25°C in deuteriochloroform with tetramethylsilane as internal reference. Chemical shifts are given in δ (ppm) scale, coupling constants were taken from the first-order analysis; in all cases they were checked by double resonance experiments. ^{13}C-NMR spectra were measured on Varian XL-200 apparatus (50·3 MHz, FT-mode) using the square-wave proton decoupling mode. Mass spectra were recorded on a JEOL JMS D-100 spectrometer at 75 eV. The samples were introduced using a direct inlet heated to 120—150°C, the ion source was maintained at 150°C. Elemental compositions of all reported ions were determined by peak matching method using perfluorokerosene as a reference. The decompositions of metastable ions in the 1st field-free region were monitored by using the accelerating voltage scan method. The ^{18}O- contents in different samples of the ketone *X* were determined by mass spectrometry. The intensities of the oxygen-containing ions ($M^{+\cdot}$, $(M—C_3H_5)^+$, $(M—Br)^+$ and $(M—Br—CH_3)^+$) were recorded by means of a data system at a constant total ion current and the scan rate of 60 min/mass decade. Over 1 000 points were collected at each peak profile and the peak areas were computed using the CAS 241 program developed in this laboratory. The processed intensities were corrected for natural abundance of ^{13}C, ^{2}H and ^{18}O, using the values of Beynon and Williams[3]. The CD spectra were recorded on a Dichrographe II (Jouan-Roussel) in dioxane unless otherwise stated. The identity of the samples prepared by different routes was checked by mixture melting point determination, thin-layer chromatography (TLC), infrared, ^{1}H-NMR and mass spectra. Usual workup 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*.

19-Nor-10β-vinyl-5-cholestane (*V*)

The mesylate[2] *IV* (2 g) was dissolved in a mixture of 1,2-dimethoxyethane (10 ml) and dioxane (20 ml) and stirred with sodium iodide and powdered zinc (2 g) at 80°C for 2 h. The inorganic material was filtered off, the filtrate was concentrated by evaporation *in vacuo*, the residue was diluted with ether and water, the ethereal layer was washed with water, aqueous 5% solution of hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, a 5% aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was crystallized from a mixture of ether and acetone to give the diene *V* (1·1 g), m.p. 52—54°C, identical with an authentic sample[1].

19-Nor-10β-vinyl-5α-cholestan-5-ol (*VIIa*)

The epoxide[1] *VI* (400 mg) in ether (10 ml) was treated overnight with lithium aluminum hydride (10 mg) at room temperature. The mixture was decomposed with water, treated with ether and a 5% aqueous hydrochloric acid solution and the organic phase was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (80 : 20) and filtered through a column of aluminum oxide. The filtrate was evaporated to yield the alcohol *VIIa* (430 mg), $[\alpha]_D^{20}$ +57° (*c* 5·1). For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·07% H; found: 83·77% C, 12·01% H.

5-Methoxy-19-nor-10β-vinyl-5α-cholestane (*VIIb*)

The alcohol *VIIa* (300 mg) in tetrahydrofuran (10 ml) was treated with sodium hydride (50 mg) and methyl iodide (0·5 ml) at 60°C for 3 h while stirring. The mixture was decomposed with water, diluted with ether and water and the ethereal layer was worked up as usual. The redisue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was crystallized from aqueous acetone to yield the methyl ether *VIIb* (180 mg), m.p. 68—70°C, $[\alpha]_{20}^{D}$ +49° (*c* 2·0). ^{1}H-NMR spectrum: 0·60 (3 H, s, 18-H), 3·07 (3 H, s, CH_3O). For $C_{29}H_{50}O$ (414·7) calculated: 83·99% C, 12·15% H; found: 83·86% C, 12·21% 12·21% H.

Addition of Hypobromous Acid to Compounds *VIIa* and *VIIb*

The unsaturated compound (0·25 mmol) was dissolved in dioxane (5 ml) and water (0·5 ml) and treated with 10% perchloric acid (0·2 ml) and N-bromoacetamide (50 mg; 0·3 mmol) for 15 min at room temperature. The mixture was diluted with water and the product extracted with ether. The ethereal solution was washed with water, aqueous sodium thiosulfate solution, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on two silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (96 : 2 : 2) as eluent to yield the oily product *X*; $[\alpha]_D^{20}$ —24° (*c* 1·4). ^{1}H-NMR spectrum: 0·77 (3 H, s, 18-H), 2·35 (3 H, m, 7β-H overlapped by two other protons), 2·87 (1 H, ddd, J = 12·7, 12·7 and 4·4 Hz, 7α-H), 3·29 (1 H, dd, J = 10·0 and 10·0 Hz, 19-H), 3·56 (1 H, dd, J = 10·0 and 1·6 Hz, 19-H). ^{13}C-NMR spectrum: 12·00, 18·63, 22·57, 22·83, 23·84, 24·84, 25·77, 25·90, 28·03 (2 C), 28·90, 31·31, 34·93, 35·79, 36·11 (2 C), 39·53, 39·81 (2 C), 42·38, 42·75, 46·36, 53·66, 56·04, 56·99, 64·19. Mass spectrum: *m/z* 478, 480 ($M^{+\cdot}$, $C_{28}H_{47}BrO$), 437, 439 $(M—C_3H_5)^+$, 399 $(M—Br)^+$, 384 $(M—Br—CH_3)^{+\cdot}$, 381 $(M—Br—H_2O)^+$, 370 $(M—Br—CHO)^{+\cdot}$. IR spectrum: 1 708 cm^{-1}. For $C_{28}H_{47}BrO$ (479·6) calculated: 70·12% C, 9·88% H, 16·66% Br; found: 70·18% C, 8·73% H, 16·81% Br.

Cyclopentane-1′-spiro-5-(7a-homo-des-A-cholestan-6-one) (*XI*)

The bromo derivative *X* (60 mg) in benzene (5 ml) was refluxed with a benzene solution of tri-n-butyltin hydride (310 mg/ml; 0·2 ml) and a catalytic amount of 2,2′-bis(azo-2-methyl-propionitrile) for 30 min. The solvent was evaporated, the residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was chromatographed on a plate (20 × 20 cm) of silica gel using a mixture of light petroleum and ether (94 : 6) as eluent. The corresponding zone was collected, eluted with ether and the eluate was evaporated to yield the oily *XI* (51 mg); $[\alpha]_D^{20}$ —6° (*c* 2·0). Mass spectrum: *m/z*, 400 ($C_{28}H_{48}O$, $M^{+\cdot}$), 382 $(M—H_2O)^{+\cdot}$, 359 $(M—C_3H_5)^+$, 341 $(M—C_3H_5—H_2O)^+$, 332 (M—

$-C_5H_8)^{+\cdot}$, 287 $(M-C_8H_{17})^+$. For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·07% H; found: 83·80% C, 12·04% H.

6β,19-Epoxy-cyclopentane-1′-spiro-5-(7a-homo-des-A-cholestane) (*XIII*)

The bromo ketone *X* (100 mg) in ether (5 ml) was treated overnight with lithium aluminum hydride (50 mg) at room temperature. The mixture was decomposed with water, diluted with ether and a 5% aqueous hydrochloric acid and the ethereal layer was worked up as usual. The residue was chromatographed on a preparative silica gel plate (20 × 20 cm) using a mixture of light petroleum, ether and acetone (90 : 5 : 5) as eluent. Corresponding zone was collected, eluted with ether and evaporated to yield the oily epoxide *XIII* (65 mg); $[\alpha]_D^{20}$ +34° (*c* 1·4). ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 3·70 (1 H, d, J = 8·0 Hz, 19-*exo*-H), 3·80 (1 H, d, J = 5·2 Hz, 6α-H), 4·18 (1 H, dd, J = 8·0 and 8·0 Hz, 19-*endo*-H). ^{13}C-NMR spectrum: 12·67, 18·63, 22·50. 22·70, 23·85 (2 C), 24·60, 25·90 (2 C), 28·04, 28·24, 29·12, 29·73, 32·08, 32·99, 35·83, 36·13, 39·54, 40·27, 40·99, 43·30, 53·18, 54·75, 55·85, 56·31, 56·82, 79·08, 85·06. Mass spectrum: m/z 400 $(M^{+\cdot}$, $C_{28}H_{48}O)$, 382, $(M-H_2O)^{+\cdot}$, 369 $(M-CH_2OH)^+$, 332 $(M-C_5H_8)^{+\cdot}$. For $C_{28}H_{48}O$ (400·7) calculated: 83·93% C, 12·07% H; found: 83·72% C, 12·04% H.

The elemental analyses were carried out in the Analytical Laboratory of this Institute (under the direction of Dr J. Horáček). The 60 MHz ^{1}H-NMR *spectra were recorded by Mrs J. Jelínková and Mrs M. Snopková. The* IR *spectra were recorded by Mrs K. Matoušková and interpreted by Dr S. Vašíčková.*

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Translated by V. Černý.