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NEIGHBORING GROUP PARTICIPATION AND REARRANGEMENT IN HYPOBROMOUS ACID ADDITION TO 10β-VINYL-CHOLESTANES

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Abstract: Hypobromous acid addition to the diol Ia yields two epimeric dibromo 6β,19a-epoxides III and VII in a 83:17 ratio . Under the same conditions the 6β-acetoxy derivative Ib gives three products: III (46%), its epimer VII (5%) and the spirocyclic ketone V (49%).

Electrophilic addition to a double bond can be strongly influenced by intramolecular participation of other functionalities in the substrate molecule[1]. In preceeding papers[2-6] we dealt with the participation of hydroxyl, methoxyl and acetoxyl group standardly located at $C_{(19)}$, while the double bond was situated in different positions in A and B rings of the steroid skeleton. In order to check some conclusions[5], inferred from the investigation of the reactivity of these compounds, we prepared further models Ia and Ib.

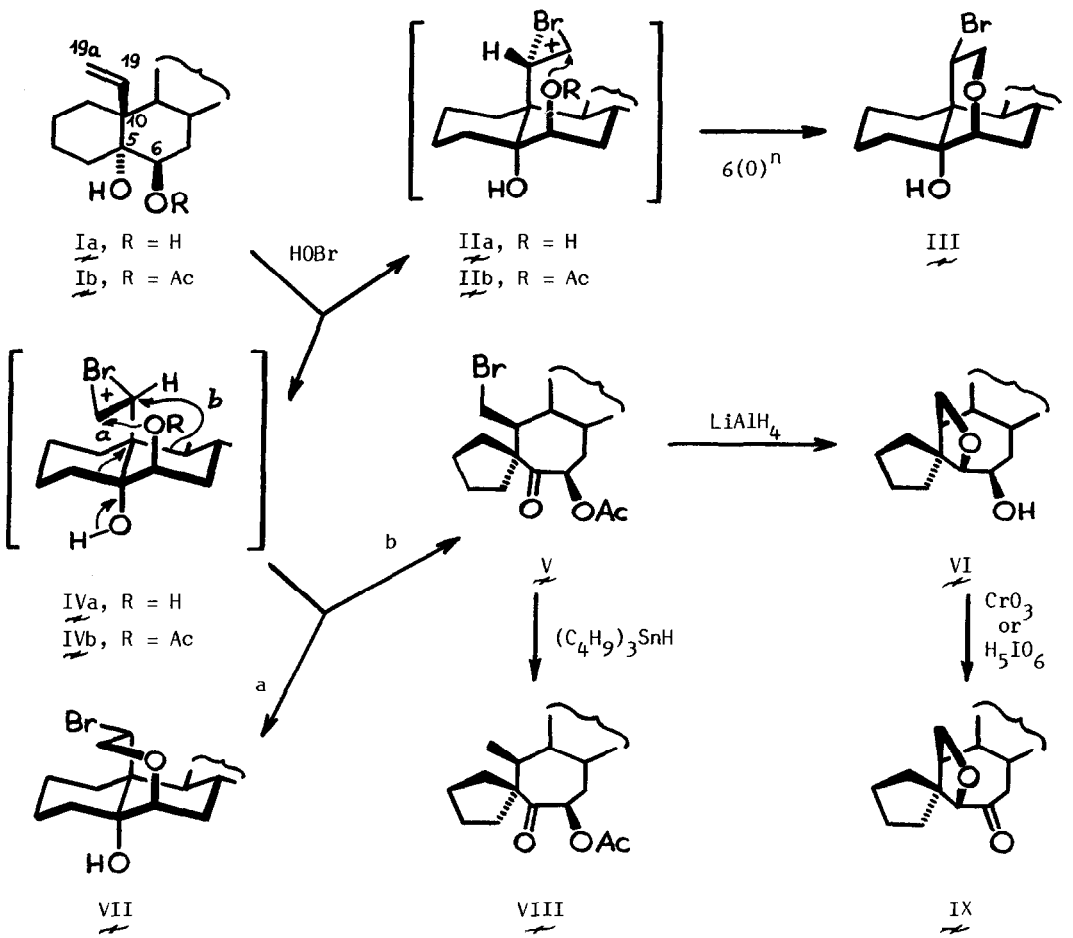
When treated with hypobromous acid (generated *in situ* from N-bromoacetamide and perchloric acid in aqueous dioxane) the unsaturated diol Ia afforded a mixture of the cyclic dibromoethers III and VII in a 83:17 ratio[7,8]. The reaction proceeds via two epimeric bromonium ions IIa and IVa which are further stereo- and regioselectively cleaved at $C_{(19a)}$ to give the corresponding products of $6(0)^n$ participation (for notation cf. ref.[6]), the epimers III and VII. The anti-Markovnikov cleavage of the bromonium ions IIa and IVa is probably due to steric hindrance at $C_{(19)}$ and easier approach of participating hydroxyl to $C_{(19a)}$ than to $C_{(19)}$ so that the cleavage at $C_{(19a)}$ is preferred. In previous papers[4-6] we demonstrated that neighboring group participation may proceed against the Fürst-Plattner rule in the cleavage of bromonium ions and epoxides. The present case may serve as an example of violation of the Markovnikov rule.

In contrast to the unsaturated diol Ia, the monoacetate Ib reacts with hypobromous acid in a more complex way, giving rise to three products: III (46% of the total yield), VII (5%) and the spirocyclic ketone V (49%). We assume the formation of two epimeric bromonium ions IIb and IVb in the first step. The (19S)-epimer IIb is cleaved by ether oxygen of the ambident 6β-acetoxy group in a normal course of a $6(0)^n$ participation to afford the cyclic ether III. On the other hand, 6β-acetoxyl-assisted fission of the epimeric bromonium ion IVb (path a) is relatively slow which results in formation of only trace amount of VII in the reaction mixture. Instead, the (19R)-bromonium ion IVb is rearranged (path b), the reaction being completed by conversion of the 5α-hydroxyl to a keto group. The facile rearrangement of IVb can be explained by the antiperiplanarity of

migrating bonds, which is secured by both the stereochemistry of the addition and the rigidity of the A/B ring junction. The rearrangement of the (19R)-bromonium ion IVb is probably enabled by decreased nucleophilicity of the ether oxygen of the 6β-acetoxy group which makes the competing $6(0)^n$ participation much slower than in 6β-alcohol (cf. ref. [5]).

The structure of the spirocyclic ketone V was deduced from the spectral data and will be discussed in detail in full paper. In order to confirm the proposed structure V we carried out some chemical transformations. Reduction of V with tri-n-butyltin hydride led to clean dehalogenation affording the acetoxy ketone VIII. Reduction of V with lithium aluminum hydride is accompanied by intramolecular displacement of the bromine atom so that a new oxygen-containing ring is formed (compound VI). This fact confirms the β-configuration of the CH_2Br group. Oxidation of VI with Jones' reagent and (rather surprisingly) periodic acid afforded the ketone IX.

The mechanism of the rearrangement posed some further questions as to what is the role of the oxygen-containing substituents at $C_{(5)}$ and $C_{(6)}$. In order to get a deeper insight, we prepared the 10β-vinyl-5α-hydroxy and 10β-vinyl-5α-methoxy derivatives Xa and Xb assuming that the

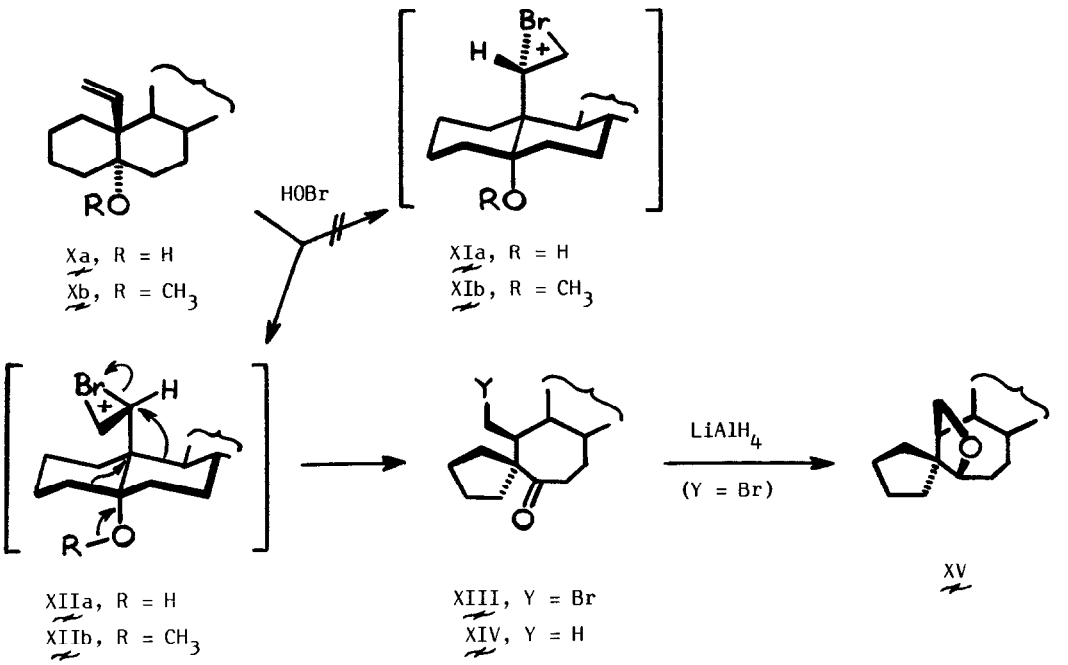


hydroxyl and methoxyl group could show a different propensity for conversion into the carbonyl group.

When treated with hypobromous acid, the unsaturated alcohol Xa as well as the methyl ether Xb furnished the spirocyclic ketone XIII as a single product in high yield. This compound was reduced with tri-n-butyltin hydride to the 10β-methyl derivative XIV, while reduction with lithium aluminum hydride led to the transannular epoxide XV.

The stereoselective formation of the ketone XIII can be explained analogously as described for V: in the first step, the attack of hypobromous acid upon the 10β-vinyl group leads to the (19R)-bromonium ion XII which is subsequently cleaved with concomitant shifts of C-C bonds. The non-involvement of the epimeric (19S)-bromonium ion XI is peculiar and it cannot be safely deduced from simple stereochemical considerations.

In 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.



Xa, R = H
Xb, R = CH_3

XIa, R = H
XIb, R = CH_3

XIIa, R = H
XIIb, R = CH_3

XIII, Y = Br
XIV, Y = H

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REFERENCES AND NOTES

1. Capon B., McManus S.P.: Neighboring Group Participation, Vol.1, Plenum Publishing Corpor., London 1976.
2. Kočovský P., Černý V.: Collect.Czech.Chem.Commun. 42, 155, 163, 353 (1977), 43, 327, 1924, 1933 (1978), 44, 128, 1496 (1979), 45, 925, 3023, 3030, 3190, 3199 (1980).
3. Kočovský P.: Collect.Czech.Chem.Commun. 45, 2998, 3008 (1980).
4. Kočovský P.: Tetrahedron Lett. 21, 555 (1980).
5. Kočovský P., Kohout L., Černý V.: Collect.Czech.Chem.Commun. 45, 559 (1980).
6. Kočovský P., Černý V., Synáčková M: ibid 44, 1483 (1979).
7. All compounds gave sufficient elemental analysis.
8. Physical and spectral data of the compounds:
   III. H-NMR: 0.68 (s, 18-H), 3.69 (1H,dd, J=10.3 and 3.7 Hz, 19a-exo-H), 3.92 (1H,dd, J=10.3 and 9.1 Hz, 19a-endo-H), 4.14 (1H,d, J=4.0 Hz, 6α-H),4.69 (1H,dd, J=9.1 and 3.7 Hz, 19-H). Mass: m/z 560, 558, 556, 545, 543, 541, 479, 477, 461, 459, 397, 380, 355.
   V. H-NMR: 0.66 (3H,s, 18-H), 2.12 (AcO), 3.61 (1H,dd, J=9.8 and 9.8 Hz, 19-H), 3.87 (1H,dd, J=9.8 and 2.0 Hz, 19-H), 5.38 (1H,dd, J=8.9 and 7.4 Hz, 7α-H). C-NMR: 12.10, 18.56, 20.57, 22.52, 22.76, 23.73, 24.52 (2C), 25.45, 27.84, 27.94, 32.48, 33.94, 35.64, 35.99, 36.41, 37.27, 38.38, 38.49, 39.43, 42.37, 47.90, 54.87, 56.04, 56.20, 60.98, 75.44, 172.8. Mass: m/z 538, 536, 497, 495, 478, 476, 457, 437, 435, 428, 415, 397, 379, 369, 368. IR: 1242, 1720, 1746 cm^{-1}. CD: $\Delta\varepsilon$ = +2.37, 288 nm.
   VI. H-NMR: 0.73 (3H,s, 18-H), 3.67 (1H,dd, J=7.7 and 1.0 Hz, 19-endo-H), 3.76 (1H,d, J=5.0 Hz, 6α-H), 4.03 (1H,ddd, J=5.0, 3.0 and 3.1 Hz, 7α-H),4.17 (1H,dd, J=7.7 and 8.1 Hz, 19-exo-H). Mass: m/z 416, 398, 368, 356, 317, 274, 137. IR: 3425, 3615 cm^{-1}.
   VII. H-NMR: 0.69 (3H,s, 18-H), 3.56 (1H,dd, J=10.1 and 4.1 Hz, 19a-H), 3.73 (1H,dd, J=10.1 and 10 Hz, 19a-H), 4.12 (1H,m, overlapped, 6α-H), 4.23 (1H,dd, J=9.5 and 4.1 Hz, 19-H).
   VIII. H-NMR: 0.65 (3H,s, 18-H), 1.10 (3H,d, J=7.1 Hz, 19-H), 2.13 (AcO), 5.52 (1H,dd, J=6.4 and 5.2 Hz, 7α-H). Mass: m/z 458, 430, 417, 398, 370, 330, 301. IR: 1250, 1416, 1712, 1738 cm^{-1}. CD: $\Delta\varepsilon$= -1.54, 288 nm.
   IX. H-NMR:0.67 (3H,s, 18-H), 1.89 (1H,d, J=6.2 Hz, 10α-H), 2.14 (1H,d, J=11.8 Hz, 7aβ-H), 2.66 (1H,dd, J=11.8 and 9.7 Hz, 7aα-H), 3.79 (1H,s, 6α-H), 3.92 (1H,d, J=8.5 Hz, 19-endo-H), 4.33 (1H,dd, J=8.5 and 6.2 Hz, 19-exo-H). Mass: m/z 414, 386, 355, 317, 305, 123.
   XIII. H-NMR: 0.77 (3H,s, 18-H), 2.87 (1H,ddd, J=12.7, 12.7 and 4.4 Hz, 7α-H), 3.29 (1H,dd, J=10.0 and 10.0 Hz, 19-H), 3.56 (1H,dd, J=10.0 and 1.6 Hz, 19-H). C-NMR: 12.00, 18.63, 22.57, 22.83, 23.84, 24.84, 25.77, 25.90, 28.03 (2C), 28.90, 31.31, 34.93, 35.79, 36.11 (2C), 39.53, 39.81 (2C), 42.38, 42.75, 46.36, 53.66, 56.04, 56.99, 64.19 . Mass: m/z 480, 478, 439, 437, 399, 384, 381, 370. IR: 1708 cm^{-1}.
   XIV. Mass: m/Z 400, 382, 359, 341, 332, 287.
   XV. H-NMR: 0.72 (3H,s, 18-H), 3.70 (1H,d, J=8.0 Hz, 19-exo-H), 3.80 (1H,d, J=5.2 Hz, 6α-H), 4.18 (1H,dd, J=8.0 and 8.0 Hz, 19-endo-H). C-NMR: 12.67, 18.63, 22.50, 22.70, 23.85 (2C), 24.60, 25.90 (2C), 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: m/z 400, 382, 369, 332.

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