THE ACID-CATALYZED OXIDO-REDUCTION OF SPIROKETALS. EVIDENCE FOR STEREOELECTRONIC CONTROL IN HYDRIDE TRANSFER TO CYCLIC OXENIUM IONS†

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Tricyclic spiroketal 1 undergoes an acid-catalyzed oxidation-reduction reaction which yields equatorial bicyclic ether aldehyde 5 specifically. Similarly, spiroketals 2, 3, and 4 gave equatorial bicyclic ether ketone 12. These results are interpreted by invoking an internal hydride transfer from an alcohol function to a cyclic oxenium ion which takes place with stereoelectronic control.

We have recently shown that the 1,7-dioxaspiro[5.5]undecane and its derivatives provide a very convenient system for the study of stereoelectronic effects (anomeric and exo-anomeric effects) in the acetal function (1, 2). In the course of that study, we observed that these spiroketals undergo an acid-catalyzed oxidation-reduction reaction. We wish to report that investigation.

We have studied the tricyclic spiroketal 1[1] and the three isomeric methyltricyclic spiroketals 2[1], 3[1], 4[1] (Scheme I).

Treatment of tricyclic spiroketal 1 with hydrogen bromide in ether-pentane gave stereospecifically the bicyclic ether aldehyde 5[2] (≈40% yield). Reduction ($LiAlH_4$, ether) of compound 5 gave the corresponding alcohol 6[2] which was further characterized by formation of the acetate derivative 7[2]. The structure and the stereochemistry of bicyclic ether alcohol 6 was established by comparison with an authentic sample.

Authentic samples of compound 6 and its isomer 8 were obtained from the monocyclic ketone mesylate 9[3]. Reduction of compound 9 ($NaBH_4$, CH_3OH) gave a mixture of the isomeric alcohols 10[2]

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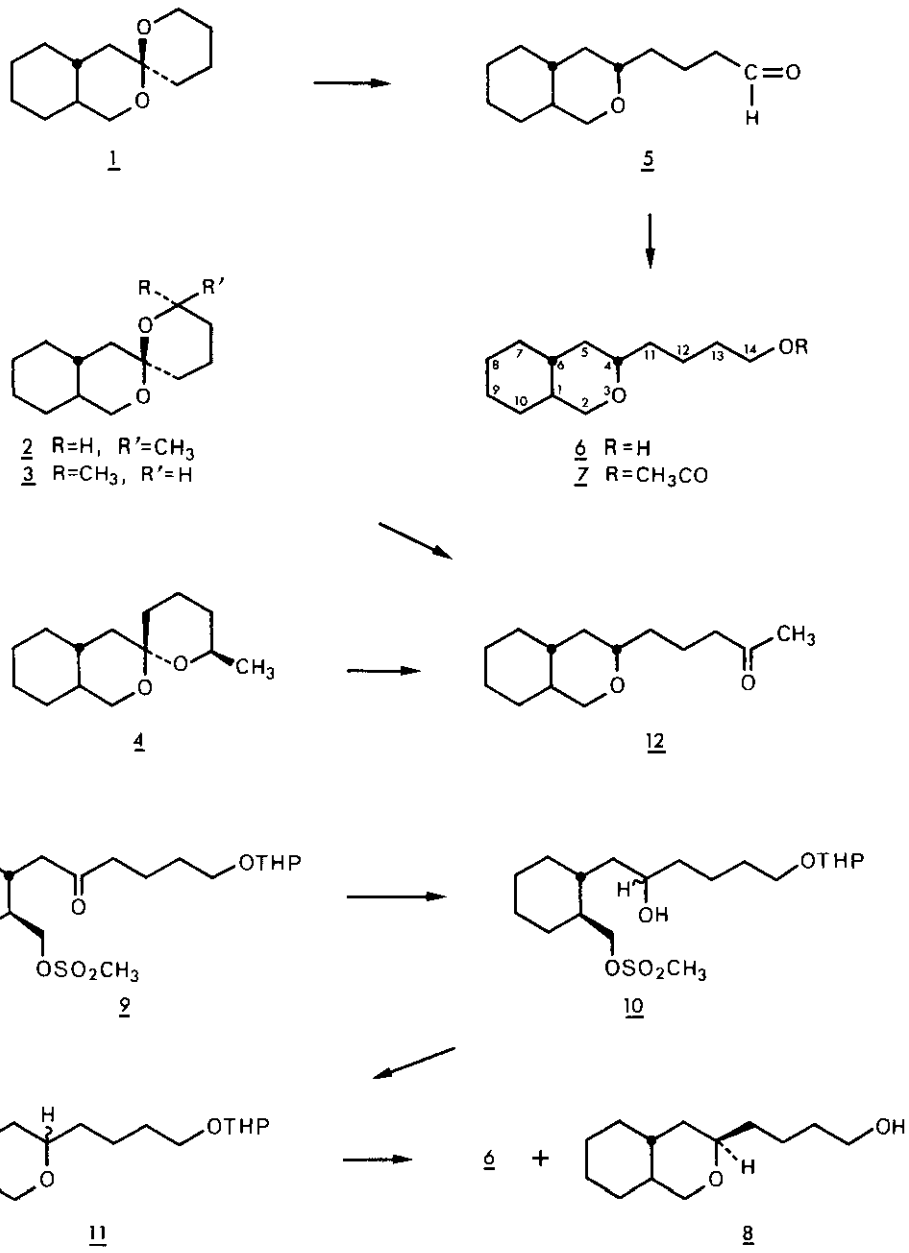
† We are pleased to dedicate this article to Professor Tetsuji Kametani.

1 The preparation of this compound is described in reference 1.

2 All new compounds gave satisfactory spectroscopic data. High resolution ms were obtained for alcohols 6 and 8, to which other new compounds are chemically converted.

3 The preparation of compound 9 is described in reference 3.

which was transformed (KH, THF) into the isomeric mixture of THP-bicyclic ethers 11[2]. Acid hydrolysis of the mixture 11 gave the bicyclic ether alcohols 6[2] and 8[2] which were separated by chromatography. The relative stereochemistry of isomers 6 and 8 was established by carbon nuclear



SCHEME 1

magnetic resonance spectroscopy. In particular, the carbons 2, 4, and 6, γ, α, and γ respectively to C_{11} of the side chain, show shieldings of 7.7, 4.8, and 5.8 ppm (4) on passing from 6 to its axial epimer 8.

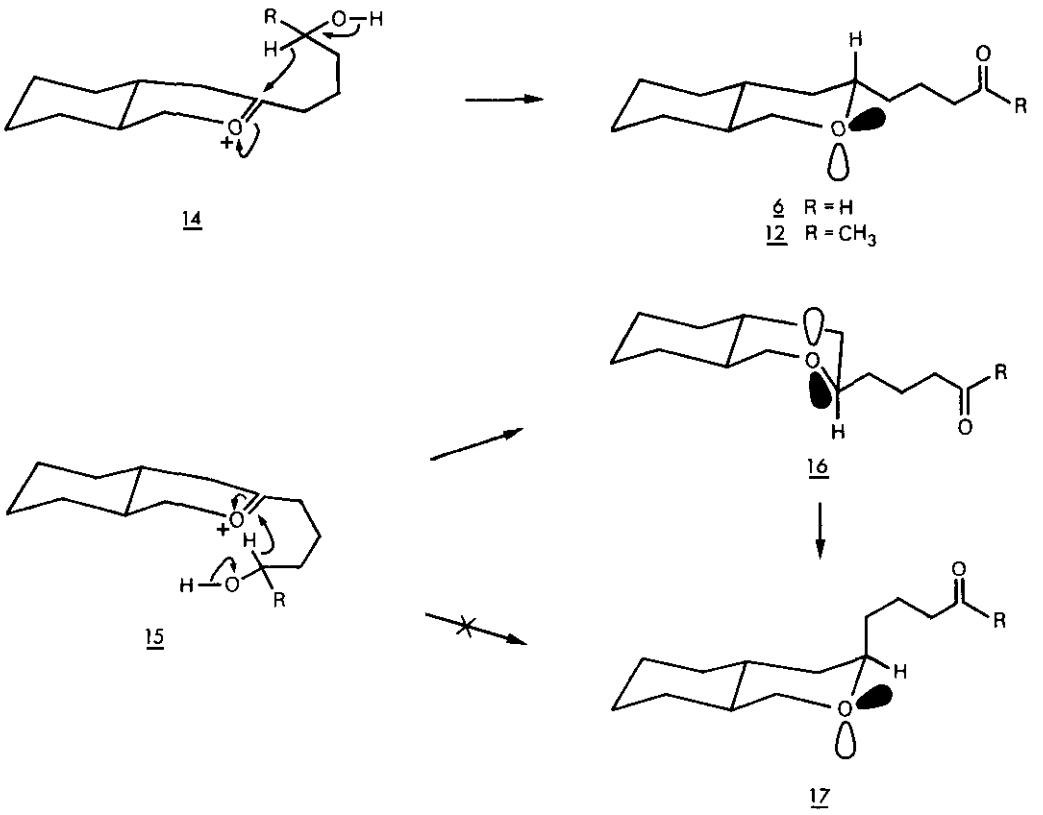
We have also observed that the tricyclic spiroketal 2 or its isomer 3 gave the bicyclic ether methyl ketone 12[2] (≃100% yield) with aqueous hydrochloric acid under reflux conditions. Similarly, treatment of the isomer 4 (which is interconvertible with 3 under mild acidic conditions (1)) gave compound 12 upon reflux with aqueous hydrochloric acid. The structure and the stereochemistry of the bicyclic ether methyl ketone 12 was rigorously established by its conversion into the bicyclic ether alcohol 6 (NaOBr, NaOH; $LiAlH_4$).

The acid-catalyzed oxido-reduction reactions described above can be readily explained by the opening of the spiroketals giving an hydroxy bicyclic oxenium ion intermediate such as 13 which undergoes an internal hydride transfer to yield the bicyclic ether 6 or 12. This mechanism is very similar to the one proposed by Woodward, Sondheimer, and Mazur (5) to explain the acid-catalyzed interconversion of the normal and the iso sapogenins. Their proposal was also supported by strong experimental evidence.

13 → 6 R=H; 12 R=CH_3

The stereospecific formation of the equatorial bicyclic ethers 6 and 12 can be explained if stereoelectronic effects (6) are taken into consideration. If we accept that the hydride transfer will take place with minimum energy only when the intermediate oxenium ion can develop an electron pair which will become antiperiplanar to the newly formed C—H bond in the final product, the above results can be easily rationalized.

It can be readily seen that the β-attack on 13, i.e. 14 → 6 or 12 can occur with stereoelectronic control whereas the α-attack on 13 (i.e. 15) cannot yield directly the axial bicyclic ether in its more stable conformation 17. The α-attack on 13 must first give conformer 16 having its ring B twisted in order to fulfill the orbital alignment requirement. Conformer 16 would then give the most stable conformation 17. The transformation 15 → 16 → 17 requires more energy than 14 → 6 (or 12). Consequently, the formation of 17 cannot compete with the formation of equatorial bicyclic ether 6 or 12.



SCHEME 2

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