

## Reaction of Ozone with Steroidal Allylic Alcohols: Evidence for Intramolecular Interception of the 'Criegee Carbonyl/Carbonyl Oxide Intermediate'

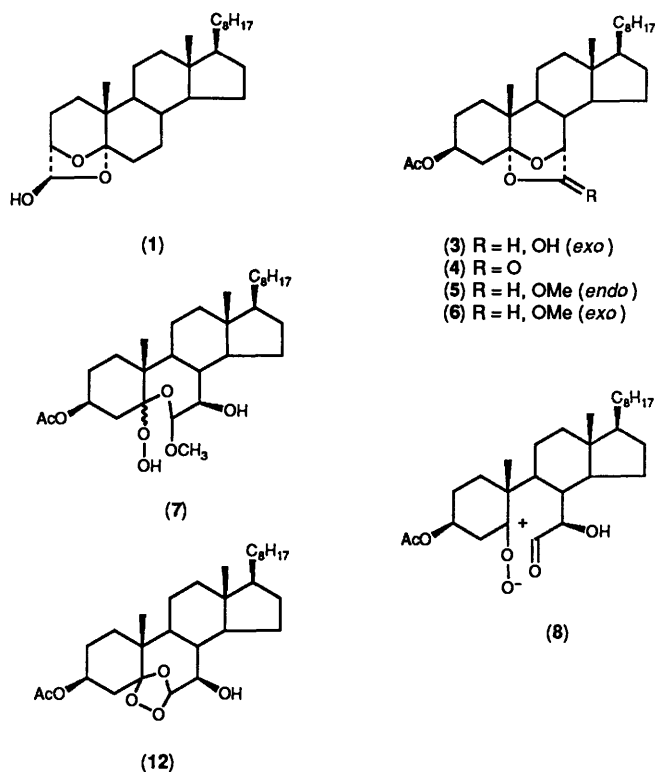
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The reaction of 3 $\beta$ -acetoxycholest-5-en-7 $\beta$ -ol with ozone at  $-70^\circ\text{C}$  gives 3 $\beta$ -acetoxy-7 $\beta$ -hydroxy-5,7a $\beta$ -epoxy-5 $\beta$ -*B*-homo-6-oxacholestane (3) and 3 $\beta$ -acetoxy-7 $\beta$ -hydroperoxy-5,7a $\beta$ -epoxy-5 $\beta$ -*B*-homo-6-oxacholestane (11) resulting from the interception of a classical carbonyl/carbonyl oxide intermediate by intramolecular nucleophilic attack of the allylic hydroxy group on the carbonyl carbon atom. It is shown also that the two possible modes of cleavage of the primary ozonide are realized.

Ozonolysis of olefins is a standard method for oxidative cleavage of carbon-carbon double bonds. In alicyclic olefins, the structure of primary ozonolysis products depends on the structure of an olefin and the reaction conditions.<sup>1</sup> In the steroid field the reaction is not frequently used,<sup>2,3</sup> besides for degradative purposes.<sup>4</sup> Also not much work has been devoted to the structure determination of oxidation products resulting from the reaction of ozone with steroidal olefins.<sup>5</sup> Dry ozonations of steroids adsorbed on silica gel as a method of functionalization of unactivated carbons was developed.<sup>6</sup> Recently, ozonolysis of cholesterol in participating<sup>7</sup> and non-participating<sup>8</sup> solvents has been reported. There seems to be no report on ozonation of steroidal substrates, which besides the reactive double bond comprise an additional group capable of interaction with intermediates postulated in the Criegee mechanism of ozonolysis.<sup>9</sup> Only very recently, participation of a hydroxy group in the ozonation of diterpenoidal  $\delta$ -hydroxy olefins has been reported.<sup>10</sup>

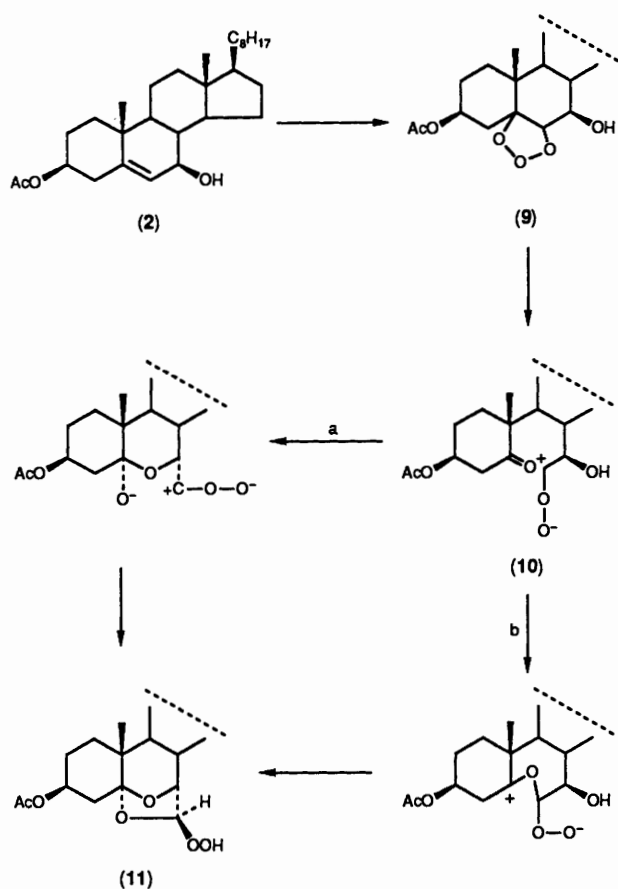
In the course of our investigation of the reaction between ozone and crowded olefinic double bonds present in alicyclic systems of steroid type<sup>5</sup> we found that reaction of ozone with a steroidal allylic alcohol, cholest-4-en-3 $\beta$ -ol, afforded an oxygenated product of structure (1). A similar, unique arrangement of atoms, that is the structure comprising the dioxolanone fragment, is present in thysanolactone. This is a highly oxygenated triterpenoid isolated from *Thysanospermum diffusum*.<sup>11</sup>

The reaction of 3 $\beta$ -acetoxycholest-5-en-7 $\beta$ -ol (2) with ozone has been examined in order to establish the general character of intramolecular participation of a hydroxy group in the course of ozonolysis of steroidal allylic alcohols. Treatment of (2)



dissolved in ethyl acetate with ozone at  $-78^\circ\text{C}$  gave, after the reductive work-up, compound (3)† as the only product (95% yield). The hydroxy-dioxolane (3) was oxidized to the dioxolanone (4). When the reaction was carried out in chloroform-methanol the methoxy compounds (5) and (6) were obtained besides (3) after the reductive work-up of the crude reaction product. However, when the crude ozonation product from the reaction carried out in chloroform-methanol was worked-up under non-reducing conditions (evaporation of the solvent) compounds having peroxidic character were isolated. The less polar product (15% yield) was assigned structure (7) on the basis of spectral data. The hydroperoxide (7) is the product from interception of the carbonyl/carbonyl oxide intermediate (8) with the participation of methanol as an external nucleophile. The second product obtained in 12% yield was characterized on the basis of its <sup>1</sup>H NMR and IR spectra as a hydroperoxide (11). Compound (11) could be reduced to the hydroxydioxolane (3) by either zinc in acetic acid or dimethyl sulphide. The stereochemistry of the new steroidal dioxlanes

† All new compounds gave satisfactory elemental analyses and mass spectral fragmentations in accord with the assigned structures; <sup>1</sup>H NMR spectra were recorded with a JEOL FX 90Q spectrometer (CDCl<sub>3</sub>, TMS) and IR spectra with Perkin-Elmer 580 spectrophotometer (CCl<sub>4</sub>). Selected data are as follows. (3): M.p. 146–149°C;  $\delta$  5.27 (1 H, d, *J* 9.4, 6 $\alpha$ -H), 4.98 (1 H, m, 3 $\alpha$ -H), 4.00 (1 H, d, *J* 3.2, 7 $\alpha$ -H), and 2.89 (1 H, d, *J* 9.4, OH);  $\nu_{\text{max}}$  3 675 and 3 445 cm<sup>-1</sup>. (4): M.p. 125–127°C;  $\delta$  4.96 (1 H, m, 3 $\alpha$ -H), and 4.20 (1 H, d, *J* 3.2, 7 $\beta$ -H);  $\nu_{\text{max}}$  1 790 and 1 730 cm<sup>-1</sup>. (5): M.p. 123–126°C;  $\delta$  5.07 (1 H, d, *J* 3.7, 6 $\beta$ -H), 3.91 (1 H, br d, 7 $\alpha$ -H), and 3.45 (3 H, s, OCH<sub>3</sub>). (6): M.p. 110–112°C;  $\delta$  4.93 (1 H, br s, 6 $\alpha$ -H), 4.04 (1 H, d, *J* 3.4, 7 $\alpha$ -H), and 3.37 (3 H, s, OCH<sub>3</sub>). (7): Oil;  $\delta$  9.95 (1 H, s, 5-OOH), 4.89 (1 H, m, 3 $\alpha$ -H), 4.30 (1 H, d, *J* 7.6, 6-H), 4.04 (1 H, m, 7 $\alpha$ -H), and 3.54 (3 H, s, OCH<sub>3</sub>);  $\nu_{\text{max}}$  3 600, 3 330, and 1 737 cm<sup>-1</sup>. (11): Oil;  $\delta$  9.80 (1 H, s, OOH, disappears upon D<sub>2</sub>O addition), 5.47 (1 H, br s, 6 $\alpha$ -H), 4.98 (1 H, m, 3 $\alpha$ -H), and 4.09 (1 H, d, *J* 3.2, 7 $\alpha$ -H);  $\nu_{\text{max}}$  3 380 and 1 730 cm<sup>-1</sup>. (12): Oil;  $\delta$  5.46 and 5.45 (1 H, two s, 6-H), 5.11 (1 H, m, 3 $\alpha$ -H), and 3.45 (1 H, m, 7 $\alpha$ -H).



Scheme.

reported here follows from the characteristic coupling patterns in their  $^1\text{H}$  NMR spectra.

Isolation of the hydroperoxides (7) and (11) provides evidence that the primary ozonation product, a 1,2,3-trioxolane (9), gives two 'seco' intermediates (8) and (10), both having a carbonyl/carbonyl oxide feature. While (8) reacts with an external nucleophile, the Criegee intermediate (10) is, in turn, intercepted as a result of intramolecular nucleophilic attack of the originally allylic 7-hydroxy group on the carbonyl carbon atom C-5 to give formation of (11). The final ozonide, 1,2,4-trioxolane (12) was not found among the ozonation products when the reaction was carried out in methanolic solution. It was found, however, that the reaction of (2) with ozone is dependent on the polarity of the solvent. For example, in hexane, the expected ozonide (12) (as a mixture of C-6 epimers) was isolated (26%) besides compounds (3) (25%) and (4) (12%).

A plausible mechanism for this new transformation of the

steroidal allylic alcohol with ozone is shown in the Scheme. It is difficult to draw a firm conclusion about the stepwise character of the reaction. Both routes (a) and (b) require C(7)–C(8) bond rotation by *ca.*  $120^\circ$ . A high degree of concertedness in the process leading from (9) to (11) may not be excluded, however.

The reactions described represent a new case of intramolecular nucleophilic interception of carbonyl/carbonyl oxide intermediate, formation of which is considered as an essential step in the widely accepted Criegee mechanism of the reaction of ozone with alkenes. The present work shows also that both possible modes of cleavage of the ozonide are realized, as indicated by products (7) and (11), derived from (8) and (10), respectively. The synthetic value and the general character of this new reaction is under investigation. Consequently, our synthetic results, especially the isolation of the hydroperoxide (11), suggest the necessity of reinvestigating the structure of the principal product formed in the reaction of cholesterol in participating solvents.

#### Acknowledgements

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