

## Selective Hydrocarbon Oxidation: Dry Ozonation of Steroids on Silica

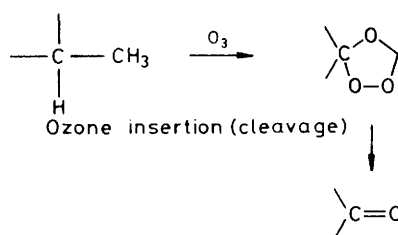
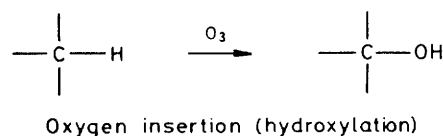
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Dry ozonation of steroids on silica gives ring- $\alpha$  oxidised products, including isomeric ozonides, which confirm the postulated mechanism of saturated C–C bond cleavage.

Dry ozonation of saturated hydrocarbons adsorbed on silica gel or other inorganic supports results in oxygenation, with a pronounced selectivity for tertiary centres<sup>1</sup> (Scheme 1). It has been shown that oxygen insertion into C–H bonds is stereospecific and that in complex molecules regioselective reactions can result from the directing effect of substituents.<sup>2,3</sup> We report products from dry ozonation of the steroid nucleus which demonstrate selectivity even in the absence of polar substituents and shed light on the mechanism of C–C bond cleavage.

In a representative experiment 5 $\alpha$ -cholestanyl-3 $\beta$ -acetate (**1**) was adsorbed onto Woelm GIII silica gel (1% w/w) and treated with ozone at  $-30 \pm 10$  °C for 1 h. After allowing the apparatus to warm to room temperature the reaction mixture was fractionated by short column chromatography. The most polar mobile product was identified as the 14 $\alpha$ -alcohol (**2**), ( $m/z$  446), by spectroscopic examination and dehydration to the known  $\Delta^{14}$ -olefin.<sup>4</sup> Fractionation of the products of intermediate polarity by h.p.l.c. gave three compounds, the most polar of which was identified as 14 $\alpha$ ,15 $\alpha$ -epoxycholestanyl-3 $\beta$ -acetate (**3**), [ $m/z$  444, <sup>1</sup>H n.m.r. spectrum,  $\delta$  0.838 (3H, s, 18-

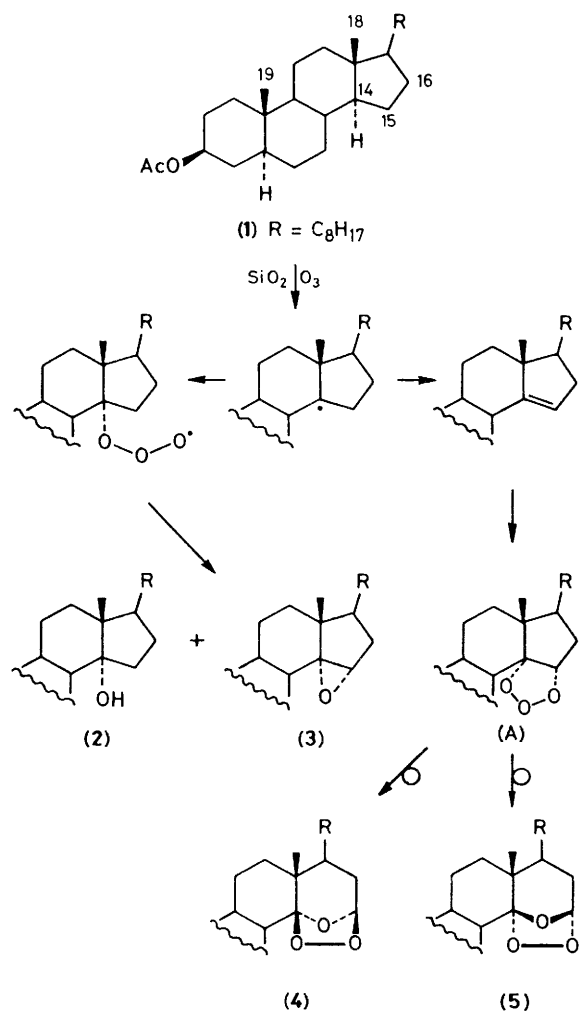


Scheme 1

CH<sub>3</sub>), 0.842 (3H, s, 19-CH<sub>3</sub>): (calc.,  $\delta$  0.833, 0.850),<sup>5</sup> 3.30 (1H, br. s, 15-H)].<sup>14</sup> Assignment was confirmed by synthesis from the  $\Delta^{14}$ -olefin.

The two less polar products, present in a 1:1 ratio gave physical data consistent with their assignment as isomeric ozonides, formed by cleavage of the C-14–C-15 bond. For each compound chemical ionisation mass spectrometry showed a molecular ion at  $m/z$  476 and accurate mass measurements identified the major fragments as  $M - H_2O$ ,  $-O_2$  with subsequent loss of the sidechain. The more polar ozonide is assigned structure (4) since the  $^1H$  n.m.r. spectrum contained a characteristic broad doublet ( $J$  7, 1.5 Hz) at  $\delta$  5.75, assigned to 15-H, together with ring methyl signals at  $\delta$  0.797 (19- $CH_3$ ) and  $\delta$  0.944 (18- $CH_3$ ). The corresponding signals for the second isomer (5) were at  $\delta$  5.72 (br. t,  $J$  ca. 1 Hz), 0.789 and 0.978. Assignment of stereochemistry at C-14 and C-15 in (5) is based on the unusually small coupling constant observed for 15-H, resulting from steric interaction of the peroxide bridge and C-17, which forces the sidechain into a pseudo-equatorial conformation.

The yields of (2)–(5) were shown to be strongly dependent on ozonation time, temperature, and rate of warming to room temperature following ozonation. Under the conditions described the isomeric ozonides accounted for 20% of the material balance, the epoxide and alcohol for 10%, and the starting material for 60%. Polar unidentified residues, which increase in amount as more complete ozonation is attempted, constituted the remaining fraction. Hydroxylation at C-25 was not observed under these conditions.<sup>2</sup> Under similar



Scheme 2

conditions 5 $\alpha$ -cholestane, 5 $\alpha$ -cholestan-3-one, and 5 $\alpha$ -androstan-3-one afforded as major products the corresponding ozonides and epoxide in the same proportions.

The results demonstrate that, in contrast with their inertness to ozone in solution, saturated steroids adsorbed on silica gel undergo both C–C and C–H bond cleavage reactions. Furthermore, the predominance of reaction at C-14 is largely a function of particular C–H bond strengths or orientation on the surface of the support, since there is no significant influence of polar ring-A substituents on product distribution. It is also evident that, following initial attack of ozone, the subsequent reactions leading to ozonide formation are influenced by the support, since ozonolysis of 5 $\alpha$ -cholest-14-enyl-3 $\beta$ -acetate in carbon tetrachloride gives only isomer (4) while, on silica gel, (4) and (5) are again formed in a 1:1 ratio.

We conclude that silica gel mediates in the initial attack by the biradical ozone molecule at C-14<sup>7</sup> (radical abstraction at C-14 in the steroid nucleus is well known<sup>8</sup> and that the radical produced either captures another ozone molecule, leading to formation of (2) and (3), or undergoes loss of 15-H<sup>9</sup> to give the intermediate  $\Delta^{14}$ -olefin, which is then ozonolysed (Scheme 2). [Dehydration of (2) was not observed under the reaction conditions.] The formation of (4) and (5) may be regulated by specific interaction between the support and the intermediates involved in rearrangement of the primary ozonide (A), permitting formation of the thermodynamically unfavoured isomer (5).

The peculiar stability of the steroidal 14,15-ozonides has permitted the first isolation of a postulated intermediate in saturated hydrocarbon C–C bond cleavage by ozone, in a reaction that is also of preparative value for steroid ring-D transformations. Advantages of using silica gel as a support for alkene ozonolysis have recently been reported.<sup>10</sup>

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