Remote Oxidation of Fatty Acid Esters

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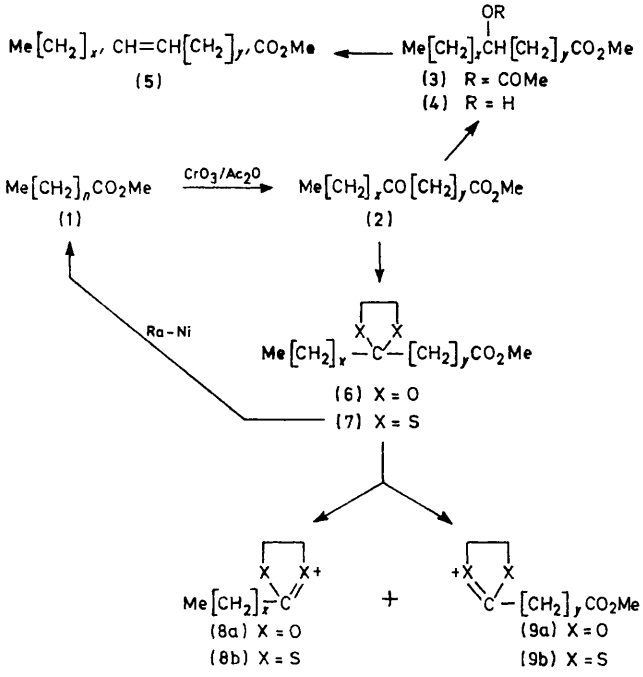
Summary The direct conversion of methyl stearate and homologous esters into monoketo derivatives is described.

REGIOSPECIFIC oxidation of compounds at non-activated positions is a characteristic feature of certain enzymic reactions and numerous attempts have been made to duplicate these transformations in the laboratory.[1] A recent review[2] outlines the potential significance of such processes in organic synthesis and provides an excellent description of recent approaches which have been used, with varying success, to oxidise biologically important substrates at specific unreactive positions.

Our approach differs from those previously described since it is based on the notion that certain molecules are intrinsically susceptible to oxidation at centres which are generally considered to be unreactive.

To test this idea we have examined the oxidative vulnerability of various natural product systems† and in this report we describe the direct oxidation of fatty acid esters. Treatment of pure methyl stearate (1; $n = 16$) in acetic acid–acetic anhydride with chromium trioxide in acetic anhydride[3] at room temperature for 24 h provided a mixture of methyl ketostearates (2; $x + y = 15$) and starting material. [*Warning:* the oxidising solution (CrO_3–Ac_2O) can be explosive and must be made up and used under



controlled conditions (< 25 °C)]. The keto-esters‡ were separated from starting material by column chromatography and their identification as methyl monoketostearates is based on m.s., i.r., and n.m.r. data. This structural assignment was supported by reduction to the corresponding hydroxy-esters (4), acetoxy esters (3) and unsaturated esters (5). The relative amounts and identification of each of the monoketo-derivatives of methyl stearate present in the product mixture was deduced from the mass spectra§ of the corresponding ethylene acetals

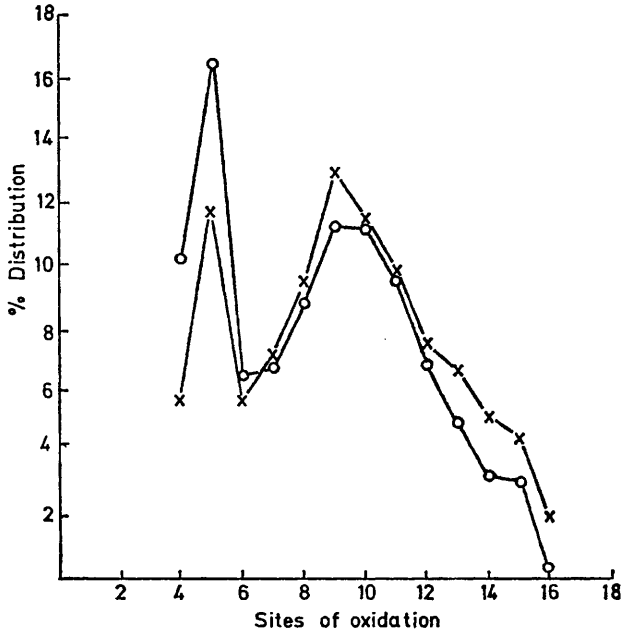


FIGURE 1. Oxidation of methyl stearate [data from low resolution (15 eV) spectrum of acetals (6; $x + y = 15$): –×——×– based on fragment (8a): –○——○– based on fragment (9a)].

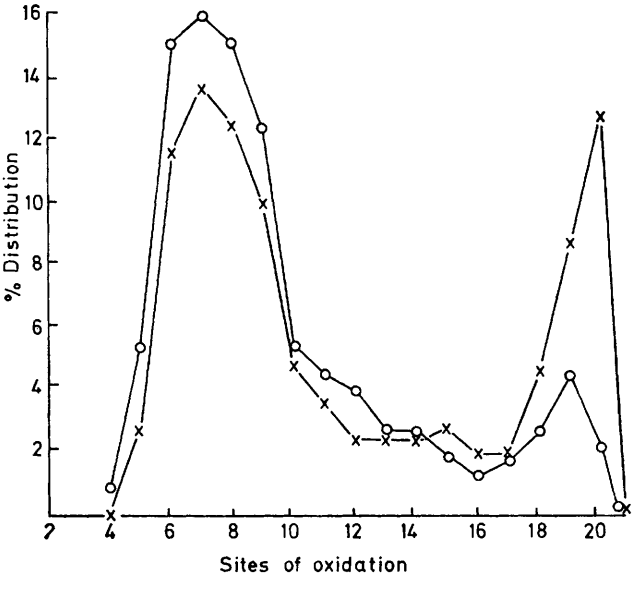


FIGURE 2. Oxidation of methyl docosanoate [data from low resolution (15 eV) mass spectrum of thioacetals (7; $x + y = 19$): –×——×– based on fragment (8b): –○——○– based on fragment (9b)].

† Our initial results, obtained with terpenoid compounds, will be described in a later report.
‡ The yield of recovered methyl x-ketostearates was 65% based on consumed starting material. G.l.c. examination of the crude reaction product indicated a much higher yield.
§ The low and high resolution mass spectra were recorded at 15 eV and 70 eV on Atlas CH-4 and A.E.I. MS 902 instruments.

(**6**; $x + y = 15$) and ethylene thioacetals (**7**; $x + y = 15$).¶ In the low resolution spectra of (**6**) and (**7**) measured at 15 eV the only significant peaks are due to fragments (**8a,b**) and (**9a,b**).†† However, the fragmentation process was non-random when the acetal or thioacetal group was located towards the end of the chain and this is reflected in the differences between the two sets of results displayed in Figure 1. In spite of these limitations it seems reasonable to conclude that methyl stearate is susceptible to oxidation and that there is modest selectivity for attack at biologically interesting positions.

Subsequent studies demonstrated that methyl decanoate (**1**, $n = 8$), methyl myristate (**1**, $n = 12$), methyl palmitate (**1**, $n = 14$) and methyl docosanoate (**1**, $n = 20$) were also converted into a mixture of monoketo-derivatives when treated with chromyl acetate solution. In each case the characterisation and estimation of the relative amounts of isomeric keto-esters was accomplished by the procedures described above. The results, which will be presented in detail in a more comprehensive report, indicate that the oxidation of methyl stearate (*cf.* Figure 1) and methyl docosanoate (*cf.* Figure 2) is more regiospecific than that of the lower homologues.

While the mechanism of these reactions remains uncertain it seems reasonable to suggest that the partially selective oxidation of fatty acid esters may be associated with the preferred conformation(s) of these compounds in the reaction medium.

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¶ We are grateful to Professor R. Breslow (Columbia) for his advice on this method of analysing mixtures of straight-chain ketones.

†† The mass spectrum (measured at 15 eV) of an authentic mixture of acetals derived from equal amounts of methyl 9- and 10-ketostearate shows clean fragmentation and provides a quantitative estimation in reasonable agreement with the known composition of the mixture.

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[2] R. Breslow, *Chem. Soc. Rev.*, 1972, **1**, 553.

[3] *Cf.* J. Bredt and A. Goeb, *J. Prakt. Chem.*, 1921, **101**, 273; N. J. Toivonen and A. Halonen, *Suomen Kemistilchti*, 1946, **19B**, 1 (*Chem. Abs.*, 1946, **41**, 5487).