Synthesis and characterization of long-chain 1,2-dioxo compounds

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Abstract

A series of long-chain methyl esters with vicinal oxo groups (1,2-diones; 1,2-diketones) were synthesized by potassium permanganate-based oxidation of methyl esters of mono-unsaturated fatty acids. The presence of two additional carbonyl groups may facilitate the synthesis of other derivatives. The starting materials were selected in such a fashion to give the 1,2-dioxo moiety in consecutive positions from the methyl ester group. The compounds were characterized by mass spectrometry and nuclear magnetic resonance spectroscopy. In mass spectrometry, both electron and chemical ionization (methane as reagent gas) were investigated. The position of the dioxo moiety can be determined in both ionization modes, however, in electron ionization mode the corresponding fragment ions are considerably stronger. In electron ionization mode, a fragmentation mechanism depending on the position of the 1,2-dioxo moiety occurs while the spectra derived from chemical ionization mode are mainly characterized by peaks around the molecular ion with both ionization modes appearing suitable. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Long-chain dioxo compounds; Mass spectrometry; Nuclear magnetic resonance; Oxidation; Potassium permanganate; 1,2-Dioxo compounds

1. Introduction

Oxygenated fatty acids are well-known and many such compounds containing hydroxy or keto groups have been described. In the realm of oxo fatty acids, mainly those containing one such functionality have been isolated, synthesized or characterized (Brechany and Christie, 1992, 1994; Nakano and Foglia, 1982; Plattner et al., 1983; Ryhage and Stenhagen, 1960a; Tulloch, 1977; Weihrauch et al., 1974). Among the diketo fatty acids, 1,4-dioxo fatty acids (or esters) of chain lengths ≤ C₁₄ have been reported (Brown et al., 1984; Stetter and Lorenz, 1985). The 1,2-dioxo fatty acids (1,2-diones; 1,2-diketones) are easily accessible in one step from the corresponding
mono-unsaturated fatty acids (Scheme 1). A procedure (Jensen and Sharpless, 1974) using potassium permanganate-based oxidation has been usually employed in the literature. Historically, the permanganate-based oxidation of stearolic acid (9-octadecynoic acid) to 9,10-dioxostearic acid was investigated (Khan and Newman, 1952, and references therein) as was the conversion of stearolic acid with oxidizing reagents such as chromic acid and nitric acid (Nicolet and Jurist, 1922). The oxidation of double bonds with potassium permanganate, a classic oxidation reagent in organic chemistry, often in combination with co-reagents, to give diones, diols, and even double bond cleavage, has found considerable attention in the literature (for a review, see Fatiadi, 1987). A discussion of that chemistry is beyond the scope of the present paper.

A systematic characterization of long-chain 1,2-dioxo fatty acids has been lacking in the literature. In this paper, the synthesis and systematic characterization of such compounds in form of their methyl esters is reported. Specifically, compounds with vicinal oxo groups in consecutive positions (5,6-positions to 13,14-positions) from the methyl ester moiety were synthesized using the aforementioned literature procedure (Jensen and Sharpless, 1974) and the appropriate starting materials. These 1,2-diones may serve as synthons for other derivatives (for a recent example, see Lie Ken Jie et al., 2001) besides being worthy of investigations for applications of their own.

2. Experimental

Fatty acid methyl esters (all double bonds with cis configuration) were acquired from Nu-Chek-Prep, Inc. (Elysian, MN). Potassium permanganate and acetic anhydride were obtained from Fisher Chemical (Fair Lawn, NJ).

All GC-MS runs were conducted on a Hewlett-Packard (Palo Alto, CA) 5890 Series II Plus gas chromatograph (column: 30 m x 0.25 mm HP-5MS; Hewlett-Packard Co.) coupled to a Hewlett-Packard 5989B mass spectrometer. Purified compounds were analyzed by preparing samples in acetone or hexane. Electron ionization (EI) mass spectrometry (MS) was performed at 70 eV and positive chemical ionization (PCI)-MS with methane as reagent gas at 230 eV; source temperature 200 °C and source pressure 0.5 Torr. PCI spectra were background-subtracted. $^1$H (400 MHz) and $^{13}$C (100 MHz) nuclear magnetic resonance (NMR) spectra (CDCl$_3$ solutions) were obtained on a Bruker (Rheinstetten, Germany) ARX-400 spectrometer. Electronic absorption spectra (solvent: ethyl acetate) in the ultraviolet–visible (UV–Vis) range were obtained on a Beckman (Fullerton, CA) DU-70 spectrophotometer.

The 1,2-dioxo compounds were synthesized by largely following a literature procedure employing K$_2$MnO$_4$ in acetic anhydride (Jensen and Sharpless, 1974). Most reactions were conducted on 10 g scale (relative to methyl oleate as starting material) and other reagents scaled accordingly when conducting reactions on a smaller scale. While safety concerns reported in the literature for this reaction were reported not to be of concern on these reduced scales (Jensen and Sharpless, 1974), in our hands a few cases of ‘exothermic reactions’ (Jensen and Sharpless, 1974) occurred. Using acetone as solvent eliminated this problem, however, yields appear to be reduced. The following changes were conducted compared with the literature procedure as they were found to be advantageous in terms of improving or maintaining yield levels. The fatty starting material was stirred over a full weekend (ca. 72 h) with acetic anhydride under nitrogen, after which time potassium permanganate was added. The temperature in the flask was never allowed to rise above 5 °C. The work-up was facilitated by pouring the chilled aqueous solu-

![Scheme 1. Synthesis of long-chain dioxo compounds from monounsaturated fatty acids.](image-url)
Table 1
Melting points and mass spectral data of long-chain 1,2-dioxo compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point (°C)</th>
<th>Major fragments in EI-MS&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl 5,6-dioxoicosanoate</td>
<td>67.5–68</td>
<td>A 129 225 (3%) B 101 (17%)</td>
</tr>
<tr>
<td>Methyl 6,7-dioxooctadecanoate</td>
<td>42.5–43</td>
<td>A 143 183 (10%) B 111 (57%)</td>
</tr>
<tr>
<td>Methyl 7,8-dioxononadecanoate</td>
<td>47.5–48.5</td>
<td>A 157 183 (18%) B 139 (10%), 125 (62%)</td>
</tr>
<tr>
<td>Methyl 8,9-dioxoeicosanoate</td>
<td>62–62.5</td>
<td>A 171 183 (24%) B 139 (52%), 111 (51%)</td>
</tr>
<tr>
<td>Methyl 9,10-dioxooctadecanoate</td>
<td>42.5–46</td>
<td>A 185 141 (36%) B 295 (3%), 157 (3%), 153 (16%), 135 (10%)</td>
</tr>
<tr>
<td>Methyl 11,12-dioxooctadecanoate</td>
<td>48–49</td>
<td>A 213 113 (46%) B 295 (4%), 181 (8%), 163 (9%), 153 (27%), 135 (23%)</td>
</tr>
<tr>
<td>Methyl 13,14-dioxododecanoate</td>
<td>62–63</td>
<td>A 241 141 (26%) B 351 (2%), 209 (6%), 191 (3%), 181 (12%), 173 (7%), 163 (14%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The letters A and B refer to the corresponding fragment ions described in the text and Fig. 3.
<sup>b</sup> No intensities given as fragment A is the base peak (100%) in all spectra.

3. Results and discussion

A series of 1,2-diones as depicted in Scheme 1 and listed in Table 1 was synthesized from the corresponding monounsaturated fatty acid methyl esters. All compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy as well as mass spectrometry in both electron ionization and PCI (methane as reagent gas) modes.

3.1. Mass spectrometry

Fig. 1 depicts the mass spectrum of methyl 9,10-dioxooctadecanoate obtained in electron ionization mode. Fig. 2 contains the mass spectrum of methyl 8,9-dioxoeicosanoate obtained with PCI (methane as reagent gas) mode. Those two spectra will serve as examples in the following discussion. The major fragment ions of all EI mass spectra are listed in Table 1.

The major diagnostic cleavage in both ionization modes defining the position of the two carbonyl groups occurs between those two carbonyl carbons as shown in Fig. 3. The fragment ion containing the methyl ester moiety and the oxo group closer to it will be termed fragment ion A in the further discussion and the fragment ion containing the remaining oxo moiety and the terminal methyl group will be fragment ion B. Thus, in Fig. 1, the peaks at m/z 185 and 141 corresponding to fragment ions A and B, respectively, and in Fig. 2, the peaks at m/z 183 and 171 corresponding to fragment ions A and B, respectively. Note that the peaks for fragment ions A and B are much stronger in EI mode than in PCI mode. Conversely, the peaks at higher masses directly defining the molecular weight are very weak in EI mode and very strong in PCI mode.
Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^{13}$C NMR signals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2-dioxo</td>
</tr>
<tr>
<td>Methyl 5,6-dioxoeicosanoate</td>
<td>199.79, 199.04</td>
</tr>
<tr>
<td>Methyl 6,7-dioxooctadecanoate</td>
<td>200.25, 200.22</td>
</tr>
<tr>
<td>Methyl 7,8-dioxononadecanoate</td>
<td>200.11, 199.85</td>
</tr>
<tr>
<td>Methyl 8,9-dioxoeicosanoate</td>
<td>200.19, 200.02</td>
</tr>
<tr>
<td>Methyl 9,10-dioxooctadecanoate</td>
<td>200.24, 200.14</td>
</tr>
<tr>
<td>Methyl 11,12-dioxooctadecanoate</td>
<td>199.98, 199.48</td>
</tr>
<tr>
<td>Methyl 13,14-dioxododecanoate</td>
<td>200.26 (2C)</td>
</tr>
</tbody>
</table>

3.2. EI-MS

The fragmentation pattern observed in EI mode differs with the chain length. For compounds with the dioxo moiety in a remote position to the methyl ester group, the EI mass spectrum of methyl 9,10-dioxooctadecanoate (Fig. 1) may serve as example. The characteristic peaks in the spectrum of that compound can be assigned as follows. The molecular ion $M^+$ corresponds to the small peak at $m/z$ 326 and liberation of CH$_3$O gives rise to the peak at $m/z$ 295. As discussed above, the main diagnostic cleavage (Fig. 3) in all spectra occurs between the two oxo groups to give the strong peaks at $m/z$ 185 corresponding to [CH$_3$OCO-(CH$_2$)$_7$CO]$^+$ (fragment ion A) and $m/z$ 141 corresponding to [CH$_3$-(CH$_2$)$_7$CO]$^+$ (fragment B). The peak for fragment A is consistently stronger than that of the fragment ion B in all mass spectra. However, the abundance of fragment ion B increases when its size decreases, as may be noted from the data in Table 1. Loss of methanol from $m/z$ 185 leads to the peak at $m/z$ 153 of a ketene acylium ion (C$_9$H$_{13}$O; [CO=CH-(CH$_2$)$_7$-(CH=CH)$_2$-CO]$^+$). A peak at spectral investigations of fatty esters (Ryhage and Stenhagen, 1960b). A less abundant peak at $m/z$ 157 could indicate loss of CO from $m/z$ 185, but loss of 32 Da is definitely favored from fragment A. The peak at $m/z$ 135 may be explained by loss of water from $m/z$ 153 to give an unsaturated acylium-type ion (C$_9$H$_{11}$O; [CH$_2$=CH-(CH$_2$)$_7$=CH=CH$_2$-CO]$^+$). A peak at

![Fig. 1. Electron ionization mass spectrum of methyl 9,10-dioxooctadecanoate.](image-url)
Fig. 2. Chemical ionization (methane) mass spectrum of methyl 8,9-dioxoeicosanoate.

$m/z$ 107 can formally arise either through loss of 18 Da from $m/z$ 125 or 128 Da from $m/z$ 135. The peak at $m/z$ 97 ($C_7H_{13}$), which theoretically could result from loss of the second CO, is present in the spectra of compounds with the dioxo group further removed from the methyl ester group and therefore, appears attributable to the hydrocarbon cluster.

The EI mass spectrum of methyl 13,14-dioxododecanoate largely corresponds to the pattern established here for methyl 9,10-dioxooctadeconoate. However, that spectrum displays another peak not found in the MS of methyl 9,10-dioxooctadecanoate and only present in low abundance in the EI-MS of methyl 11,12-dioxo octadecanoate. That peak occurs at $m/z$ 173 in the EI-MS of methyl 13,14-dioxooctadecanoate and corresponds to loss of 18 Da from $m/z$ 191 (which is $m/z$ 135 in the EI-MS of methyl 9,10-dioxo octadecanoate).

The EI mass spectrum of methyl 5,6-dioxoeicosanoate (not shown), however, differs from that of methyl 9,10-dioxooctadecanoate. The peak at $m/z$ 129 of fragment ion A is again the base peak while the peak at $m/z$ 225 caused by fragment B at 3% abundance is the weakest of its kind in the series of compounds studied here. The other series of ions observed for methyl 9,10-dioxooctadecanoate is also lacking, however, a peak at $m/z$ 101 likely arising from loss of CO from $m/z$ 129 is relatively prominent at around 17% abundance. The existence of $m/z$ 97 here cannot necessarily be attributed to loss of 32 Da from fragment A as it may constitute part of the hydrocarbon cluster prominent at values $<m/z$ 100. The same observation holds for the observed lack of the other peaks discussed for methyl 9,10-dioxooctadecanoate. However, considering their intensity in the spectra of the other compounds, the series of peaks does not appear to exist in case of the 5,6-dixo moiety due to low abundances here. The reason is probably the proximity of the dioxo group to the methyl group giving less positions to participate in the reactions.

In the EI mass spectrum of methyl 6,7-dioxooctadecanoate, accordingly $m/z$ 143 (fragment A) is the base peak. Here, $m/z$ 111, corresponding to loss of methanol from $m/z$ 143, is the second most abundant peak. A peak at $m/z$ 83 from loss of CO is at 12% abundance but less conspicuous due to its position among the hydrocarbon fragments and may itself be largely part of the hydrocarbon cluster. No loss of 18 Da (water) as in the other spectra of the longer-chain compounds was identified here. Similarly, in the EI mass spectrum of methyl 8,9-dioxoeicosanoate peaks at $m/z$ 139 (171-32), and 111 (139-28) are observed. No loss of 18 Da was observed here either. The phenomenon of loss of water (or giving conspicuous peaks) therefore appears to commence when the dioxo moiety is at least at the 9,10 position from the methyl ester moiety.

The strong even-numbered peaks observed in the EI mass spectra of mono-oxooctadecanoic esters (Ryhage and Stenhagen, 1960a; Weihrauch et al., 1974) resulting from proton rearrangements are not observed in the dioxo compounds. The reason appears to be that in the mono-oxooctade-
3.3. CI-MS

In contrast to the mass spectra obtained with EI mode, the mass spectra obtained by chemical ionization with methane as reagent gas are dominated by clusters of peaks directly defining the molecular weight of the sample under investigation. Thus, in Fig. 2, the peak at m/z 355 is the protonated molecular ion [M + H]^+ and the peak at m/z 383 is the adduct of the molecular ion with C_2H_5 [M + C_2H_5]^+. The other significant peaks are m/z 335 [M + H–H_2O]^+, 323 [M + H–CH_2OH]^+ and m/z 305 [323-H_2O]. These assignments coincide with those made in the literature (Murphy, 1993, and references therein). As mentioned above, the peaks arising from the cleavage of the dioxo moiety are comparatively weak in CI mode. Also, in agreement with the EI-derived mass spectra, the peak corresponding to fragment ion A is consistently stronger than that of the fragment ion B. However, the CI mass spectra consistently give a small peak corresponding to the loss of 14 Da (CH_2) from fragment A (m/z 157 in Fig. 2). A low abundance of fragments in CI mode defining the location of the oxo group in a methyl mono-oxooctadecanoate was observed in the literature (Plattner et al., 1983).

The merits and disadvantages of both ionization modes are readily apparent from the two spectra in Figs. 1 and 2. While EI gives strong fragments A and B corresponding to the substitution pattern and further interesting fragmentation of fragment A, the molecular ion is stronger in CI mode. Both ionization modes appear suitable for analysis of the present compounds.

3.4. NMR

The ^1H NMR spectra consisting of a methyl ester singlet at approximately 3.60 ppm, a triplet (which can be split further in some spectra, giving a doublet of triplets) at approximately 2.70 ppm resulting from the protons α to the dioxo group, a triplet at approximately 2.28 ppm resulting from the protons at C2, CH₂ protons in the range 1.3–1.6 ppm, and a triplet caused by protons of the terminal methyl group at approximately 0.85 ppm generally coincide with literature values (Jensen and Sharpless, 1974) and resemble each other closely for all compounds and will, therefore, not be discussed further. The ^13C NMR spectra of fatty acid methyl esters with one oxo group have been reported (Tulloch, 1977) with the chemical shifts (all spectra obtained in CDCl₃) of the oxo carbons in (mono-)oxooctadecanoic acids at 193.99 ppm for the 2-oxo compound, 202.30 for the 3-oxo, 208.65 for the 4-oxo, 209.84 for the 5-oxo and values in the range of 210–211.3 ppm for more remote oxo groups. Thus, the differences in the chemical shift of functional groups in long fatty acid chains with one hydroxy or oxo moiety have been shown to be position-dependent in a fashion that allow them to be calculated or predicted (Knothe and Nelsen, 1998). Therefore, it appeared possible that the ^13C NMR spectra would show some differences depending on the proximity of the dioxo moiety to the methyl ester group. However, as the data in Table 2 show, there appears to be no significantly consistent position dependence of the chemical shifts of the dioxo moiety for the positions studied here. This can likely be attributed to the close proximity of the two oxo groups as that proximity largely negates any inductive effect from the more remote methyl ester group. Instead, the chemical shifts of the present dioxo compounds are consistently in the range of 199–200.3 ppm (also CDCl₃ as solvent) for both oxo carbons, a difference of approximately 10 ppm compared with the monooxo compounds (Tulloch, 1977). However, when the dioxo moiety is very remote from the methyl ester group, the two carbonyl signals degenerate into one as found in methyl 13,14-dioxodocosanoate, showing that the methyl ester group likely is
responsible for the separation of the signals of the two oxo carbons in positions closer to the methyl ester moiety.

3.5. Electronic spectra

The absorption maxima of 9,10-dioxostearic acid or its methyl ester were reported to be located at 425 nm and 270–275 nm (Jensen and Sharpless, 1974; Khan and Newman, 1952; Holman et al., 1945). Investigations on the spectra of the compounds synthesized here confirmed these absorptions regardless of the solvent (ethyl acetate used here, ethanol used in previous studies) position of the dioxo moiety in the chain.

The compounds synthesized here will be investigated for potential applications and/or as intermediates in the synthesis of other compounds of potential utility. For example, the two oxo groups open the possibility of introducing further branching into the fatty acid chain.

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References


