Synthesis of a Saturated Lipid Hydroperoxy-cyclic Peroxide

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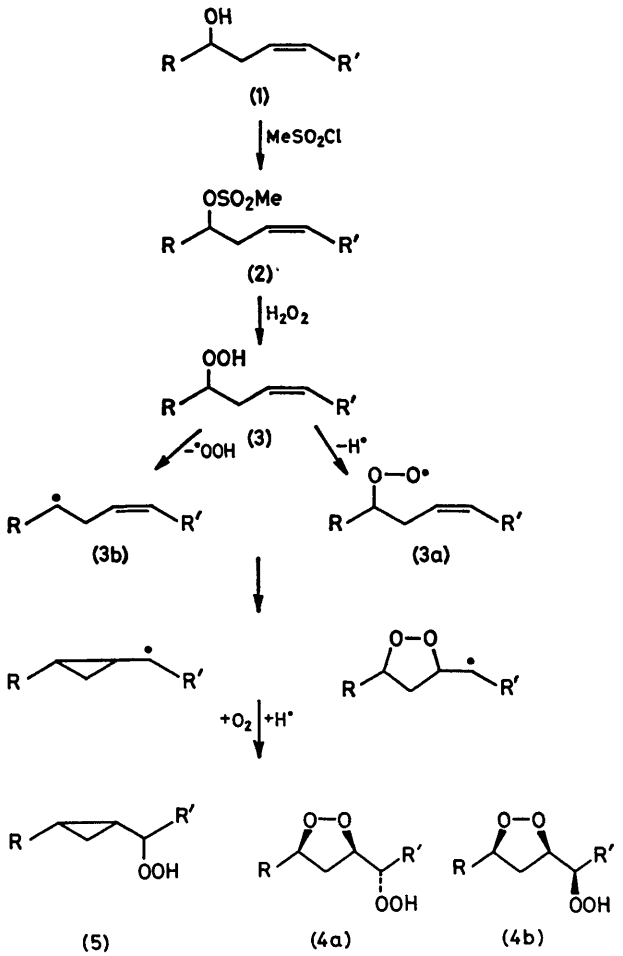
Summary A simple one-step method has been developed for the synthesis of a saturated hydroperoxy-epidioxide by allowing the methanesulphonate of methyl ricinoleate to react with 90% H_2O_2 in diethyl ether; the stereochemistry of the cyclic peroxide product has been established.

MUCH attention has been given recently to the secondary cyclic oxidation products of polyunsaturated lipids because they may play a biological role as prostaglandin-related endoperoxides.[1-3] Previous studies have identified complex mixtures of hydroperoxy-cyclic peroxides from methyl linolenate after either autoxidation[4] or enzymic oxidation.[5,6] A recent report describes the formation of a single hydroperoxy-epidioxide from linolenic acid by a two-step procedure employing an enzymic oxidation followed by autoxidation.[7] We now report an alternative nonenzymic route to synthesize in one step a useful model saturated hydroperoxy-



SCHEME. R = $[CH_2]_5Me$, R^1 = $[CH_2]_7CO_2Me$.

epidioxide starting from readily available methyl ricinoleate (**1**) (Scheme). The methane sulphonate (**2**) was allowed to react with 90% H_2O_2 (50 equiv.) in anhydrous diethyl ether at −70 °C and was then allowed to warm and was maintained at room temperature for 3—6 h. Under these conditions the expected homoallylic hydroperoxide intermediate (**3**) undergoes free radical cyclisation and further oxidation to yield the saturated hydroperoxy-epidioxide (**4**) and hydroperoxy-cyclopropane ester (**5**). The cyclic products were separated in *ca.* equal amounts (25—35% each) by silicic acid column chromatography. The diastereoisomers (**4a**) and (**4b**) were further purified by h.p.l.c. (10 micron microporous silica column, eluting with a 5:4:1 mixture of hexane–methylene dichloride–ethyl acetate, v:v:v). The spectral characteristics of (**5**) (i.r., ^1H n.m.r., and ^{13}C n.m.r.) are consistent with those of the hydroxy-derivative that was previously reported as the homoallylic rearrangement product from the reaction of (**2**) with aqueous or acidic methanol[8] or the corresponding toluene-*p*-sulphonate with aqueous acetone.[9] An S_N1 reaction producing a homoallylic carbonium ion was postulated.[8]

TABLE. ^1H (90 MHz) and ^{13}C (22·63 MHz) spectra.

(4a) δ	(4a) J/Hz	(4b) δ	(4b) J/Hz	Multiplicity	Assignment
4·18		4·18		m	12-H
4·15	7·5, 5, 3	4·11	8, 6·5, 5	ddd	10-H
3·51		3·53		m	9-H
2·53	12, 8, 3	2·71	12, 8, 6·5	ddd	11b-H
2·26	12, 8, 5	1·93	12, 8, 5	ddd	11a-H
δ/p.p.m.		δ/p.p.m.			
33·9		32·9			C-13
72·5		73·0			C-12
42·4		42·5			C-11
81·3		82·0			C-10
83·3		84·1			C-9
33·5		32·0			C-8

The stereochemistry of (**4a**) and (**4b**)† was based on n.m.r. studies and comparison of the triols obtained by hydrogenation with authentic (9*S*,10*R*,12*R*)- and (9*R*,10*R*,12*R*)-trihydroxyoctadecanoate.[10] Studies of the n.m.r. spectra for each isomer (**4a**) and (**4b**) are consistent with those reported for the unsaturated hydroperoxy-epidioxides from methyl linoleate[10] and linolenate[7] (Table). However, in contrast with the unsaturated hydroperoxy-epidioxides, the 9-H resonance for the carbon bearing the hydroperoxide and the ring methylene C-11 resonance were essentially the same in (**4a**) and (**4b**). Only the ring methylene 11a-H and 11b-H and the C-8 and C-13 resonances were sufficiently different to distinguish these diastereoisomers. Therefore, the presence or absence of unsaturation allylic to the epidioxide ring has marked effects on the n.m.r. characteristics of these compounds.

The homoallylic structure of the peroxy-radical (**3a**) is an essential feature of the cyclisation (Scheme) that is now recognized as an important process in the autoxidation of methyl linolenate[3,11] and in the sensitised photo-oxidation of methyl linoleate.[10] The homoallylic structure of radical (**3b**) is similarly required in the cyclisation producing (**5**).

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† Structures (**4a**) and (**4b**) each consist of pairs of enantiomers and only one isomer is shown.

[1] N. A. Porter and M. O. Funk, *J. Org. Chem.*, 1975, **40**, 3614.
[2] W. A. Pryor and J. P. Stanley, *J. Org. Chem.*, 1975, **40**, 3615; W. A. Pryor, J. P. Stanley, and E. Blair, *Lipids*, 1976, **11**, 370.
[3] E. N. Frankel, W. E. Neff, W. K. Rohwedder, B. P. S. Khambay, R. F. Garwood, and B. C. L. Weedon, *Lipids*, 1977, **12**, 1055.
[4] P. H. Begemann, W. J. Woestenburg, and S. Leer, *J. Agric. Food Chem.*, 1968, **16**, 679.
[5] M. Roza and A. Francke, *Biochim. Biophys. Acta*, 1978, **528**, 119.
[6] D. E. O'Connor, E. D. Mihelich, and M. C. Coleman, *J. Am. Chem. Soc.*, 1981, **103**, 223.
[7] H. W.-S. Chan, J. A. Matthew, and D. T. Coxon, *J. Chem. Soc., Chem. Commun.*, 1980, 235.
[8] F. D. Gunstone and A. I. Said, *Chem. Phys. Lipids*, 1971, **7**, 21.
[9] E. Ucciani, A. Vantillard, and M. Naudet, *Chem. Phys. Lipids*, 1970, **4**, 225.
[10] E. D. Mihelich, *J. Am. Chem. Soc.*, 1980, **102**, 7143.
[11] W. E. Neff, E. N. Frankel, and D. Weisleder, *Lipids*, 1981, **16**, 439.