Attempted Synthesis of (9Z)-Methyl 12-Hydroperoxyoctadec-9-enoate

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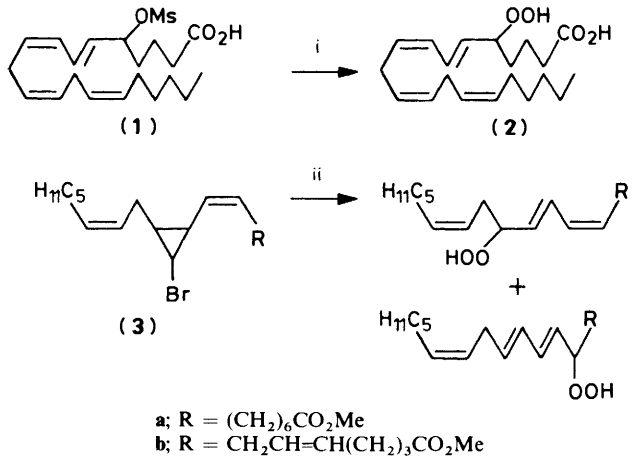
The silver trifluoroacetate-assisted reaction of alkyl halides with hydrogen peroxide has been investigated. Methyl 12-bromostearate furnished, for the first time, methyl 12-hydroperoxystearate in 34% yield. Methyl 12-bromo-oleate, however, gave cyclopropane hydroperoxides (*via* a homoallylic cation rearrangement) and hydroperoxy epidioxides (presumably *via* methyl 12-hydroperoxyoleate which could not be isolated). Methyl 9-t-butylperoxy-10,11-methyleneheptadecanoate was produced by the reaction of methyl 12-bromo-oleate with t-butyl hydroperoxide in the presence of silver trifluoroacetate. None of these transformations occurred when silver trifluoroacetate was replaced by the acetate.

The full spectrum of biological activity associated with fatty acid hydroperoxides has still to be fully elucidated, but it has already been shown that 5-hydroperoxyicosatetraenic acid, a catabolite of arachidonic acid, plays an important role in the allergic response.[1]

The synthesis of fatty acid hydroperoxides by photosensitised oxidation[2] or autoxidation[3] results in a number of positional and stereochemical isomers† which can be separated by chromatographic procedures.[4–6] Approaches to the synthesis of individual fatty acid hydroperoxides have only recently received attention. Corey *et al.*[7] prepared the allylic hydroperoxide (**2**) from the corresponding mesyloxy tetraene (**1**) by nucleophilic displacement. Porter *et al.*[8,9] used the silver ion displacement of halides for the preparation of prostaglandin endoperoxides and allylic hydroperoxides, and the same group applied this silver ion/hydrogen peroxide methodology to the ring opening of vinyl cyclopropyl bromides (**3**) with complete stereochemical control.[10] (Scheme 1).

Primary alkyl hydroperoxides have been prepared by the base-catalysed alkylation of hydrogen peroxide using the appropriate methanesulphonate[11] but attempts to prepare secondary hydroperoxides from methyl 12-mesyloxy-stearate and -oleate by this procedure failed.



a; R = $(CH_2)_6CO_2Me$
b; R = $CH_2CH{=}CH(CH_2)_3CO_2Me$

Scheme 1. *Reagents:* i, H_2O_2, −110 °C; ii, Ag^+, H_2O_2

Results and Discussion

Methyl 12-bromostearate (**4**) was prepared by bromination of methyl 12-mesyloxystearate. It was treated with hydrogen peroxide in the presence of a large excess of silver trifluoroacetate for 45 min and gave methyl 12-hydroperoxystearate (**5**) [equation (1)] in 34% yield after isolation by preparative thin layer chromatography. The only other product isolated was starting material (58%), indicating that competitive dehydrohalogenation had not occurred.

$$\underset{(4)}{Me(CH_2)_5CHBr(CH_2)_{10}CO_2Me} \xrightarrow{i} \underset{(5)}{Me(CH_2)_5CH(OOH)(CH_2)_{10}CO_2Me} \quad (1)$$

Reagents: i, Ag^+, H_2O_2

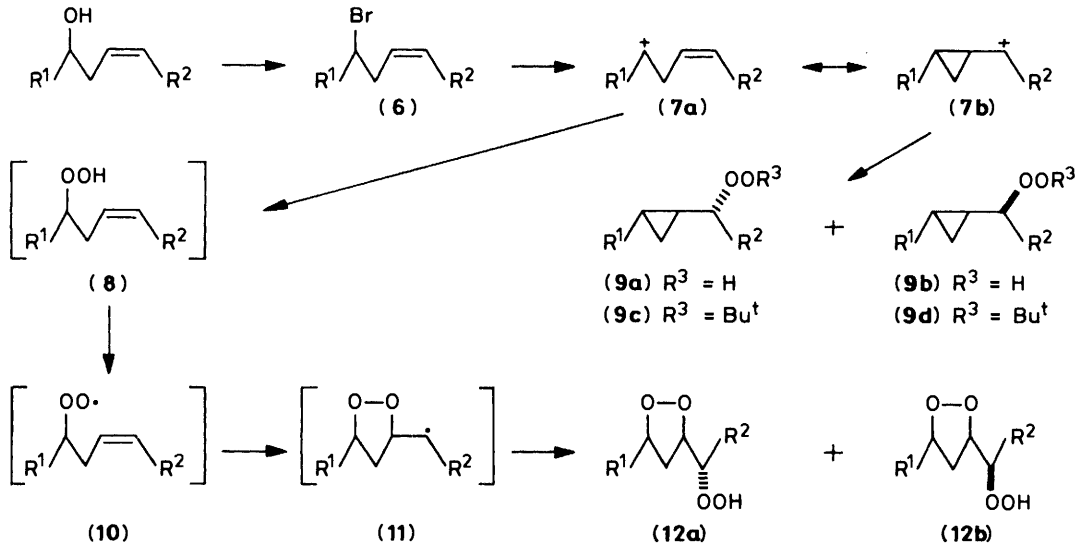
The ^{13}C and ^1H n.m.r. spectra enabled a full identification of the product to be made. The hydroperoxy-bearing carbon (C-12) has a ^{13}C shift of 85.53 p.p.m., some 13.9 p.p.m. downfield from the corresponding alcohol. Similarly, the peroxy methine in the ^1H n.m.r. spectrum of the peroxide is downfield by 0.6 p.p.m. from the hydroxy methine in the corresponding alcohol. The mass spectrum of the hydroperoxide was extremely weak with no intense peaks above *m/z* 100.

Methyl 12-bromo-oleate (**6**), prepared from methyl ricinoleate, gave a more complex product mixture on reaction with hydrogen peroxide in the presence of silver trifluroacetate. The major isolable products were the cyclopropane hydroperoxide esters (**9a**) and (**9b**) and the hydroperoxyepidioxide esters (**12a**) and (**12b**) (Scheme 2).

The S_N1 silver-assisted displacement of the bromine atom will furnish the homoallylic carbonium ion (**7a**) which can be considered as having its charge delocalised over C-12, -10, and -9. Nucleophilic addition can then occur at either C-12 [to furnish the homoallylic hydroperoxide (**8**)] and/or at C-9 [to furnish the cyclopropane hydroperoxides (**9a**) and (**9b**)]. Under our conditions the reaction was under thermodynamic control and the 9-hydroperoxy cyclopropane esters (**9a**) and (**9b**), formed *via* the more stable carbonium ion (**7b**), were marginally the major product.

The structure of the cyclopropane esters is based on chemical and spectroscopic evidence. The esters were shown to be peroxidic by reaction with methanolic 4-amino-*N*,*N*-dimethylaniline hydrochloride (2% solution) and were, in fact, hydroperoxidic since sodium borohydride reduction of the esters gave a product which was no longer peroxidic thus excluding the possibility of a cyclic peroxide. The i.r. spectrum showed bands associated with the cyclopropane C–H stretching

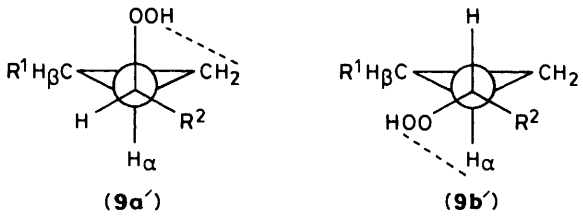
† For example, the photosensitised oxidation of methyl oleate yields two isomeric hydroperoxides (9- and 10-hydroperoxido-octadec-10- and -8-enoate) while autoxidation yields four isomers (8-hydroperoxido-Δ^9, 9-hydroperoxido-Δ^{10}, 10-hydroperoxido-Δ^8, and 11-hydroperoxido-Δ^9).



Scheme 2. $R^1 = Me(CH_2)_5$, $R^2 = (CH_2)_7CO_2Me$

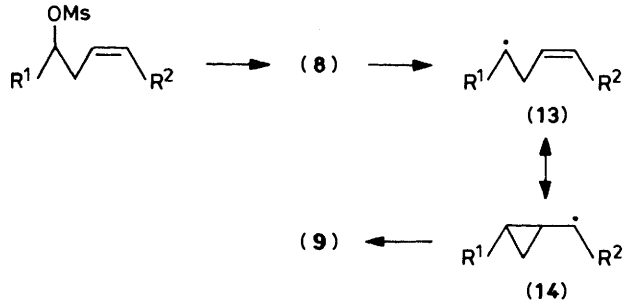
(3 020 cm^{-1}), the cyclopropane CH_2 scissoring vibration (1 432 cm^{-1}), a cyclopropane skeletal stretch (1 020 cm^{-1}), and OO–H stretching absorption (3 450 cm^{-1}). The ^1H n.m.r. spectrum showed the absence of olefinic hydrogens, but signals in the region δ 0—0.85 indicated a cyclopropane system.

As noted above, the cyclopropane esters were resolved by t.l.c. into two components which differed in chromatographic behaviour and in their ^1H n.m.r. spectra. Structures (**9a′**) and (**9b′**) show two diastereoisomeric perspectives of the 9-hydroperoxycyclopropanes in the energetically preferred antiperiplanar conformations.



Diastereoisomer (**9a′**) can only form hydrogen bonds with the cyclopropane methylene group (since H_α will be across the ring) whereas diastereoisomer (**9b′**) has the potential for hydrogen bonding with the vicinal cyclopropane methine H_α. On the premise that hydrogen bonding will lead to a downfield ^1H n.m.r. shift, we have tentatively identified the less polar of the two cyclopropane esters as diastereoisomer (**9a**), as the ring methylene is shifted downfield from its usual value of δ 0.2—1.16. We consider the more polar cyclopropane ester to be diastereoisomer (**9b**): in this case it is the ring methines which are shifted downfield.

The formation of the hydroperoxy epidoxides (**12a**) and (**12b**) may involve the 12-hydroperoxyoleate (**8**) which we were unable to detect. Formation of the peroxy radical (**10**), with subsequent cyclisation in a 5-*endo* mode, furnishes the cyclic peroxide radical intermediate (**11**) which, on further oxidation, will produce the saturated hydroperoxy epidioxides (**12a**) and (**12b**) in approximately equal amounts (*ca.* 14% each). We have assigned the stereochemistry of the cyclic peroxides on the basis of n.m.r. studies and comparison of the saturated trihydroxystearates, obtained by hydrogenation, with authentic (9*S*,10*R*,12*R*)- and (9*R*,10*R*,12*R*)-standards, as reported by

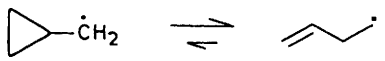


Scheme 3. $R^1 = Me(CH_2)_5$, $R^2 = (CH_2)_7CO_2Me$

Mihelich [12] and by Frankel *et al.*[13] Our assignments are based on their chromatographic data.

Frankel *et al.*[13] recently reported the formation of hydroperoxy epidioxides and cyclopropane hydroperoxides in a reaction of 12-mesyloxyoleate with 90% hydrogen peroxide in anhydrous diethyl ether at −70 °C. In this case, however, the hydroperoxy-epidioxides (**12a**) **and** (**12b**) were the major products: (**8**)→(**10**)→(**11**)→(**12a**) and (**12b**). Only one cyclopropane hydroperoxide was reported, in contrast to the two diastereoisomers formed in our silver trifluoroacetate reaction. We consider the formation of this cyclopropane hydroperoxide *via* the radicals (**13**) and (**14**) to be unlikely (Scheme 3). E.s.r. studies on the cyclopropylmethyl radicals (**15**)[14] have shown that the equilibrium lies almost exclusively on the acyclic side, as indicated by the absence of any products containing the cyclopropane ring unless the radical is stabilised[15] (as with the 4,4-diphenylbut-2-enyl radical) or the architecture of the molecule is such as to favour cyclisation.[16] No such driving force can be envisaged for the radical (**14**) and we suggest that the formation of the cyclopropane hydroperoxide follows the same reaction pathway as outlined for our 12-bromo-oleate reaction (**6**)→(**7b**)→(**9a**) and (**9b**) and by analogy with the solvolysis of 12-mesyloxy-and 12-tosyloxy-oleate.[17,18]

We have also obtained the cyclopropane t-butyl peroxides (**9c**) and (**9d**) from the reaction of 12-bromo-oleate with freshly purified t-butyl hydroperoxide in the presence of an excess of silver trifluoracetate. Two diasteroisomers were again indicated by double development chromatography, although the resolution was much poorer in this case, and the individual



(15) (16)

isomers were not separated on subsequent preparative t.l.c. No other peroxidic products were detected by spray reagents, although some unidentified polar products were observed by t.l.c.

Although the unsaturated β-bromide led almost exclusively to rearrangement products and gave none of the desired 12-hydroperoxy or 12-t-butylperoxy oleates, the reaction appears promising for the formation of secondary hydroperoxides and alkyl peroxides in which these competing reaction cannot occur.

Experimental

General experimental procedures are given in the preceding papers. Methyl ricinoleate was obtained from castor oil methyl esters by chromatography on a column of silica followed by preparative t.l.c. using PE 30 as developing solvent.

Synthesis of Methyl 12-Bromostearate.—Methyl ricinoleate (>99%, 10 g) in superdry methanol (100 ml) was hydrogenated in the presence of palladium–charcoal (10%, 400 mg). Pure methyl 12-hydroxystearate was isolated by preparative h.p.l.c.: $\nu_{max.}$ 3 345 cm^{-1} (O–H stretch), absence of C=C stretch; δ_H 3.57 (1 H, br m, HCO), 3.57 (3 H, s, CO_2CH_3), 2.20 (2 H, asym. t, *J* 7.0 Hz, CH_2CO_2Me), 1.98 (1 H, br s, OH), 1.25 (br s, chain CH_2), and 0.76 (3 H, asym. t, *J* 5.4 Hz, CH_3); intense peaks at *m/z* 297 ($M^+ - H_2O$), 229 [$M^+ - CH_3(CH_2)_5$], 197 [$(CH_2)_{10}CO_2Me - 2$], and peaks associated with the sequential loss of methylenes.

Methanesulphonyl chloride (4 ml) and pyridine (5 ml) were stirred with an ice-cold solution of methyl 12-hydroxystearate (4.5 g, 1.5 mmol) in dry methylene dichloride (10 ml) for 4 h at 0—5 °C. Ice-cold 2M-hydrochloric acid (20 ml) was then added at a rate which did not allow the temperature to rise above 10 °C. Methyl 12-mesyloxystearate was recovered: $\nu_{max.}$ 1 356 and 1 178 cm^{-1} (asymmetric and symmetric SO_2 stretching), absence of O–H stretch; δ_H 3.60 (3 H, s, CO_2CH_3), 3.55 (1 H, br m, $CHOSO_2Me$), 2.97 (3 H, s, OSO_2CH_3), 2.23 (2 H, asym. t, *J* 7.1 Hz, CH_2CO_2Me), 1.20 (br s, chain CH_2), and 0.89 (3 H, asym. t, *J* 5.4 Hz, CH_3).

A solution of lithium bromide (15 g) in dry acetone (50 ml) was added to the 12-mesyloxystearate (5.25 g, 1.4 mmol) dissolved in dry acetone (20 ml). The solution was refluxed for 16 h during which time a precipitate of lithium methanesulphonate appeared. The solution was cooled and filtered and the solvent removed at 5 °C. The crude product, extracted with ether, was freed from polar by-products by elution from silica with light petroleum containing ether (5%). The following spectroscopic data were recorded for the 12-bromostearate; $\nu_{max.}$ absence of O–H stretch; δ_H 4.10 (1 H, quint., HCBr), 3.60 (3 H, s, CO_2CH_3), 2.25 (2 H, asym. t, *J* 7.0 Hz, CH_2CO_2Me), 1.25 (br s, chain CH_2), and 0.85 (3 H, asym. t, *J* 5.4 Hz, CH_3).

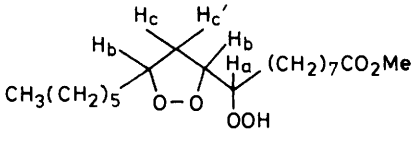
Reaction of Methyl 12-Bromostearate with Hydrogen Peroxide and Silver Trifluoroacetate.—Hydrogen peroxide (85%, 1 ml) was added to methyl 12-bromostearate (380 mg, 1 mmol) in sodium-dried ether (20 ml) and this mixture was added dropwise with vigorous shaking to silver trifluoroacetate (1.0 g, 4.6 mmol) during 5 min. The mixture was gently shaken for a further 10 min and saturated sodium chloride solution (20 ml) then added. A precipitate of silver halides was filtered off. The crude reaction product gave two bands on preparative t.l.c. Unchanged starting material (220 mg, 58%) was accompanied by methyl 12-hydroperoxyoctadecanoate (112 mg, 34%; R_F 0.42 in PE 30): $\nu_{max.}$ 3 420 (OO–H stretch); δ_H 7.95 (1 H, br s, OOH), 4.20 (1 H, br m, HCOO), 3.58 (3 H, s, CO_2CH_3), 2.22 (2 H, asym. t, *J* 7.2 Hz, CH_2CO_2Me), 1.25 (br s, chain CH_2), and 0.86 (3 H, asym. t, *J* 5.4 Hz, CH_3); δ_C 162.91 (C-1), 85.53 (C-12), 34.00 (C-2), 31.96 (C-11, -13), 31.69 (C-16), 29.61, 29.34, and 29.07 (C-4, -5, -6, -7, -8, -9, and -15), 25.27 (C-10 and -14), 24.83 (C-3), 22.49 (C-17), and 13.93 p.p.m. (C-18).

Reaction of Methyl 12-Bromo-oleate with Hydrogen Peroxide and Silver Trifluoroacetate.—Hydrogen peroxide (85%, 1 ml) was added to methyl 12-bromo-oleate (380 mg, 1 mmol) in sodium-dried ether (20 ml). This mixture was added dropwise with vigorous shaking to silver trifluoroacetate (1.0 g, 4.6 mmol) during 5 min. The product gave seven compounds (A—G) on preparative t.l.c. A (78 mg, 21%; R_F 0.73 in PE 40) was unchanged starting material; the minor components B (15 mg, 4%; R_F 0.70 in PE 40) and G (19 mg, 5%; R_F 0.27 in PE 40) were not identified.

Fraction C (78 mg, 24%; R_F 0.60 in PE 40) was 1-hexyl-2-[(1*R*)-1-hydroperoxy-7-methoxycarbonylheptyl]cyclopropane (**9a**): $\nu_{max.}$ 3 410 (OO–H stretch), 3 050 (cyclopropane ring C–H stretch), and 1 020 cm^{-1} (ring C–C stretch); δ_H 7.90 (1 H, br s, OOH), 3.65 (3 H, s, CO_2CH_3), 3.15 [1 H, br m, CH(OOH)], 2.25 (2 H, *J* 7.2 Hz, CH_2CO_2Me), 1.28 (br s, chain CH_2), 0.85 (3 H, asym. t, *J* 5.4 Hz, CH_3), and 0.70—0.25 (4 H, br m, cyclopropane H); *m/z* (mass spectrum of trimethylsilyloxy ether produced by sodium borohydride reduction of the hydroperoxide and silylation) intense fragments at 227 [10, $M^+ - (CH_2)_7CO_2Me$], 187 [15, $Me_3SiOCH(CH_2)_7CO_2Me - 74$], 129 (18), and 55 (100, C_4H_7).

Fraction D (70 mg, 21%; R_F 0.51 in PE 40) was 1-hexyl-2-[(1*S*)-1-hydroperoxy-7-methoxycarbonylheptyl]cyclopropane (**9b**): $\nu_{max.}$ 3 408 (OO–H stretch), 3 050 (cyclopropane C–H stretch), and 1 020 cm^{-1} (cyclopropane C–C stretch); δ_H 7.80 (1 H, br s, OOH), 3.65 (3 H, s, CO_2CH_3), 2.85 (1 H, br m, CHOOH), 2.28 (2 H, asym. t, *J* 7.4 Hz, CH_2CO_2Me), 1.25 (br s, chain CH_2), 0.85 (5 H, asym. t *J* 5.4 Hz, CH_3 and cyclopropane CH), and 0.27 (2 H, app. d, *J* 6.2 Hz, cyclopropane CH_2); mass spectrum identical with that for fraction C.

Fraction E (45 mg, 14%; R_F 0.41 in PE 40) was (3*R*,5*R*)-3-[(1*S*)-1-hydroperoxy-8-methoxycarbonyloctyl]-5-hexyl-1,2-dioxolane (**12a**): $\nu_{max.}$ 3 415 cm^{-1} (OO–H stretch); δ_H 8.90 (1 H, br s, OOH), 4.50—3.90 (3 H, cm, H_a, H_b), 3.65 (3 H, s, CO_2CH_3), 2.56 (1 H, m, H_c), 2.26 (3 H, asym. t, CH_2CO_2Me and H_c),* 1.30 (br s, chain CH_2), and 0.85 (3 H, asym. t, CH_3); *m/z* [the



dioxolane was catalytically reduced over Pd/C (10%) to the corresponding trihydroxystearate and examined as its tris(trimethylsily) ether] 259 [5%, $CH(OSiMe_3)(CH_2)_7CO_2Me$], 220 (3), 187 [6, $CH_3(CH_2)_5CHOSiMe_3$], 185 (5), 155 (9), 147 (21), and 74 (100).

Fraction F (39 mg, 12%; R_F 0.36 in PE 40) was (3*R*,5*R*)-3-[(1*R*)-1-hydroperoxy-8-methoxycarbonyloctyl]-5-hexyl-1,2-dioxolane (**12b**): spectra as for fraction E except for H_c at δ 2.00—1.90 (br, m) instead of δ 2.26.

* The presence of H_c is inferred from the integral although the signal to noise ratio precluded the unequivocal identification of the splitting pattern for this signal and H_a and H_b.

Reaction of Methyl 12-Bromo-oleate with t-Butyl Hydroperoxide and Silver Trifluoroacetate.—A mixture of t-butyl hydroperoxide (85%; 1 ml) and methyl 12-bromo-oleate (380 mg, 1 mmol) in sodium-dried ether (20 ml) was added dropwise with vigorous shaking to silver trifluoroacetate (1.0 g, 4.6 mmol) during 5 min. The t-butyl peroxide was isolated as the major non-polar product by preparative t.l.c. (PE 5): δ_H 3.63 (3 H, s, CO_2CH_3), 3.12 [1 H, br m, CH(OOBu^t)], 2.26 (2 H, asym. t, *J* 7.4 Hz, CH_2CO_2Me), 1.77—1.17 (shoulder and br s, chain CH_2), 1.12 (9 H, s, Bu^t), 0.82 (3 H, asym. t, *J* 5.4 Hz, CH_3), and 0.90—0.15 (4 H, cm, cyclopropane H).

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