Synthesis of Cyclic Peroxides from Methyl Oleate

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A mixture of [10(8)*E*]-9(10)-hydroperoxyoctadec-10(8)-enoates (**3a**) and (**3b**), produced by the photosensitised oxidation of methyl oleate, is a suitable substrate for the synthesis of substituted dioxolanes. Peroxymercuriation of (**3**) followed by hydrogenodemercuriation affords 3-(6-methoxycarbonylhexyl)-5-octyl- and 5-heptyl-3-(7-methoxycarbonylheptyl)-1,2-dioxolanes (**5a**) and (**5b**) in good yield (45—70%). Peroxymercuriation followed by bromodemercuriation yields the corresponding bromo substituted cyclic peroxides (epidioxides) (**9a**) and (**9b**) in higher yield (95%). Direct bromination of the allylic hydroperoxides (**3a**) and (**3b**) affords the same bromo substituted cyclic peroxides (**9a**) and (**9b**) in almost quantitative yield, presumably *via* a bromonium ion intermediate.

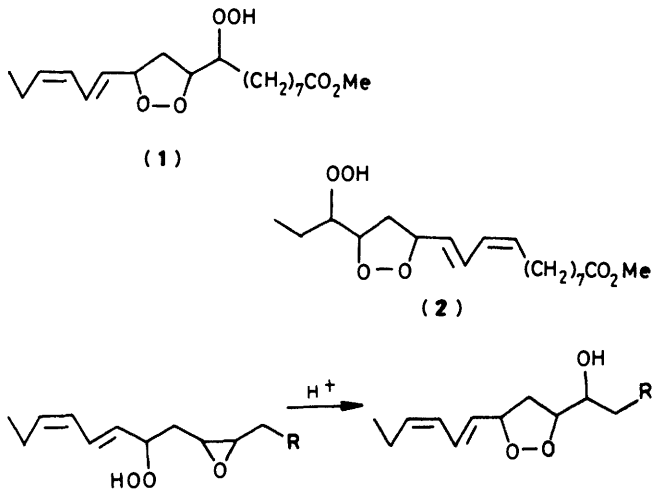
The primary oxidation products of unsaturated lipids are mono hydroperoxides formed either by addition of ground state triplet oxygen by a radical chain mechanism,[1] or by addition of singlet oxygen by a concerted ene-reaction, or *via* a peroxide intermediate.[2]

Further oxidation of lipid monohydroperoxides with more than two double bonds gives hydroperoxy cyclic peroxides as major products and dihydroperoxides as minor products.[3–10] Roza and Francke[6] isolated and identified compounds of structures (**1**) and (**2**) from the products of incubation of methyl linolenate with an aqueous extract of soyabean flour at neutral pH. These structures were similar to those assigned by Haverkemp Begeman *et al.*[7] to the cyclic peroxides obtained from autoxidised methyl linolenate. These were considered to contain six-membered ring systems on the basis of inconclusive mass spectral data from minor rearrangement products, but five-membered rings were not ruled out by the authors.

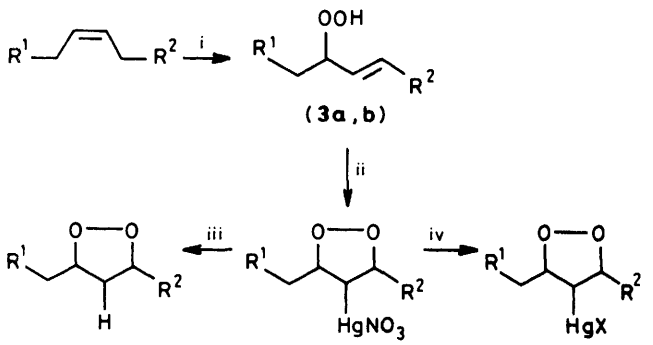
More recently there have been two independent reports on the h.p.l.c. separation of isomeric hydroperoxy cyclic peroxides from autoxidised methyl linoleate.[4,5]

Porter *et al.*[11] reported the synthesis of a hydroxy cyclic peroxide of methyl linolenate by interaction of a β-hydroperoxide with an adjacent oxirane ring (Scheme 1), whilst Frankel *et. al.*[12] prepared hydroperoxy cyclic peroxides by treating the methanesulphonate of methyl ricinoleate with 90% hydrogen peroxide in diethyl ether.

We now report that the allylic hydroperoxides from methyl oleate form cyclic peroxides when an electron-deficient site is created adjacent to the hydroperoxy group.



Scheme 1. R = $(CH_2)_6CO_2Me$



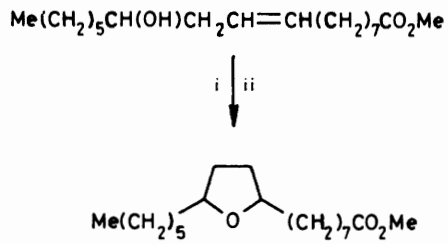
a; $R^1 = Me(CH_2)_6$, $R^2 = (CH_2)_6CO_2Me$
b; $R^1 = MeO_2C(CH_2)_6$, $R^2 = (CH_2)_6Me$

Scheme 2. *Reagents:* i, $^1O_2$; ii, $Hg(NO_3)_2$; iii, $NaBH_4$; iv, KBr or KCl

Results and Discussion

Preparation of Allylic Hydroperoxides.—The photosensitised oxidation of methyl oleate in tetrachloromethane–methanol (95:5) using Methylene Blue as sensitiser gave the two isomeric *trans*-allylic hydroperoxides (**3a**) and (**3b**) in a clean reaction in 16 h. Separation from unchanged starting material by preparative h.p.l.c. gave the hydroperoxides in 80% yield in less than 9 min, thus minimising the on-column decomposition of the labile products. The hydroperoxides were used immediately after removal of the solvent to minimise any possible isomerisation.[13]

Peroxymercuriation–Hydrogenodemercuriation.—The allylic hydroperoxides (**3a**) and (**3b**) reacted with an excess of mercuric nitrate demihydrate in dry dichloromethane at ambient temperature to furnish the organomercury nitrates (**4a**) and (**4b**) (Scheme 2). After immediate reduction *in situ* by a three-fold excess of sodium borohydride, the resulting cyclic peroxides (**5a**) and (**5b**) were separated from the other products by t.l.c. in 45—70% yield. There was no significant improvement in the yield of cyclised product when the reaction time was increased beyond 24 h; nor did increasing the amount of mercuric salt to a 2—3 fold excess have any effect.



Scheme 3. *Reagents:* i, $Hg(NO_3)_2$; ii, $NaBH_4$

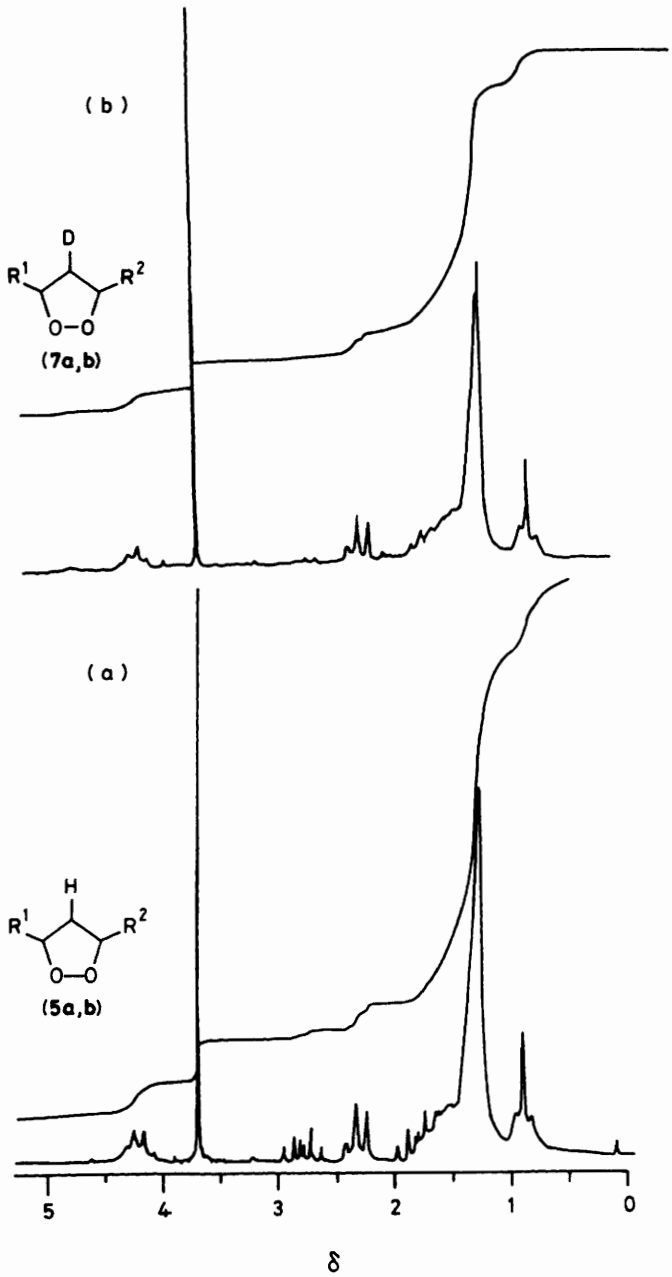


Figure 1. 90 MHz ^1H N.m.r. spectra of (a) the cyclic peroxides (**5a**) and (**5b**) (bottom trace) and (b) the deuterium derivatives (**7a**) and (**7b**) (upper trace)

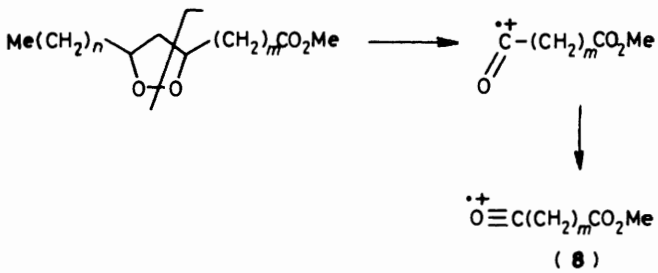
The choice of nitrate as the mercury(II) salt was based on the successful use of this salt in the synthesis of simpler compounds by Bloodworth *et al.*[14,15] and by Porter *et al.*[16] Bloodworth's results suggested that an anion with low nucleophilicity was required and that the products of intramolecular alkoxymercuriation are more stable towards stronger acids than are acyclic oxymercurials. Furthermore, oxymercuriation experiments with methyl ricinoleate gave appreciable yields of the cyclic ether (Scheme 3) with mercuric nitrate but not with the acetate, chloride, trifluoroacetate, or sulphate.[17,18] Dichloromethane was employed as the solvent even though the mercury salt had only limited solubility.

The organomercuric chlorides of simpler compounds,[14–16] have been successfully isolated, but our long-chain mercuric chlorides [(**6a**) and (**6b**), X = Cl] were viscous oils which were difficult to handle and isolate clean. It is better to reduce them *in situ* with sodium borohydride.

The ^1H n.m.r. spectrum of the cyclic peroxides (**5a**) and (**5b**) is shown in Figure 1. Decoupling at δ 1.7 altered the apparent quartet at δ 4.13 to a broad apparent doublet (*J* 7.0 Hz). The δ 2.8 triplet part of the double triplet collapsed to a singlet at δ 2.88 and an asymmetric triplet at δ 2.75. Decoupling of the peroxy methines at δ 4.13 collapsed the double triplets at δ 2.80—2.62 and 1.80—1.55 to broad doublets (*J* 12.0 Hz). A shoulder at δ 1.5 became much sharper.

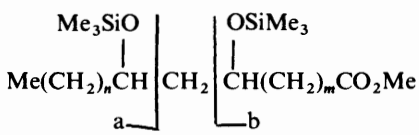
Reduction of the organomercury(II) nitrates (**4a**) and (**4b**) with sodium borodeuteride gives the [^2H]-cyclic peroxides (**7a**) and (**7b**) (Figure 1). The ^1H n.m.r. spectrum of (**7a**) and (**7b**) is similar to that of the [^1H] analogues (**5a**) and (**5b**) apart from the absence of the double triplet δ 2.80—2.62 and an apparent triplet rather than a quartet at δ 4.13. The double triplet at δ 1.80—1.55 appeared as a triplet (*J* 6.8 Hz).

The mass spectrum of compounds (**5a**) and (**5b**) was as expected on the basis of data from simpler compounds.[14,15] Intense high mass peaks resulted from cleavage α to the ring and from cleavage of the ring itself as shown below. Fragment (**8**) locates the position of the peroxide linkage and is common to a wide number of oxygenated esters.



m = 6, *n* = 7
m = 7, *n* = 6

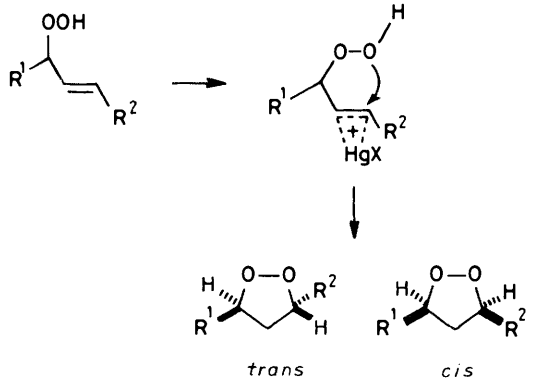
The cyclic peroxides (**5a**) and (**5b**) were catalytically reduced to the corresponding dihydroxystearates and analysed as the bis(trimethylsilyl) ethers by mass spectrometery. Characteristic fragment ions at *m/z* 201 and 259 located the peroxide link at C-9 and -11, while fragment ions at *m/z* 215 and 245 locate the peroxide at C-8 and -10.



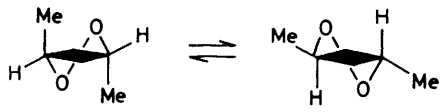
n = 6, *m* = 7; a = 201, b = 259
n = 7, *m* = 6; a = 215, b = 245

Diastereoisomerism, Conformation, and Configuration.—The photosensitised oxidation of methyl oleate generates allylic

hydroperoxides as racemic mixtures of positional isomers. Subsequent intramolecular peroxymercuriation can proceed by electrophilic attack on either face of the double bond, thereby affording diastereoisomeric cyclic products from each enantiomeric and positional isomer. Attack of one face in preference to the other may be favoured on grounds of steric hindrance, especially if the reaction is under thermodynamic control.



Bloodworth *et al.*,[14b] discussing the conformational aspects of 3,4-dimethyl-1,2-dioxacyclopentanes, concluded that the ring exists in two half-chair or envelope conformers (as illustrated for a *trans*-isomer) with the alkyl groups in pseudo-equatorial or -axial positions.



Five-membered ring systems are pseudo-rotational systems with little or no potential energy barrier.[19,20] The introduction of bulky substituents and/or heteroatoms into the ring is expected to raise the barrier above the pseudo-rotational energy levels and the ring will adopt either an envelope or half-chair form, whichever is the more stable.[19,20] The replacement of two methylenes in cyclopentane with two oxygen atoms as in 1,2-dioxacyclopentanes will reduce Pitzer strain in these heterocyclic ring systems and hence lead to a more planar structure than the corresponding carbocyclic system. *cis*-1,3-Dimethylcyclopentane is 0.6 kcal/mol * lower in energy than its *trans*-isomer.[21] This difference arises from the fact that in the *cis* configuration both methyl groups can assume pseudo-equatorial positions while in the *trans*-isomer one methyl must assume the unfavourable axial position. A MINDO/3 study on the conformation of the 3,5-dimethyl-1,2-dioxacyclopentanes gave an energy difference of 0.26 kcal between the *cis*- and *trans*-isomers, the *trans* being lower in energy. This value is consistent with the ring being more planar: as the ring approaches planarity the pseudo-axial and -equatorial substituents become equivalent. The calculated geometry suggests that the ring is very nearly planar.[22]

The ring methylenes of the *cis*-isomer are reported to give double triplets at δ 1.71 and 2.77 in the ^{1}H n.m.r. spectrum while the *trans*-isomer methylenes form a triplet at δ 2.19. For compounds (**5a**) and (**5b**) double triplets were observed at δ 1.74 and 2.74, but any triplet at δ 2.19 would be obscured by the methylenes adjacent to the carboxy group at δ 2.25. The integral of the *cis* ring methylenes is difficult to evaluate since the δ 1.74 double triplet occurs on the edge of the signal due to the methylenes of the alkyl chain. However, from the integral of the δ 2.25 peak relative to the methyl ester peak at δ 3.6, the *trans*-isomer if present must be less than 10%. Thus, the predominant isomer is the *cis*-isomer which will exist as two half-chair or envelope conformers for each positional isomer, with the alkyl groups preferring the pseudo-equatorial positions.

The presence of a single intense peroxy-bearing carbon signal in the ^{13}C n.m.r. spectrum at 81.04 p.p.m. also supports the preferential formation of one configurational isomer, though the presence of small amounts of the *trans*-isomer cannot be precluded from the available spectral data.

Peroxymercuriation–Bromodemercuriation.—Bromodemercuriation of acyclic and cyclic peroxymercurials takes place under mild conditions and is generally a clean reaction.[14–16] The bromodemercuriation of compounds (**4a**) and (**4b**) was no exception, and the bromoperoxides (**9a**) and (**9b**) were easily separated by preparative thin layer chromatography. These were identified by ^{1}H n.m.r., ^{13}C n.m.r., i.r., and mass spectroscopy and the major diastereoisomer was considered to be the *cis*-dialkyl cyclic peroxide on the premise that it was the *cis*-isomer that predominated in the hydrogenodemercuriation. Confirmation of the proposed structure was also obtained by the independent synthesis of compounds (**9a**) and (**9b**) by bromination of the allylic hydroperoxides (Scheme 4).

(9a,b)

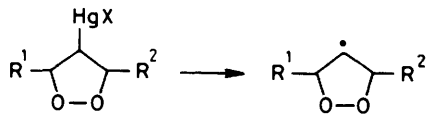
a; $R^1 = Me(CH_2)_6$, $R^2 = (CH_2)_7CO_2Me$
b; $R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_6CO_2Me$

Scheme 4. *Reagents:* i, Br_2

The cleanness of the reaction warrants a brief comment. Bromodemercuriation is believed to involve a free radical chain mechanism.[23] Such a mechanism requires that bromodemercuriation proceeds through the same intermediate peroxy alkyl radicals as are involved in the hydrogenodemercuriation which leads to competing reactions (see later) and produces oxygenated by-products. The formation of by-products in the bromodemercuriation is, however, almost negligible, probably because abstraction of a bromine atom by the alkyl radical is diffusion-controlled, the rate constant being about 10^3-fold greater than that for the most favoured ring closure.[24,25] Alkyl mercury compounds react with sodium borohydride to yield the corresponding alkyl radical[26–28] by a radical mechanism involving the intermediate alkyl hydrido mercury compound RHgH.[26] If this mechanism holds for the reduction of the

$$R\cdot + R\text{–}Hg\text{–}H \longrightarrow R\text{–}H + Hg + R\cdot$$

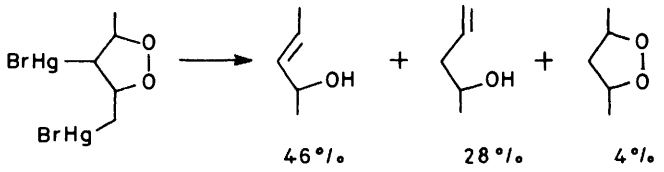
peroxymercuriated compounds (**4a**) and (**4b**), then an endocyclic β-peroxy group can be envisaged.



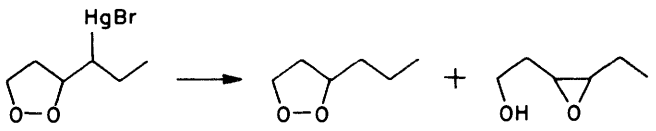
Reagents: $NaBH_4$, R.

It has been reported that cycloperoxymercurials containing *endocyclic* mercurio substituents have a strong tendency to

* 1 cal is 4.184 J.



Scheme 5. *Reagent:* $NaBH_4$



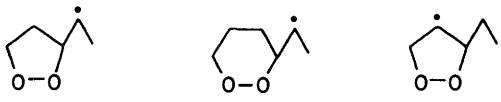
(10a) (10b)

Scheme 6.

deoxymercuriate under the reduction conditions used.[15] Poor yields of peroxides can be expected, the major products being unsaturated alcohols (Scheme 5).

This is in contrast to cycloperoxymercurials containing *exocyclic* mercurio substituents, which generate an exocyclic β-peroxy radical when reduced. The products expected from such radicals are the cyclic peroxide (**10a**) resulting from H atom abstraction, and the epoxy alcohol (**10b**) resulting from S_Hi radical attack on the peroxide linkage[16,19] (Scheme 6).

The relative amounts of products resulting from H atom abstraction or S_Hi attack will be dependent on the structure of the intermediate radical. Porter *et al.*[29] suggested that the critical geometric parameter for the S_Hi reaction is the dihedral angle θ about the O–C bond between the attacking radical and the leaving oxygen. Maximum S_Hi reactivity occurs when this dihedral angle is 180°, *i.e.* when the peroxide linkage and the radical centre are colinear. For the analogous radical derived from a five-membered ring the O–C dihedral angle is substantially less than 180° having a maximum of approximately 165° in the most favourable conformation for S_Hi attack. Hence the amount of S_Hi product from radical (**11**) is substantially less than for the analogous six-membered radical (**12**), which can adopt a dihedral angle of 180°. It is impossible for endocyclic radicals such as (**13**) to assume the required conformation since

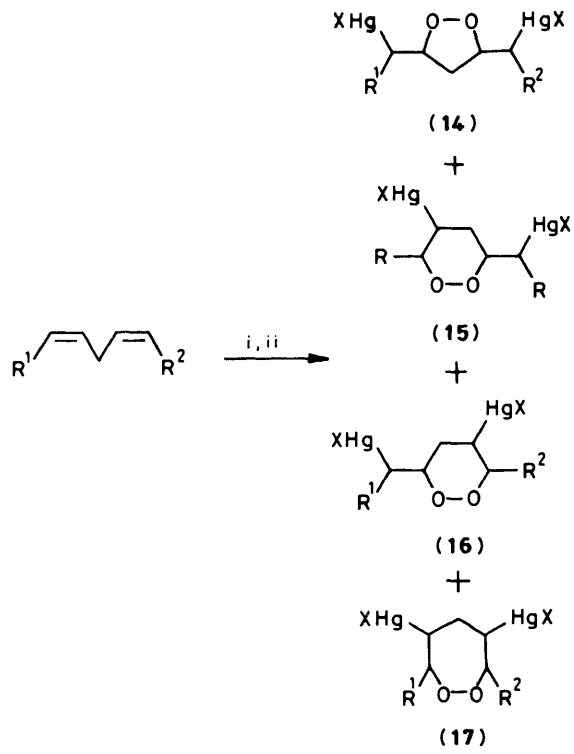


(11) (12) (13)

the radical centre is located within the ring. As a consequence no S_Hi reaction is expected from such radicals.

These observations are consistent with the products formed by the sodium borohydride reduction of compounds (**4a**) and (**4b**) when no epoxy alcohol is detected by t.l.c., and are in contrast to results we obtained in the peroxymercuriation of methyl linoleate (Scheme 7) which could give rise to products (**14**)—(**17**).

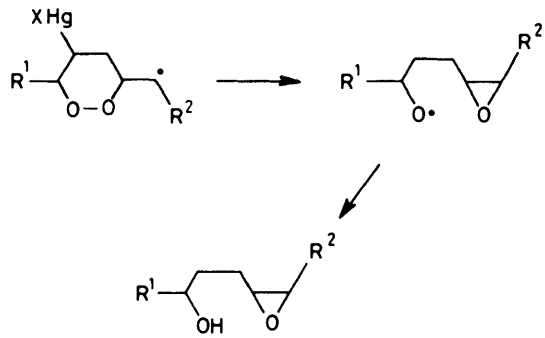
The predictions for cyclisation developed by Baldwin[30] are not well defined for nucleophilic attack on three-membered rings such as the mercurinium ion. However, from molecular model studies and from the results obtained by Porter *et al.*[16] it is apparent that *exo* modes are likely to be favoured while 6-*endo* cyclisation will be disfavoured. Hence, one would expect structures (**14**)—(**16**) to predominate. Sodium borohydride



$R^1 = Me(CH_2)_4$, $R^2 = (CH_2)_7CO_2Me$

Scheme 7. *Reagents:* i, H_2O_2; ii, HgX_2 (X = NO_3)

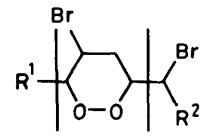
reduction of the peroxymercurials, however, yielded a complex mixture of products from which unsaturated epoxides and epoxy alcohols were identified as the major reaction products. Tentative evidence from ^1H n.m.r. and mass spectra suggests that (**15**) and (**16**) may be formed only as minor products. These results are consistent with the hypothesis that six-membered rings containing exocyclic β-peroxy radicals are likely to undergo extensive S_Hi rearrangement to form epoxy alcohols.[16]



$R^1 = Me(CH_2)_4$, $R^2 = (CH_2)_7CO_2Me$

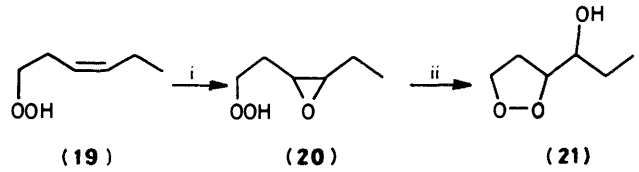
Bromodemercuriation of our peroxymercurials gave an isomeric mixture of the dibromo cyclic peroxides (**18a**) and (**18b**) which show weak molecular ion peaks in the mass spectrum at *m/z* 484, 486, and 488 in the 1 : 2 : 1 ratio expected for dibromo peroxides. Also present were peaks resulting from cleavage adjacent to the ring in (**18a**) and (**18b**).*

* Although we have interpreted the mass spectrum in terms of the six-membered cyclic peroxides, the presence of five- and/or seven-membered rings cannot be discounted from our available data.



(18a, b)

a; $R^1 = (CH_2)_7CO_2Me$, $R^2 = (CH_2)_4Me$
b; $R^1 = (CH_2)_4Me$, $R^2 = (CH_2)_7CO_2Me$



(19) (20) (21)

Scheme 8. *Reagents:* i, MCPA; ii, H^+

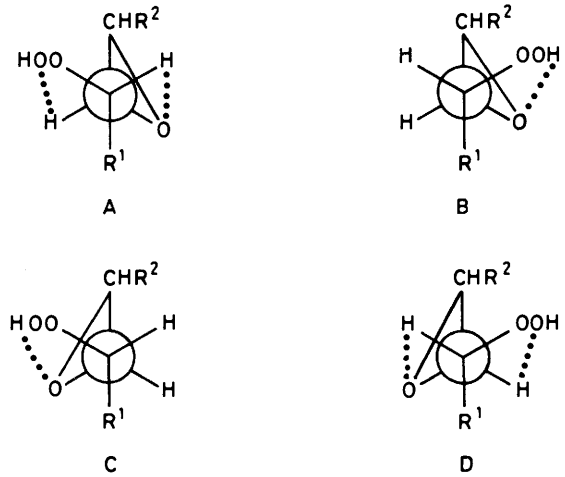


Figure 2. Diastereoisomers of the hydroperoxyoxiranes (**22**). Dotted lines indicate the possibility of hydrogen bonding

The ^{13}C n.m.r. spectrum of the isomeric dibromoperoxides showed peaks in the regions 80—82 p.p.m. (peroxy bearing carbons) and 56—58 p.p.m. (bromo bearing carbons). The i.r. spectrum showed no OOH absorption, confirming the dialkyl nature of the peroxide. The ^1H n.m.r. spectrum contained two two-proton signals in the region δ 4.0—4.6 indicative of two peroxy- and two bromo-bearing methines. No olefinic protons were observed. The fraction showed several spots on t.l.c. analysis (R_F 0.65—0.70; light petroleum–diethyl ether, 80:20) but none was completely resolved and preparative t.l.c. separation of the individual components was not attempted. It is presumed that these were positional isomers and diastereoisomers, of which there would be 32 possibilities.

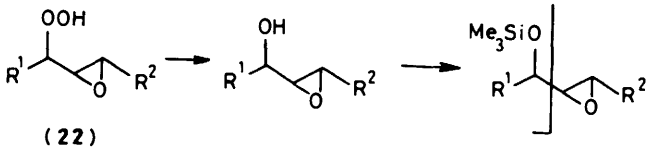
Epoxidation of Allylic Hydroperoxides and Attempted Cyclisation of the Products.—Cyclisation of unsaturated hydroperoxides can be induced by generating an electron-deficient site from the double bond. For example the hexenyl hydroperoxide (**19**) is converted into the α-hydroxy cyclic peroxide (**21**) *via* the oxirane (**20**)[12] (Scheme 8). α-Hydroxy cyclic peroxides are reported to have interesting pharmacological properties.[31]

Epoxidation of our allylic hydroperoxides (**3a**) and (**3b**) in dichloromethane–sodium hydrogencarbonate solution with *m*-chloroperoxybenzoic acid (MCPA) furnished an organic product which showed two broad spots on t.l.c., both of which gave a positive peroxide spray test. Repeated development chromatography suggested that, as with the cyclic peroxides (**5a**) and (**5b**), each spot contained at least two components.

The two bands were separated by preparative t.l.c. on silica gel G. The ^1H n.m.r. spectra showed that both compounds were hydroperoxides (HCOO at δ 9.45 and 8.97 for bands A and B respectively). The less polar product showed two one-proton multiplets between δ 3.10—2.83 whereas the more polar product showed only one multiplet at δ 2.86.

Epoxidation of compounds (**3a**) and (**3b**) can give rise to two diastereoisomers for each positional isomer. For two isomers there is hydrogen bonding between the hydroperoxy O–H and the oxirane oxygen. For the other isomers, hydrogen bonding can be envisaged between the peroxy group and the oxirane methines (Figure 2). On the basis of these conformational preferences we consider the less polar of the two peroxidic fractions to comprise isomers A and D and the more polar band isomers B and C. In isomers A and D the ^1H n.m.r. shifts of the peroxy methine and of the oxirane methine β to the peroxy group will both be downfield from the corresponding hydrogens in isomers B and C as a result of hydrogen bonding. Furthermore, the hydrogen bonding in isomers B and C between the hydroperoxy hydrogen atom and the oxirane oxygen results in a broad OOH signal: the OOH signal for isomers A and D is much sharper. Each pair of diastereoisomers will also be a mixture of positional isomers, and it is probably the positional isomers which show a slight chromatographic separation after multiple development.

The mass spectra of the sodium borohydride reduced products, after conversion into the trimethylsilyl derivatives, confirmed that each spot was a mixture of positional isomers since both mass spectra showed fragments characteristic of the two positional isomers. The most intense high mass peaks resulted from cleavage between the trimethylsilyl ether group and the epoxide ring as shown.



(22)

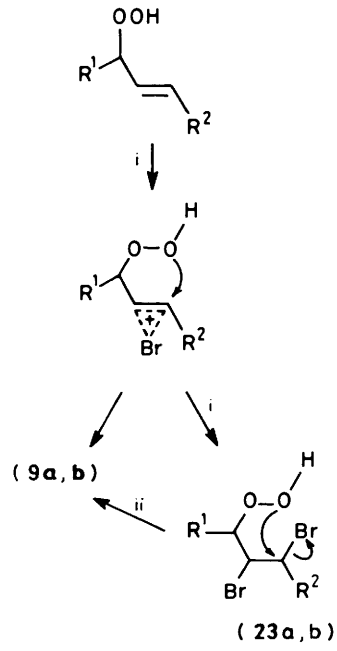
a; $R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_6CO_2Me$
b; $R^1 = MeOCO(CH_2)_7$, $R^2 = (CH_2)_6Me$

Attempted acid-catalysted cyclisation of the hydroperoxy oxiranes was unsuccessful with either trichloro- or trifluoroacetic acid.[11]

Bromination of the Allylic Hydroperoxides.—The allylic hydroperoxides (**3a**) and (**3b**) react smoothly with bromine at 0—5 °C in dry dichloromethane in the dark. The two major bands observed on t.l.c. analysis gave red spots when sprayed with peroxide detecting reagents. A further minor unidentified component was not peroxidic but very polar. The first band (80—85% yield as judged by t.l.c.) was identical with the products (**9a**) and (**9b**) of the bromodemercuriation of the peroxymercurials (**4a**) and (**4b**). The other component (10—15%) was identified as the dibromohydroperoxides (**23a**) and (**23b**) by ^1H n.m.r. and i.r. spectroscopy.

The total product of bromination was kept at room temperature for 1 h with silver trifluoroacetate. Yields of the bromo cyclic peroxides (**9a**) and (**9b**) by this route were good, but it is evident that the majority of the cyclisation occurs prior to the addition of silver trifluoroacetate (Scheme 9).

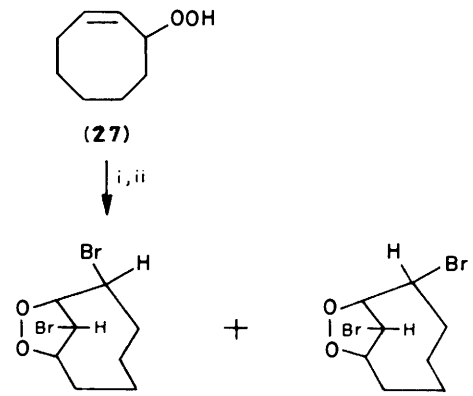
Eight diastereoisomers can be expected from the reaction for each positional isomer, giving a total of 16 isomers in all. We were unable to separate these isomers chromatographically, if



(23a,b)

a; $R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_5CO_2Me$
b; $R^1 = MeOCO(CH_2)_7$, $R^2 = (CH_2)_6Me$

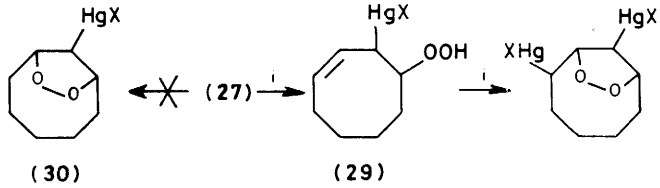
Scheme 9. *Reagents:* i, Br_2; ii, Ag^+



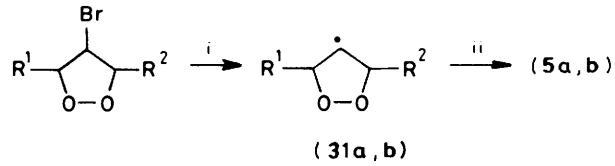
Scheme 10. *Reagents:* i, $Hg(OCOCF_3)_2$; ii, Br_2

indeed they are all present. The ^{13}C n.m.r. spectrum for the bromo cyclic peroxides showed only one peroxidic carbon resonance (89.08 p.p.m.) and only one bromo methine resonance (57.18 p.p.m.); however, the spectral quality was such that a second isomer below 5% would not easily be detected. The difference in the ^{13}C chemical shifts reported for the peroxy-bearing carbons of the *cis*- and *trans*-isomers of 3,5-dialkyl-1,2-dioxacyclopentanes is less than 1.2 p.p.m.;[14,15] replacement of the methyl group by long-chain groups may well decrease this difference and the signals observed could be a composite of one or more of the diastereoisomers.

The bromo cyclic peroxides (**9a**) and (**9b**) generated by bromodemercuriation of the oxymercurials (**4a**) and (**4b**) were spectroscopically and chromatographically identical with those produced by bromination of the allylic hydroperoxides (**3a**) and (**3b**). Bloodworth and Leddy[32] reported that peroxymercuriation–bromodemercuriation of the cycloalkenyl allyl hydroperoxides (**27**) gave the cyclic peroxides (**28a**) and (**28b**) in



Scheme 11. *Reagents:* i, HgX_2



$R^1 = Me(CH_2)_7$, $R^2 = (CH_2)_6CO_2Me$ or
$R^1 = MeOCO(CH_2)_7$, $R^2 = (CH_2)_6Me$

Scheme 12. *Reagents:* i, Bu_3Sn; ii, Bu_3SnH

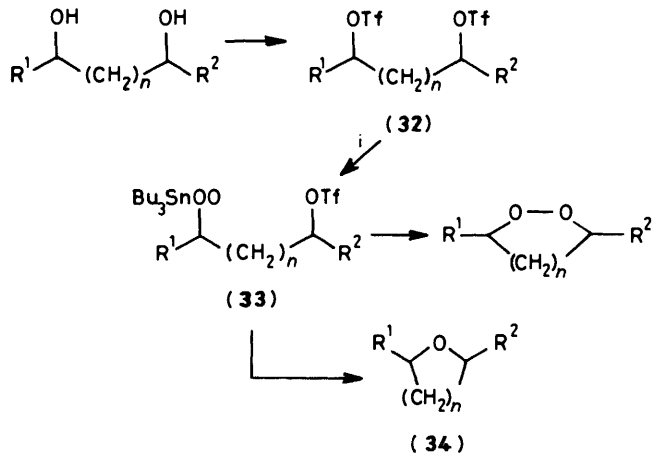
very poor yields (0.6 and 2.7% respectively); more importantly, these cyclic peroxides contain two bromo substituents (Scheme 10). To account for these products, Bloodworth *et al.*[32] concluded that allylic mercuriation occurs to give compound (**29**), followed by 5-*exo*-cyclisation in preference to the 5-*endo*-cyclisation required for the formation of (**30**) (Scheme 11). We have repeated the reaction with cyclohexenyl hydroperoxide using mercuric nitrate in place of mercuric trifluoroacetate as the mercury salt, and have arrived at essentially the same result, namely the formation of a cyclic peroxide with two mercury substituted sites.

Thus the cyclic alkenyl hydroperoxides undergo a 5-*exo*-cyclisation *via* allylic mercuriation in preference to the disfavoured 5-*endo*-cyclisation. The fact that the bromo cyclic peroxides (**9a**) and (**9b**) can be synthesised both by oxymercuriation–bromodemercuriation and by direct bromination of the allyl hydroperoxides (**3a**) and (**3b**) confirms that for the acyclic allylic hydroperoxides (**3a**) and (**3b**), 5-*endo*-cyclisation occurs to the exclusion of allylic mercuriation. We are unable at present to rationalise the discrepancy between the cyclic and acyclic systems, but steric constraints imposed by the medium ring sizes may be significant.

One aim of the synthesis of these cyclic peroxides was to produce compounds which might be pharmacologically active. To this end the bromo substituent is not an attractive substituent to have in the molecule; reduction with tributyltin hydride (Scheme 12) appears to be a promising route for the replacement of bromine.[15,29] The reaction involves abstraction of the bromine atom of the trialkyltin radical.

Reaction between tributyltin hydride and the bromo cyclic peroxide furnished the desired cyclic peroxides (**5a**) and (**5b**) in 75% yield, comparable with the best yields obtained from the hydrogenodemercuriation reaction. This cyclic peroxide was identified by t.l.c., ^1H n.m.r., and i.r. spectral comparison with the authentic material. Attempts to compare mass spectra were unsuccessful owing to contamination of the product with organotin material which we were unable to remove completely either by t.l.c. chromatography or by repeated washing.[33] This complication makes this route less attractive for preparative purposes.

Peroxide transfer between the tin peroxides and alkyl trifluoromethanesulphonates (triflates) or bis(triflates) to furnish dialkyl and cyclic peroxides has been used to prepare simple peroxides in fair to excellent yields by the route shown below.[34]



Scheme 13. *Reagents:* i, $(Bu_3SnO)_2$ Tf = CF_3SO_2

$$2ROTf + BuSnOOSnBu \longrightarrow ROOR + 2BuSnOTf$$

Tf = CF_3SO_2

We failed, however, to extend the peroxide transfer reaction to the synthesis of fatty acid cyclic peroxides. Methyl 9,12- and 10,12-dihydroxystearates were prepared by oxymercuriation of methyl ricinoleate [18] and the planned strategy for the synthesis of the product is outlined in Scheme 13.

The procedure involves the initial formation of the mono *trans*-alkylated tin peroxide (**33**) followed by a second intramolecular *trans*-alkylation. However, reaction of the bistriflates (**32**) with di-t-butyltin peroxide furnished only one non-polar product which was identified as the cyclic ether (**34**) by ^1H n.m.r., mass, and i.r. spectroscopy. The absence of the desired peroxidic products was disappointing.

Experimental

General experimental procedures are given in the preceding paper.[35] Mercury(II) nitrate demihydrate and sodium borohydride were stored in closed bottles over silica gel in a desiccator to protect them from moisture. Hydrogen peroxide (85%), kindly donated by Laporte Industries Limited, was stored at 0 °C; the required amounts were measured by a glass pipette assuming the density to be 1.33 g cm^{-3}. The peroxide content was checked periodically.[36]

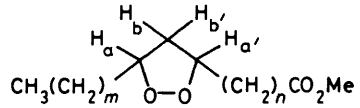
Methyl 9(10)-Hydroperoxyoctadec-10(8)-enoates (**3a**) *and* (**3b**).—Methyl oleate (99.9%, 1 g) was placed in a photochemical reactor with an inner and outer water cooling jacket[35] along with a solution of Methylene Blue (50 mg), in tetrachloromethane–methanol (95:5, 250 ml). Oxygen was bubbled through the solution at a rate of 40—50 ml/min for 16 h whilst the flask was illuminated (3 × 150-W light bulbs). Evaporation of the solvent at 2 mmHg and 5 °C gave a product still containing Methylene Blue, but this was retained on a short column of sorbsil when the hydroperoxides were eluted with dry ether. The resulting pale yellow oil showed only two spots in t.l.c. The less polar compound was unchanged starting material and the more polar (R_F 0.41 in PE 30) gave a red colour when sprayed with peroxide-detecting reagents. Preparative h.p.l.c. on a partisil column gave pure hydroperoxide (75—83% yield) using light petroleum–isopropyl alcohol (97.5:2.5) as the eluting solvent. The following spectroscopic data was recorded for the hydroperoxides (**3a**) and (**3b**): $\nu_{max.}$ 3 480 (OO-H stretch) and 973 cm^{-1} (*trans*-CH=CH stretch); δ_H 8.40 (1 H, br s, OOH), 5.92—5.10 (2 H, m, olefinic H), 4.18 (1 H, q, CHOO), 3.60 (3 H, s, CO_2CH_3), 2.23 (2 H, asym. t, *J* 7.0 Hz, CH_2CO_2Me), 1.99 (2 H, q, *J* 6.0 Hz, $CH{=}CHCH_2$), 1.48 (br s, chain CH_2), and 0.80 (3 H, asym. t, *J* 5.6 Hz, CH_3); δ_C (where double assignments are given these refer to the 9- and 10-hydroperoxides respectively) 174.17 (C-1), 136.18, 135.79, 128.87, and 128.55 (olefinic carbons), 86.50 (C-9, -10), 33.78 (C-2), 32.26 (C-8, -11), 32.09 and 31.94 (C-12, -7), 31.59 (C-16), 29.23 and 28.83 (C-4, -5, -6, -13, -14, -15), 24.98 (C-7, -12), 24.61 (C-3), 22.38 (C-17), and 13.78 p.p.m. (C-18). The allylic alcohols produced by sodium borohydride reduction of the hydroperoxides were examined as their trimethylsilyl ethers. They showed intense fragments at *m/z* 227 [$CH_3(CH_2)_6CH{=}CHCHOSiMe_3$] and 271 [$MeO\text{-}CO(CH_2)_6CH{=}CHCHOSiMe_3$] resulting from cleavage α to the allylic ether, with the charge being carried by the allylic fragment.

Peroxymercuriation of the Hydroperoxides (**3a**) *and* (**3b**).—A solution of the mixed hydroperoxides (**3a**) and (**3b**) (320 mg, 1 mmol) in dry dichloromethane (5 ml) was added to a vigorously stirred suspension of mercury(II) nitrate demihydrate (370 mg, 1.1 mmol) in dry dichloromethane (15 ml). The mixture was stirred for 24 h at ambient temperature and the solvent removed to furnish the crude organomercury nitrate (**4a**) and (**4b**).

Hydrogenodemercuriation of Compounds (**4a**) *and* (**4b**).—Sodium borohydride (138 mg, 3.5 mmol) in distilled water–tetrahydrofuran (1:1, 10 ml) was added during 35 min to the crude organomercury nitrate, maintaining the temperature of the solution below 0 °C. The mixture was stirred for a further 30 min, and then allowed to warm slowly to room temperature, and the product was extracted with ether (3 × 10 ml). Analytical t.l.c. showed five spots when developed with PE 25 or 30, but only one (R_F 0.41) gave a positive peroxide spray test. Five components were isolated by preparative t.l.c. The following spectroscopic data were recorded; the quoted yields represent the range from seven experiments.

Band A (16—19 mg, 5—6%; R_F 0.51 in PE 30), no O–H or C=O stretch in the i.r. spectrum; δ_H 5.37 (2 H, m, olefinic H), 3.65 (3 H, s, CO_2CH_3). 2.30 (2 H, asym. t, CH_2CO_2Me), 2.00 (2 H, m, allylic CH_2), 1.61 (shoulder) and 1.25 (br s, chain CH_2), and 0.86 (3 H, asym. t, CH_3).

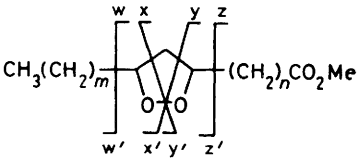
Band B (144—200 mg, 45—70%, R_F 0.41 in PE 25) was identified as a mixture of 3-(6-methoxycarbonylhexyl)-5-octyl- (**5a**) and 5-heptyl-3-(7-methoxycarbonylheptyl)-1,2-dioxolane (**5b**). No O–H or C=O stretch in the i.r. spectrum; δ_H 4.11 (2 H, br q, H_a), 3.65 (3 H, s, CO_2CH_3), 2.74 (1 H, dt, J_{ab} 6.0, $J_{bb'}$ 12.0 Hz, H_b), 2.25 (2 H, asym. t, *J* 7.4 Hz, CH_2CO_2Me), 1.74 (1 H, dt, J_{ab} 6.0, $J_{bb'}$ 12.0 Hz, H_b), 1.50 (br s, chain CH_2), and 0.90 (3 H, asym. t, *J* 5.7 Hz, CH_3); δ_C [where double assignments are given



m = 7, *n* = 6 or *m* = 6, *n* = 7

these refer to (**5b**) and (**5a**) respectively] 174.06 (C-1), 81.04 (peroxidic carbons), 51.27 (OCH_3), 46.27 (C-10, -9), 33.81 (C-2, -8, -12 and C-2, -7, -11), 31.72 (C-16), 29.38 and 29.02 (C-4, -5, -6, -14, -15 and C-4, -5, -13, -14, -15), 26.21 (C-7, -13 and C-6, -12), 24.77 (C-3), 22.52 (C-17), and 13.93 p.p.m. (C-18); *m/z* (symbols such as wa refer to the fragment w from isomer a) 229 (0.4, wb), 215 (0.7, wa), 185 (10, yb − H and/or z'a), 171 (20, z'b and/or

x'a − H), 155 (8, zb − 2), 143 (4, za), 141 (10, za − 2 H), 55 (100), and other unlisted values.



a; $m = 7, n = 6$
b; $m = 6, n = 7$

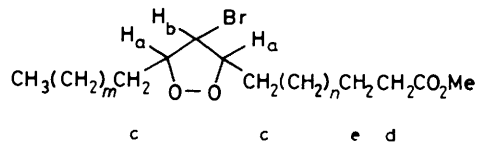
Band C (25—56 mg, 8—18%; R_F 0.25 in PE 30) was identified as a mixture of allylic alcohols. The i.r. and mass spectra were like those produced from the allylic hydroperoxides after sodium borohydride reduction; δ_H 5.50 (2 H, m, olefinic H), 4.02 [1 H, asym. q, (HCO)], 3.60 (3 H, s, CO_2CH_3), 2.32 (2 H, asym. t, J 7.4 Hz, CH_2CO_2Me), 2.00 (2 H, asym. q, allylic CH_2), 1.32 (br s, chain CH_2), and 0.87 (3 H, asym. t, J 5.6 Hz, CH_3).

Band D (14—35 mg, 4—10%; R_F 0.20 in PE 30); $\nu_{max.}$ 3 500—2 900 (O–H stretch), 1 760 (ester C=O stretch), 1 720 (C=O stretch), and 840 cm^{-1}; δ_H 8.15 (br s), 5.50 (m, olefinic H), 3.73 (3 H, s, CO_2CH_3), 2.37 (asym. t, J 7.4 Hz, CH_2CO_2Me), 2.07 (2 H, asym. q, allylic CH_2), 1.65 (shoulder), and 1.32 (br s, chain CH_2), and 0.97 (asym. t, J 5.6 Hz, CH_3).

Band E (35—50 mg, 10—15%; R_F 0.1—0.0) was not identified.

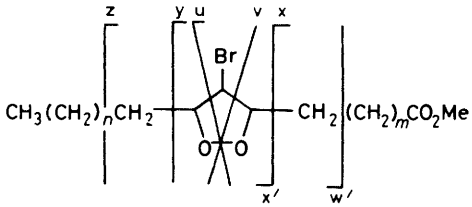
Catalytic Hydrogenation of Compounds (**5a**) *and* (**5b**).—Palladium–charcoal (10%, 10 mg), methanol (1 ml), and compounds (**3a**) and (**3b**) (20 g) were stirred together for 30 min at room temperature. The charcoal was filtered off and washed with methanol (2 × 5 ml). After trimethylsilylation the reduction product showed only one peak on g.l.c. analysis (see Discussion section).

Bromodemercuriation.—Bromine (180 mg, 1.13 mmol) in dry dichloromethane (10 ml) was added to a vigorously stirred suspension of the organomercury nitrates (**2a**) and (**2b**) in dichloromethane (5 ml) at 0 °C. The mixture was stirred for 12 h in the dark, filtered through a short column of sorbsil to remove the precipitate of mercury(II) bromide, and the solvent removed under a stream of dry nitrogen to furnish a pale yellow-brown oil. Analytical t.l.c. showed one major product (>95%, R_F 0.79 in PE 30) with a slight tail and traces (*ca.* 4—5%) of more polar material. The major product was isolated by preparative t.l.c. and identified as an isomeric mixture of 5-heptyl-3-(7-methoxycarbonylheptyl) (**9a**) and 3-(6-methoxycarbonylhexyl)-5-octyl-4-bromo-1,2-dioxolanes (**9b**) on the basis of the following spectroscopic data: $\nu_{max.}$ 1 553, 820 (C–O ring breathing) and 714 cm^{-1} (C–Br stretch); absence of O–H stretch and HC=CH stretch; δ_H 4.75 (2 H, q, J 6.0 Hz, H_a), 4.29 (1 H, asym. t, J 5.6 Hz, H_b), 3.60 (3 H, s, CO_2CH_3), 2.25 (2 H, asym. t, J 7.0 Hz, H_d), 1.55 (6 H, shoulder, H_c and H_e), 1.25 (br s, chain CH_2), and 0.81 (3 H, asym. t, J 5.6 Hz, CH_3); δ_C [where double assignments are given



c c e d

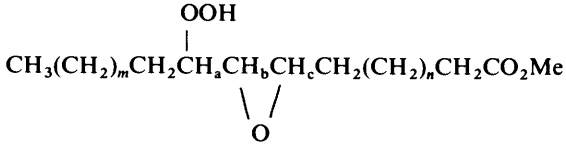
these refer to (**9a**) and (**9b**) respectively] 89.08 (peroxide carbons), 57.18 (C-9, -10), 51.21 (OCH_3), 33.85 (C-7, -11 and C-8, -12), 31.54 (C-16), 29.21, 29.02, and 28.84 (C-4, -5, -13, -14, -15 and C-4, -5, -6, -14, -15), 25.71 (C-6, -12 and C-7, -13), 24.68 (C-3), 22.44 (C-17), and 13.87 p.p.m. (C-18); m/z (symbols such as x'a refer to the fragment x' from molecule a) 359 and 357 (0.5%, $M^+ - 31 - 18$), 293 (2, $M^+ - Br - H_2O_2$), 279 and 277 (2, ua − H and/or w'a), 265 and 263 (1, ub − H and/or w'b), 251 and 249 (6 and 7, x'a), 187 and 185 (21, va ± H), 175 and 173 (9 and 13, vb ± H), 155 (50, xa − 2 H), 141 (xb − 2 H), and other unlisted values.



a; $n = 5, m = 6$
b; $n = 6, m = 5$

Epoxidation of Compounds (**3a**) and (**3b**).—A solution of *m*-chloroperbenzoic acid (85%, 260 mg, 1.1 mmol) in anhydrous dichloromethane (5 ml) was added to a stirred solution of the allylic hydroperoxides (**3a**) and (**3b**) (320 mg, 1 mmol) in dichloromethane–saturated aqueous sodium hydrogencarbonate (50:50, 20 ml). The reaction mixture was stirred at room temperature for 16 h. The organic layer was separated and washed in saturated sodium hydrogencarbonate solution (2 × 10 ml), brine (2 × 10 ml), and distilled water (10 ml). The aqueous washings were re-extracted with a small volume of dichloromethane (10 ml) and the product was recovered from the combined organic phases. Analytical t.l.c. showed two major spots at R_F 0.42—0.36 and 0.24—0.20 in PE 40, together with minor amounts of unidentified polar material (*ca.* 5—8%). Both major spots gave a red colour when sprayed with peroxide detecting sprays. Preparative t.l.c. afforded pure fractions of each component.

Band A (138 mg, 41%; R_F 0.42—0.36 in PE 40, see text for assignment) gave the following spectroscopic data: $\nu_{max.}$ 3 330 (OO–H stretch), and 890 cm^{-1} (C–O ring breathing); δ_H 9.45 (1 H, app. d, OOH), 3.98 (1 H, m, H_a), 3.65 (3 H, s, CO_2CH_3), 3.10 (1 H, m, H_c), 2.83 (1 H, dd, H_b), 2.28 (2 H, asym. t, CH_2CO_2Me), 1.43 (2 H, shoulder, H_d), 1.27 (br s, chain CH_2), and 0.86 (3 H, asym. t, CH_3); δ_C (where double assignments are given these refer



a; $m = 5, n = 6$
b; $m = 6\ n = 5$

to the 9- and 10-hydroperoxides respectively) 174.12 (C-1), 82.51 (C-9, -10), 60.27 (C-10, -9), 56.52 (C-11, -8), 51.28 (OCH_3), 33.88 (C-2), 31.62 (C-16), 31.46 (C-12), 29.90, 29.43, 29.16, 29.03, and 28.82 (C-4, -5, -6, -8, -14, -15 and C-4, -5, -11, -13, -14, -15), 25.78, 25.58, 25.30, and 25.22 (C-7, -13 and C-6, -12), 24.69 (C-3), 22.48 (C-17), and 13.89 p.p.m. (C-18). The hydroperoxides were reduced to the hydroxy derivatives with sodium borohydride and analysed as the trimethylsilyl (TMS) derivatives: m/z 385 (M^+ − Me), 370 (M^+ − 2Me), 369 (M^+ − Me − MeOH), 311 (M^+ − OTMS), 259 [$MeO_2C(CH_2)_7CHOSiMe_3$], 227 (259 − 32), 215 [$CH_3(CH_2)_7CHOSiMe_3$], and other unlisted values.

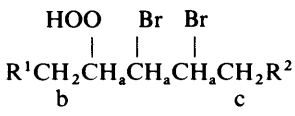
Band B (131 mg, 39%; R_F 0.24—0.20 in PE 40 (see text for assignment) gave the following spectroscopic data : mass and i.r. spectra were identical with those from band A; δ_H (assignment labels as for band A) 8.97 (1 H, br s, OOH), 3.65

(3 H, s, CO_2CH_3), 3.8—3.5 (1 H, m, H_a), 2.86 (2 H, asym. d, *J* 5.0 Hz, H_b, H_c), 2.29 (2 H, asym. t, CH_2CO_2Me), 1.30 (br s, chain CH_2), and 0.86 (3 H, asym. t, CH_3); δ_C (where double assignments are given these refer to the 9-and 10-hydroperoxides respectively) 174.09 (C-1), 85.23 (C-9, -10), 59.66 (C-10, -9), 55.91 (C-11, -8), 51.27 (OCH_3), 33.87 (C-2), 31.62 (C-16), and 29.46, 29.03, and 28.83 (C-4, -5, -6, -8, -14, -15 and C-4, -5, -11, -13, -14, -15), 25.74, 25.57, and 25.22 (C-7, -13 and C-6, -12), 24.68 (C-3), 22.45 (C-17), and 13.87 p.p.m. (C-18).

Bromination of Methyl 9(10)-*Hydroperoxyoctadec*-10(8)-*enoate* (**3a**) *and* (**3b**).—Bromine (180 mg, 1.13 mmol) was added to a solution of compounds (**3a**) and (**3b**) (320 mg, 1 mmol) in dry dichloromethane at 0 °C in the dark and the mixture was stirred for 45 min. Evaporation of the solvent gave a red-brown oil which showed three spots on analytical t.l.c. at R_F 0.77, 0.67, and 0.57 in PE 30. Preparative t.l.c. afforded two major bands A and B, and a minor unidentified streak (5 mg).

Band A (342 mg, 85%; R_F 0.77 in PE 30) was identified by comparison of its ^1H n.m.r., ^{13}C n.m.r., i.r., and mass spectra with those from the product of the bromodemercuriation reaction.

Band B (53 mg, 11%; R_F 0.67 and 0.57 in PE 30) was identified as an isomeric mixture of methyl 9(10)-hydroperoxy-10,11(8,9)-dibromo-octadecanoates (**23a**) and (**23b**). The following spectroscopic data were recorded: $\nu_{max.}$ 3 420 (OO–H stretch), 815 (C–O stretch), and 712 cm^{-1} (C–Br stretch); δ_H 4.23 (3 H, asym. t, *J* 6.0 Hz, H_a), 3.60 (3 H, s, CO_2CH_3), 2.25 (2 H, asym. t, *J* 7.1 Hz, CH_2CO_2Me), 1.55 (4 H shoulder, H_b, H_c), 1.25 (br s, chain CH_2), and 0.81 (3 H, asym. t, *J* 5.7 Hz, CH_3).



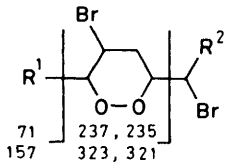
$R^1 = Me(CH_2)_5$, $R^2 = (CH_2)_6CO_2Me$ and
$R^1 = (CH_2)_5CO_2Me$, $R^2 = Me(CH_2)_6$

Attempted Silver Trifluoroacetate-induced Cyclisation of Compounds (**23a**) *and* (**23b**).—Silver trifluoroacetate (330 mg, 1.5 mmol) was added all at once to the crude bromination product with vigorous stirring which was continued for 25 min. The reaction was quenched by the addition of ether (50 ml) and the organic solution washed with saturated brine (20 ml) followed by distilled water (20 ml). Preparative t.l.c. gave a major product (95%) whose spectroscopic and chromatographic properties were identical with those of the bromo cyclic peroxides (**9a**) and (**9b**) obtained by bromodemercuriation.

Tin Hydride Reduction of the Bromo Cyclic Peroxides.—Tri-n-butyltin hydride (87 mg, 0.3 mmol) was added by microsyringe to the bromo cyclic peroxides (**9a**) and (**9b**) (50 mg, 0.13 mmol) in dry hexane (5 ml). The mixture was stirred at room temperature for 4 h then washed with water (2 × 5 ml), saturated brine (5 ml), and water (5 ml). Isolation of the organic product gave a colourless oil. T.l.c. showed a product distribution similar to that for the sodium borohydride reduction of (**2a**) and (**2b**). The major component, isolated by preparative t.l.c. in 75% yield, was shown to be identical with the cyclic peroxide previously obtained by t.l.c., ^1H n.m.r., and i.r. spectroscopy.

Peroxymercuriation–Bromodemercuriation of Methyl Linoleate.—Methyl linoleate (300 mg, 1 mmol) in dry dichloromethane (5 ml) was added to a vigorously stirred suspension of mercury(II) nitrate monohydrate (370 mg, 1.1 mmol) in dry dichloromethane. The mixture was stirred for 24 h at ambient temperature and the solvent removed on a rotary film evaporator.

Bromine (180 mg, 1 mmol) in dry dichloromethane (10 ml) was added to a vigorously stirred suspension of the crude peroxymercurial in dichloromethane (5 ml) at 0 °C for 12 h. The mixture was worked up as previously described (bromodemercuriation) to give a pale yellow oil. Analytical t.l.c. (PE 25) showed a broad non-polar band (R_F 0.75—0.65) and some more polar material. The non-polar band gave a positive peroxide test with peroxide-detecting spray. Isolation of the peroxidic material by preparative t.l.c. gave a pale yellow oil (179 mg, 40%) which is considered to be a mixture of the dibromo cyclic peroxides (**18a**) and (**18b**) on the basis of the following spectroscopic data: δ_H 4.38 (2 H, m, CHOO), 4.00 (2 H, m, CHBr), 3.65 (3 H, s, CO_2CH_3), 3.02—2.5 (m), 2.27 (2 H, asym. t, *J* 7.4 Hz, CH_2CO_2Me), 1.60 (br s, chain CH_2), and 0.87 (3 H, asym. t, *J* 5.4 Hz, CH_3); *m/z* 488 (0.1%), 486 (0.2), 484 (0.1), 323 (1), 321 (1), 237 (3), 235 (3), 157 (12), and other unlisted values.



a; $R^1 = Me(CH_2)_4$, $R^2 = (CH_2)_7CO_2Me$
b; $R^1 = (CH_2)_7CO_2Me$, $R^2 = (CH_2)_4Me$

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