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BIFUNCTIONAL COMPOUNDS FROM REACTION OF ALKOXY HYDROPEROXIDES WITH METAL SALTS

G. Cardinale, J. A. M. Laan, D. van der Steen
and J. P. Ward
Unilever Research Laboratorium Vlaardingen, P.O. Box 114, 3130 AC Vlaardingen, The Netherlands

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Abstract—Alkoxy hydroperoxides, obtained by ozonizing olefins in alcoholic solution, were treated with ferrous sulfate. C—C bond scission and radical formation was followed by dimerization of the radicals formed. Ozonides reacted similarly. Acyclic and cyclic olefins, including a cyclic enol ether, gave rise to a range of α,ω-disubstituted products in modest yields. By using ferric chloride, ω-chloro esters were obtained from the alkoxy hydroperoxides derived from olefinic esters.

The chemical reactivity of alkoxy hydroperoxides towards metal salts has been rationalized by postulating radical mechanisms to explain C—C bond splitting, whereby further reactions by a number of pathways then become possible. Milas *et al.* described the formation of mainly ethyl acetate from the reaction of α-hydroperoxyethyl ether and ferrous sulfate by postulating an electron transfer reaction in which the intermediate was a free radical (Scheme 1).[1]

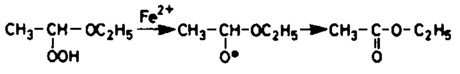
Murai *et al.* also assumed a radical mechanism in the decomposition of 1-ethoxy-n-heptyl hydroperoxide to ethyl heptanoate with ferrous sulfate.[2] Kochi showed that the radicals can react with metal chlorides in two ways; by ligand transfer in which alkyl chlorides are formed, or via an electron transfer leading to a carbonium ion.[3] Kumamoto *et al.* described the reaction of 2-tetrahydropyranyl hydroperoxide with stochiometric amounts of ferrous and cupric chlorides in aqueous solution to form 4-chlorobutyl formate (Scheme 2) and they pointed out the possible preparative utility of these and similar reactions.[4]

A practical example was the preparation in 69% yield of methyl 6-chlorohexanoate from cyclohexanone, hydrogen peroxide and a mixture of ferrous and cupric salts (Scheme 3).[5]

This together with the observation of Murai *et al.*[2] that treatment of 1-ethoxyheptyl hydroperoxide with mixtures of ferrous sulfate and cupric chloride led to n-hexyl chloride and dodecane by radical coupling, was the starting point for our present work (Scheme 4).

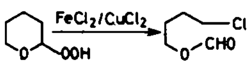
Furthermore, decomposition of 1-hydroxy-1-hydroperoxy dicyclohexyl peroxide with ferrous salts gave a mixture of products containing the coupling product of the radical, 1,12-dodecandioic acid,[6,7] and this strengthened our impression that the decomposition of alkoxy hydroperoxides by metal salts could be used for the synthesis of bifunctional compounds from suitable starting materials by dimerization of the radical intermediates.

Alkoxy hydroperoxides can be prepared conveniently by ozonizing olefins in alcoholic solutions.[8] We have described a number of syntheses of olefinic aldehydes on the basis of the reaction of alkoxy hydroperoxides with mixtures of ferrous and cupric salts.[9] We now show how a range of bifunctional compounds can be prepared from readily available starting materials using the same reaction sequence but employing only iron salts. The products formed provide circumstantial evidence for the postulated reaction mechanism.

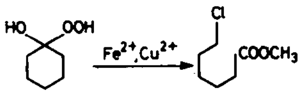


$$\mathrm{CH_3-\underset{\displaystyle OOH}{CH}-OC_2H_5 \xrightarrow{Fe^{2+}} CH_3-\underset{\displaystyle O\bullet}{CH}-OC_2H_5 \longrightarrow CH_3-\underset{\displaystyle \overset{\|}{O}}{C}-O-C_2H_5}$$

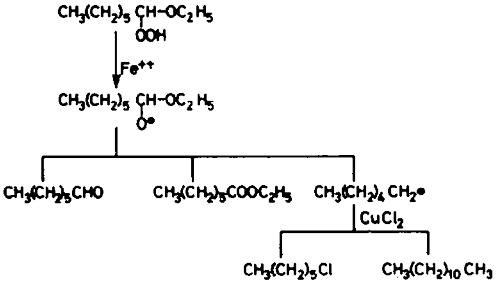
Scheme 1.



Scheme 2.



Scheme 3.

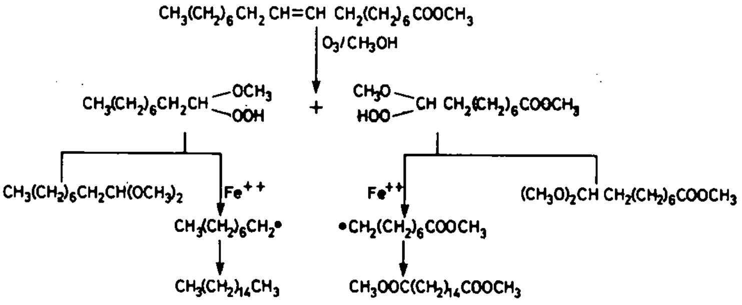


Scheme 4.

RESULTS

The olefinic starting materials used included acyclic and cyclic olefins, and a cyclic enol ether derived from a readily available medium large cyclic ketone, cyclododecanone. They were treated with ozone in methanol, and the mixtures of methoxy hydroperoxides formed were then reacted with ferrous sulfate. This led to fragmentation with loss of one carbon atom, as described earlier,[9] radical formation and coupling of the radicals.

1-Dodecene, 1-hexadecene and 4-phenyl-1-butene



Scheme 5.

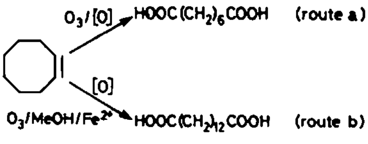
were converted in modest yields to eicosane, octacosane and 1,4-diphenylbutane, respectively. Methyl oleate and methyl 10-undecenoate were converted similarly to dimethyl esters of 1,16-hexadecanedioic acid and 1,18-octadecanedioic acid. The case of methyl oleate is shown in Scheme 5. 10-Undecenol and 10-undecenyl acetate reacted analogously, forming 1,18-dihydroxyoctadecane and its diacetate, respectively.

The general applicability of the radical coupling reaction to form α,ω-disubstituted alkanes was demonstrated by using cyclic olefins. Cyclohexene, cyclooctene and cyclododecene afforded 1,10-decanedioic, 1,14-tetradecanedioic and 1,22-docosanedioic acid derivatives, respectively. An additional oxidation step is required in this sequence of conversions to dicarboxylic acids. However, the process should be distinguished from others in which cyclic olefins are converted to α,ω-dicarboxylic acids using ozone (cf. e.g. Refs 10 and 11). The traditional process is exemplified by ozonization of cyclooctene, with further oxidation, to 1,8-octanedioic acid (route a, Scheme 6).

The essential feature of the present work is coupling (dimerization) of the radicals formed on scission of the alkoxy hydroperoxide, with formation of 1,14-tetradecanedioic acid (route b, Scheme 6). In addition it was shown that the ozonides of the olefins, obtained by ozonolysis in light petroleum, underwent the same fragmentation and radical dimerization reaction when submitted to ferrous sulfate treatment.

The efficiency of the radical couplings is not great, so that the "conventional" products were also formed in our experiments. It could be predicted, therefore, that mixtures of olefins would lead to very complex mixtures of products when subjected to the process of ozonization and treatment of the alkoxy hydroperoxides with metal salts. Nevertheless, use of an equimolar mixture of methyl 10-undecenoate and 10-undecenol led, by cross-coupling of the two radicals formed to methyl 18-hydroxyoctadecanoate, albeit in poor yield. A better strategy might be to use one of the reactants in large excess.

A fortunate circumstance was that a number of the bifunctional products described here were only sparingly soluble, and so they could be readily isolated by crystallization. This frequently occurred spontaneously during the reaction.



Scheme 6.

The alkoxy hydroperoxides derived from methyl oleate and methyl 10-undecenoate were also treated with ferric chloride. The bifunctional products, as expected, were methyl 8-chlorooctanoate and methyl 9-chlorononanoate, which were obtained in high purity by distillation. The enol ether 1-ethoxy-1-cyclododecene, prepared from cyclododecanone, when reacted with ozone and ferrous sulfate, afforded diethyl 1,22-docosanedioate directly.

EXPERIMENTAL

Starting materials. Cyclohexene (BASF), GLC pure; cyclooctene (Aldrich), GLC 88%; cyclododecene (Columbian Carbon Co.), GLC 90%, *cis/trans* 30:70; cyclododecanone, 10-undecenol and 10-undecenyl acetate (Fluka); 10-undecenoic acid and oleic acid (Merck); 4-phenyl-1-butene (K and K Laboratories Inc.); 1-hexadecene and 1-dodecene (Fluka); Perhydrol (30% H_2O_2, Merck).

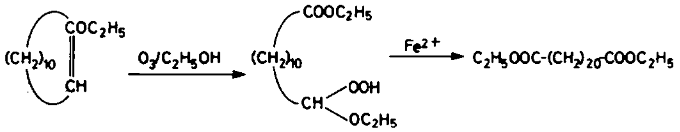
Ozone in oxygen was produced with a Stage K.G. ozonizer supplying about 0.1 mol O_3 h^{-1}.

Methyl esters of 10-undecenoic and oleic acid were prepared using methanol and BF_3 etherate. 1-Ethoxy-1-cyclododecene was prepared from cyclododecanone by the method of Schmidt and Grafen.[12]

Combustion analyses. These were carried out by Mr A. Bernhart, Microanalytical Laboratory, Max Planck Institute for Coal Research, Mülheim, Federal Republic of Germany.

GLC analyses. The GLC analyses were carried out on SE 30, and/or PEGA 5% on Diatoport S 80-100 at suitable temperatures.

NMR and IR spectroscopy. Proton magnetic resonance spectra of the products were run on a Varian HA-100



Scheme 7.

spectrometer, and IR spectra on an Infracord. The spectra were, in the majority of cases, compared with those of authentic samples prepared by literature methods, and they served as confirmation of identity.

1,4-*Diphenylbutane.* A soln of 4-phenyl-1-butene (25 g, 0.19 mol) in 250 ml MeOH was treated with O_3 in O_2 until reaction was complete. The MeOH soln was then added to 74.0 g $FeSO_4 \cdot 7H_2O$ (0.27 mol) in 500 ml MeOH with stirring. The mixture was evaporated to dryness (30°/1.6 kPa), the residue acidified with 1 M H_2SO_4 and extracted with ether, the extract washed with water, dried (Na_2SO_4) and evaporated. The crude product contained 1,4-diphenylbutane, 3-phenylbutanal and its dimethyl acetal, and methyl 3-phenylpropionate (GLC). Distillation gave 6.7 g (33.7% of theory) 1,4-diphenylbutane, b.p. 104–109°/5 Pa, which was crystallized from MeOH; 6.5 g, m.p. 52.5–54° (lit.[13] m.p. 50.5–51.5°). IR: 700, 752 (monosubstituted benzene), 1495, 1502, 1602 and 3030 cm^{-1}. (Found: C, 91.4; H, 8.8. $C_{16}H_{18}$ requires: C, 91.41; H, 8.59.)

Octacosane and eicosane. 1-Hexadecene (0.2 g, 0.9 mmol) in 10 ml MeOH was ozonized as above and the soln shaken with 0.4 g (1.4 mmol) $FeSO_4 \cdot 7H_2O$. The crude product (0.23 g) obtained on evaporation of the MeOH contained tetradecane (22%), methyl pentadecanoate (49%) and octacosane (21%) by GLC.

1-Dodecene (1 g, 6 mmol) in 20 ml MeOH was ozonized similarly and the soln added to 1.7 g $FeSO_4 \cdot 7H_2O$ (6 mmol) in 20 ml MeOH. The solvent was evaporated, the residue acidified with 1 M H_2SO_4 and extracted with ether. The crude product obtained gave 0.3 g pure eicosane, m.p. 36–37° from EtOH (lit.[14] m.p. 36–37°); yield 36.5% of theory.

1,18-*Octadecanediol.* A soln of 10-undecenol (50 g, 0.29 mol) was ozonized in 1 l MeOH as above. The volume was reduced to 500 ml by evaporation at 30°/1.6 kPa and this soln was added to a soln of 122.7 g $FeSO_4 \cdot 7H_2O$ (0.44 mol) in 500 ml MeOH. After the exothermic reaction, part of the reaction product crystallized spontaneously as the mixture cooled. It was filtered off, dissolved in ether, washed with 2 M H_2SO_4, and water, dried ($MgSO_4$) and recovered by evaporation of the ether; 12.6 g 1,18-octadecanediol, m.p. 98–99° (lit.[14] m.p. 97–98°); yield 30.0% of theory. The first methanolic mother liquors were acidified with 2 M H_2SO_4 and extracted with CH_2Cl_2 and evaporated. The residue (33.5 g) contained 1,1-dimethoxy-10-hydroxydecane and 10-hydroxydecanal as main components (GLC).

1,18-*Diacetoxyoctadecane.* 10-Undecenyl acetate (50 g, 0.24 mol) in 1 l light petroleum was ozonized as above, with cooling in an ice bath. The solvent was evaporated (35°/2.7 kPa) and the residue was added to 92.5 g $FeSO_4 \cdot 7H_2O$ (0.33 mol) dissolved in 720 ml MeOH, with stirring. On cooling, part of the product crystallized out. It was isolated as above. Recrystallization from light petroleum gave 21.2 g 1,18-diacetoxyoctadecane, m.p. 59.5–61° (lit.[15] m.p. 59.0–59.3°); yield 66.6% of theory. (Found: C, 71.3; H, 11.2; O, 17.1. $C_{22}H_{42}O_4$ requires: C, 71.34; H, 11.38; O, 17.28.) IR: 1738 (CO) and 1373, 1245, 1037 and 968 cm^{-1} (acetate). The methanol filtrate was concentrated, acidified with 2 M HCl and extracted with CH_2Cl_2. The residue obtained (26.7 g) was a mixture of undecanyl acetate (21%), 10-undecenyl acetate (14%), 10,10-dimethoxydecanyl acetate (36%) and methyl 10-acetoxydecanoate (22%) by GLC.

1,10-*Decanedioic* (*sebacic*) *acid.* A soln of 25 g cyclohexene (0.30 mol) in 225 ml MeOH was ozonized as above, with cooling to −70°. The mixture was warmed to 40° for 1 hr and then added to a soln of 119 g $FeSO_4 \cdot 7H_2O$ (0.43 mol) in 750 MeOH. After stirring for 1 hr the solvent was evaporated and the residue extracted with light petroleum, followed by CH_2Cl_2. Each extract was washed with water, dried (Na_2SO_4) and evaporated. The combined residues (42.5 g) were oxidized with 95 ml H_2O_2 soln (30% soln, Perhydrol) in 170 ml formic acid for 16 hr at 20°. Water (200 ml) was added and the ppt, 8.2 g, was filtered off; GLC of the methyl esters (diazomethane) showed 96% sebacic and 2.5% adipic acid. The product was crystallized from $CHCl_3$; m.p. 127–131° (sebacic acid, lit.[14] m.p. 134.5°); yield 26.6% of theory. The first aqueous filtrate (above) was boiled for 4 hr, and evaporated to dryness. The residue (22.5 g) contained 80% adipic and 20% sebacic acid (GLC of methyl esters). Adipic acid (13.8 g, m.p. 145–149°) was obtained by crystallization from water; lit.[14] m.p. 149–150°; yield 31.0%.

1,14-*Tetradecanedioic acid.* A soln of 50 g cyclooctene (GLC 89%; 0.41 mol) in 500 ml MeOH was ozonized at −35°. The soln was added to 145 g $FeSO_4 \cdot 7H_2O$ (0.52 mol) in 2 l MeOH at 20° and stirred for 2 hr. MeOH was evaporated (35°/2.7 kPa) and the residue was acidified (4 M HCl), and extracted with ether. The extracted material was oxidized with 80 ml Perhydrol in 250 ml formic acid for 16 hr at 20° with stirring. The mixture was then boiled for 2 hr, evaporated and the residue esterified by refluxing in 750 ml MeOH containing 40 ml BF_3 etherate. The solvent was evaporated, water was added to the residue, and it was extracted with ether, dried (Na_2SO_4), evaporated and distilled, giving 31.5 g dimethyl suberate, b.p. 91–95°/13 Pa (purity 95% by GLC); yield 38.5% of theory, and 21.8 g 1,14-dimethyl tetradecanedioate, b.p. 137–155°/13 Pa, m.p. 41–42° (from MeOH) (lit.[16] m.p. 43°); yield 37.7%. IR: 1742 (CO) and 1172, 1436 and 1382 cm^{-1}. A sample was saponified to 1,14-tetradecanedioic acid, m.p. 123–125° (lit.[16] m.p. 125.8°).

Dimethyl 1,18-*octadecanedioate.* (1) A soln of 20 g methyl 10-undecenoate (0.10 mol) in 180 ml MeOH was ozonized as above, the volume was reduced *in vacuo* and the residual oil was added to 40.0 g $FeSO_4 \cdot 7H_2O$ (0.14 mol) in 800 ml MeOH at 20°. After the exothermic reaction (to 45°), crystals of the diester separated on cooling; 2.3 g, m.p. 58–59°. The methanolic soln was taken to dryness, acidified (2 M H_2SO_4) and extracted with ether, the extract washed, dried and evaporated. The residue recrystallized from MeOH gave a further 2.6 g dimethyl 1,18-octadecanedioate, m.p. 56–57° (lit.[16] m.p. 57°); total yield 28.4%. The balance, 13.2 g oil recovered from the mother liquor, was a mixture containing methyl nonanoate (53%), methyl 8-nonenoate (28%) and dimethyl sebacate (1,10-decanedioate) by GLC.

(2) Alternatively, 30 g (0.15 mol) methyl 10-undecenoate in 500 ml light petroleum was ozonized, the solvent evaporated (30°/2.7 kPa) and the residual oil (36 g) added to 51.1 g $FeSO_4 \cdot 7H_2O$ (0.18 mol) in 1 l methanol. The temp rose to 36°. After 15 min the solvent was evaporated, the residue acidified with 0.5 M H_2SO_4, extracted with ether, the extract washed, dried and evaporated giving 18.0 g crystalline material. Recrystallization from methanol gave 12.6 g pure dimethyl 1,18-octadecanedioate, m.p. 58–59°; yield 48.6%.

Dimethyl 1,16-*hexadecanedioate.* Methyl oleate (50 g, 92% by GLC, 0.15 mol) in 250 ml MeOH was treated with O_3 in O_2 until reaction was complete. The volume was reduced *in vacuo* and the residual oil was poured into a mixture of 47.3 g $FeSO_4 \cdot 7H_2O$ (0.17 mol) in 700 ml MeOH. When the mixture cooled, crystalline material separated which was filtered off, washed with MeOH and recrystallized; yield 12.1 g dimethyl 1,16-hexadecanedioate, m.p. 51–51.5° (lit.[16] m.p. 51.6°); 49.6% of theory.

Methyl 18-*hydroxyoctadecanoate.* A mixture of 20 g methyl 10-undecenoate (0.10 mol) and 17 g 10-undecenol (0.10 mol) in 500 ml MeOH was ozonized as above until reaction was complete. The volume was reduced by evaporation and the residual oil poured into a mixture of 55.6 g $FeSO_4 \cdot 7H_2O$ (0.20 mol) in 500 ml MeOH. The mixture was evaporated to dryness, acidified with 1 M H_2SO_4, extracted with ether, and the extract washed, dried and evaporated. The residue (32 g) was chromatographed on 500 g silica eluting with ether in light petroleum with stepwise increases from 5 to 25% ether (v/v). Fractions containing methyl 18-hydroxyoctadecanoate (TLC, IR) were collected, and the combined residue crystallized from MeOH; 2.6 g, m.p. 58–60° (lit.[14] m.p. 63°); yield 7.9%; identical (IR) with a product prepared from 18-hydroxyoctadecanoic acid of natural origin.

Cyclododecenyl-1-*ethyl ether.* This was prepared from cyclododecanone and triethyl orthoformate, with H_2SO_4 as catalyst.[12] EtOH was split off at 110° with *p*-toluenesulfonic acid as catalyst. Yield 58%, b.p. 80°/2.7 Pa, n^{20} 1.4833 (lit.[12] b.p. 133°/2 kPa, n^{20} 1.4851). GLC showed 86% cyclododecenyl-1-ethyl ether, and 14% cyclododecanone.

Diethyl and dimethyl 1,22-docosanedioate. (1) A soln of 30 g cyclododecyl-1-ethyl ether (86%; 0.13 mol) in 300 ml EtOH was added dropwise in 90 min to 600 ml EtOH, cooled to about 10° in ice, through which a stream of O_3 in O_2 was passing. The solvent was evaporated (35°/2 kPa), the residue was dissolved in 200 ml EtOH and added to 55.5 g $FeSO_4 \cdot 7H_2O$ (0.20 mol) in 370 ml EtOH. Part of the diethyl ester crystallized on cooling overnight; 12.3 g, after recrystallization from light petroleum 11.9 g, m.p. 61–62° (lit.[17] m.p. 59.5–61°); yield 45.5%. (Found: C, 73.4; H, 11.8; O, 14.7. $C_{26}H_{50}O_4$ requires: C, 73.23; H, 11.76; O, 15.00.) IR: 1742 (CO), 1383, 1193, 1177, 1032 and 934 cm^{-1}.

(2) A soln of 50 g cyclododecene (90%; 0.27 mol) in 500 ml MeOH was ozonized at 25°. The soln was added to 105 g $FeSO_4 \cdot 7H_2O$ (0.38 mol) in 1.5 l MeOH. Evaporation of the solvent, acidification and extraction with ether gave a residue which was oxidized with 80 ml Perhydrol in 350 ml formic acid for 16 hr at 20°. The mixture was taken to dryness *in vacuo* and the residue esterified with 500 ml MeOH containing 35 ml BF_3 etherate by refluxing for 2 hr. Distillation of the methyl esters (57 g, crude) gave 17.0 g (b.p. 63–127°/9 Pa) containing cyclododecane, methyl undecanoate and dimethyl 1,12-dodecanoate, followed by 15.5 g dimethyl 1,12-dodecanedioate, b.p. 137–150°/9 Pa; 96% pure by GLC; yield 22.2%. The pot residue (22.5 g) was crystallized twice from MeOH giving 15.8 g dimethyl 1,22-docosanedioate, m.p. 67–68°; yield 29.3%. IR: 1742 (CO), 1172, 1436 and 1382 cm^{-1} (lit.[18] m.p. 69–70°).

Methyl 8-chlorooctanoate. 50 g Methyl oleate (0.16 mol) in 500 ml light petroleum was ozonized as above. The solvent was evaporated and the residue (57 g) added to 108 g $FeCl_3 \cdot 6H_2O$ (0.40 mol) in 400 ml MeOH. The mixture was extracted with light petroleum, dried, evaporated and the product distilled, giving 8.5 g methyl 8-chlorooctanoate, b.p. 55–60°/7 Pa, n^{25} 1.4380; yield 28.4%. (Found: C, 56.2; H, 8.9; Cl, 18.4; O, 16.8. $C_9H_{17}ClO_2$ requires: C, 56.12; H, 8.85; Cl, 18.41; O, 16.62.) IR: 1740, 1435, 1247, 1197, 1170 (methyl ester) and 655 cm^{-1} (CH_2—Cl).

Methyl 9-chlorononanoate. A soln of 25.8 g (0.13 mol) methyl undecenoate in 250 ml MeOH was ozonized as above and added to a boiling soln of 113 g (0.42 mol) $FeCl_3 \cdot 6H_2O$ in 420 ml MeOH within 4 min. Boiling was continued for 15 min, the mixture was cooled, evaporated, extracted with light petroleum and the product recovered was distilled to give 13.8 g methyl 9-chlorononanoate, b.p. 77–84°/20 Pa, n^{20} 1.4458 (lit.[19] b.p. 80–84°/40 Pa, n^{18} 1.392); yield 51.3%.

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