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PREPARATION OF TERMINAL ALKENIC ESTERS BY AN OXIDATIVE RADICAL REACTION

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Abstract A general method is described for the conversion of (mono)alkenic esters with the double bond at the n^th C atom to terminal alkenic esters of (n − 1) C atoms in length, with the double bond at n − 2. Ozonolysis, either in methanol or in light petroleum, is followed by reaction with a mixture of ferrous and cupric salts. Methyl 10-undecenoate, methyl oleate (methyl (*Z*)-9-octadecenoate) and methyl erucate (methyl (*Z*)-13-docosenoate) were converted to methyl 8-nonenoate, methyl 7-octenoate and methyl 11-dodecenoate respectively. An improved preparation of 5-hexenoic acid is also described.

Alkoxy hydroperoxides derived from cycloalkenes by ozonolysis in an alcohol are converted to terminal alkene derivatives when treated with mixtures of metal salts.[1] We have now extended this scheme of reaction to the mixtures of alkoxy hydroperoxides formed when acyclic alkenes, in particular fatty acid esters of natural origin, are similarly treated. The reaction products include short length terminal alkenic esters which are useful synthetic intermediates.

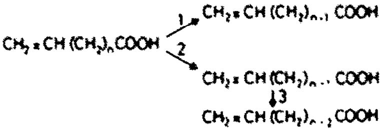
Aliphatic acids, or esters, with an alkenic bond at the end of the chain remote from the carboxyl group are important strategic compounds in the synthesis of polyunsaturated fatty acids since they can readily be converted to the corresponding alkynic compounds. These in turn lend themselves to C—C coupling reactions, with retention of the yne bond, which at a later stage can be selectively reduced to a *Z* (*cis*) or an *E* (*trans*) alkenic bond (for a review, see lit.[2]).

A number of widely different methods have been described for the preparation of terminal unsaturated carboxy acids and their esters, frequently employing eliminations (Scheme 1) from substituted aliphatic acids (esters), or chain lengthening and chain shortening (Scheme 2) of alkenic acids (esters). The following examples are illustrative. Base catalysed elimination of HCl from 7-chloroheptanoic acid in a two-stage process led to 6-heptenoic acid in 72% yield.[3] In our hands, the pyrolysis[4] of methyl 10-acetoxydecanoate, prepared from 10-hydroxy decanoic acid,[5] afforded methyl 9-decenoate in about 40% yield on a laboratory scale, but the reaction was difficult to control. Pyrolysis of macrocyclic lactones, a related method, was described for preparing 5-hexenoic acid.[6] The low conversion (5%) may not be typical, since ε-methyl-ε-caprolactone afforded 6-heptenoic acid in 96% yield. Lactones were converted to ω-alkenic esters via intermediate selenolates[7] and oxidative decarboxylation of α,ω-dicarboxylic acids led either to lactones or to terminal alkenic acids, depending on reaction conditions.[8] Elimination of water from ω-hydroxy acids by pyrolysis also required fairly extreme temperatures.[9] The latter reference gives a useful survey of methods for the synthesis of terminal alkenic acids.

$$X\text{-}CH_2CH_2(CH_2)_n COOR \xrightarrow{-HX} CH_2{=}CH(CH_2)_n COOR$$

X	n	method	lit
Cl	4	base catalysed	(3)
OAc	7	pyrolyses	(18)
HO	5	pyrolyses	(9)

Scheme 1.



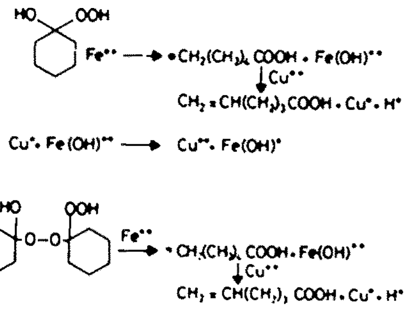
method	n	lit
1 Arndt-Eistert	2	9
2 Barbier-Wieland	8	11
3 Barbier-Wieland	7	18

Scheme 2.

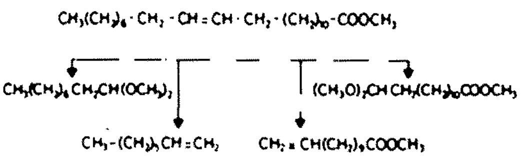
Carbon chain extensions are exemplified by the use of the Arndt–Eistert reaction (Scheme 2) to prepare 5-hexenoic acid from 4-pentenoic acid,[9] and by the malonic ester synthesis to prepare 6-heptenoic acid from 5-bromo-1-pentene.[10] The chain shortening of methyl 10-undecenoate by the Barbier–Wieland procedure afforded 9-decenoic acid in 50% yield.[11] We repeated this procedure on 9-decenoic acid and obtained 8-nonenoic acid in 32% overall yield from methyl 10-undecenoate, but this sequence is inelegant compared with our general method for the synthesis of aliphatic ω-alkenic acids. The starting materials, alkenic acids (esters), are subjected to splitting and fragmentation at the alkenic bond, followed by regeneration of a terminal alkenic bond in each of the fragments.

RESULTS AND DISCUSSION

The starting point for our synthesis was the preparation by Kochi *et al.*[12] of 5-hexenoic acid from a mixture of cyclohexanone peroxides, treated with a mixture of ferrous and cupric sulfates. The mechanism they proposed for this reaction is given in Scheme 3. The yield of 5-hexenoic acid was 57% based on reacted cyclohexanone from the first step (23% based on the starting amount). A large excess of inorganic salts was used, dissolved in acidified water, and added to the peroxides. We improved this method by starting with the better defined compound 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide.[13] The subsequent



Scheme 3.



Scheme 6.

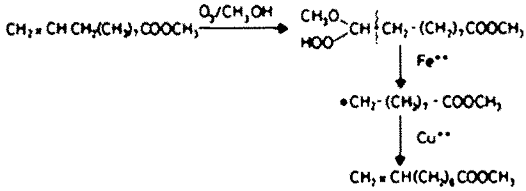
oxidative radical reaction was carried out with an empirically optimal mixture of ferrous sulfate and cupric acetate in methanol solution, to which the peroxide was then added instead of *vice versa*. Rapid dissolution in the methanol solution was followed by an exothermic reaction. Pure, distilled 5-hexenoic acid was obtained in 50% yield based on the starting cyclohexanone and on the hydrogen peroxide used in the initial step. The stoichiometry of the reaction, which is included in Scheme 3, has not been definitely established.

The same oxidative radical reaction was applied to the mixture of methoxy hydroperoxides obtained on ozonising an alkenic ester in methanol solution.[14] Methyl 10-undecenoate was smoothly converted into methyl 8-nonenoate in 35% yield of theory (Scheme 4). Competing reactions led to the formation of methyl 10,10-dimethoxy decanoate (35% of theory) and dimethyl 1,18-octadecanedioate (3%), but the mixture was easily separated by distillation. The reaction is also applicable to the ozonides, and the yield of terminal alkenic ester in that case was even somewhat better (46%).

Methyl oleate (methyl (*Z*)-9-octadecenoate) in which the alkenic bond is centrally placed in the carbon chain is the least favourable kind of reactant; because of lack of symmetry about the alkenic bond no less than four products can be formed in comparable molar and, in this case, weight percent amounts (Scheme 5). This was confirmed in practice, and methyl 7-octenoate was obtained in only 20% yield of theory (14% by weight, based on methyl oleate), after a tedious isolation procedure which included saponification and re-esterification.

In the case of methyl erucate (methyl (*Z*)-13-docosenoate) we limited our study to GLC analysis of the reaction products and the isolation of methyl-11-dodecenoate. This had the added advantage that aldehydic reaction products could then be reduced to primary alcohols with sodium borohydride, and this greatly facilitated the isolation of methyl 11-dodecenoate (Scheme 6).

Our approach provides a short, convenient route to 5-hexenoic acid from cyclohexanone and to 8-nonenoic acid from 10-undecenoic acid, even though the yields are modest. The generalised method is optimal for a particular product either whenever the substrate is completely symmetrical about the reacting centre, or just the opposite as in methyl 10-undecenoate. If the alkoxy hydroperoxides or ozonides are prepared by ozonolysis of an alkene with a centrally placed double bond, but which is not symmetrical about this bond, as in methyl oleate and methyl erucate for example, then the useful yields of any one product are predictably low. But the advantages of directness and convenience remain.



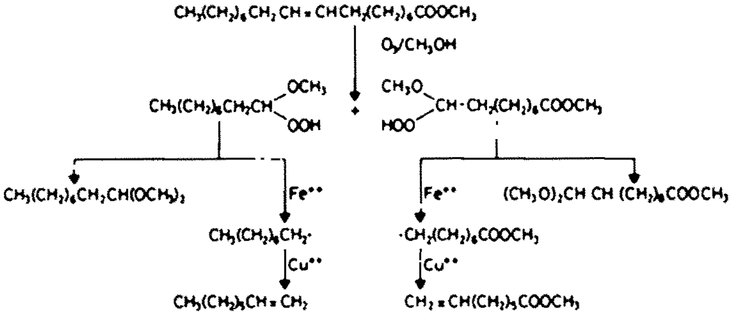
Scheme 4.

EXPERIMENTAL

Materials. Ferrous sulfate heptahydrate, cupric acetate monohydrate, and hydrogen peroxide (30%) were commercial products, and the fatty acids likewise. The latter were esterified with methanol, using BF_3 as catalyst.

Ozone in a stream of O_2 was generated using a Stage K.G. ozoniser producing about 0.1 mol O_3 in O_2/hr.

GLC analysis. GLC was carried out on a silicone elastomer SE 30 or on PEGA 5% (support Diatoport S 80-100). Results were compared with those of authentic samples.



Scheme 5.

NMR, IR and mass spectroscopy. The proton magnetic-resonance spectra were run in CCl_4 solns at 30° on a Varian HA-100 spectrometer or in $CDCl_3$ at 20° on a Brucker AM360 operating at 360 MHz. δ-Values are quoted in ppm downfield from internal TMS and are accurate to within ±0.01 ppm. The coupling constants are accurate to within ±0.2 Hz. IR spectra were recorded with an Infrascan and an Infracord spectrophotometer.

1 - *Hydroxy - 1′ - hydroperoxydicyclohexyl peroxide.*[13] CAUTION! 113.3 ml H_2O_2 (30%; Merck) was added to a mixture of 98.0 g cyclohexanone (1 mol) and 10 ml 2 M HCl in a 500 ml 3-necked flask fitted with stirrer, thermometer and dropping funnel. The mixture became homogeneous and its temp rose to 35°. After 45 min white, solid lumps separated. After another 15 min 100 ml cold water was added, the pieces were broken up with a glass rod, filtered onto a sintered glass filter and washed with 3 × 100 ml cold water. The moist product was used for the following step. It should not be allowed to dry out ON ANY ACCOUNT because of the danger of it exploding.

5-Hexenoic acid (*cf lit.*[12]). In a 4 l 3-necked flask fitted with stirrer, ice bath, and a wide funnel for solids, 139 g $FeSO_4\cdot 7H_2O$ (0.5 mol; analytical grade; Merck) were dissolved in 2 l methanol. To this solution (colour: green brown) was added 175 g copper acetate monohydrate (0.88 mol; analytical grade; Noury Baker). When the resultant suspension became a brown colour, the moist peroxide (above) was added quickly in about 1 min. The soln became hot and was cooled externally with ice. After 1 hr the colour had turned dark green and the reaction was complete. The MeOH was distilled off on a Rotavap (40°) to about one quarter the original volume, and the residue was acidified with 250 ml 2 M H_2SO_4. The precipitated inorganic salts were filtered off, washed with 500 ml light petroleum and this was then used to extract the aqueous MeOH phase. Two more extractions (500 ml light petroleum each) and one with ether (500 ml) gave on drying and evaporation 85.3 g reaction product. On distillation, the first fractions contained some AcOH and cyclohexanone, followed by 5-hexenoic acid, b.p. 92–96°/1.2 kPa, n_D^{20} 1.4339; GLC 99%. Yield 57.7 g (51% of theory based on cyclohexanone). Lit.[15] b.p. 95–96°/0.9 kPa; n_D^{20} 1.4338.

Methyl 8-nonenoate from methyl 10-undecenoate. Methyl 10-undecenoate (200 g, 1.01 mol, b.p. 78–80°/8 Pa, n_D^{25} 1.4362) was dissolved in 2 l MeOH and a stream of O_3 in O_2 was passed in until reaction was complete. The internal temp of the mixture was about 29°. MeOH was removed on a rotary evaporator under vacuum (1.3 kPa), water bath temp 40°, until about 0.5 l of mixture remained in the flask. This was poured out into a freshly prepared mixture of 200 g $FeSO_4\cdot 7H_2O$ (0.72 mol) and 300 g copper acetate monohydrate (1.5 mol) in 3 l MeOH contained in a 5 l Erlenmeyer flask. The mixture, which became warm, was shaken and swirled by hand for a few min, and allowed to stand overnight. The mixture was evaporated (as above) to a volume of about 1 l, diluted with H_2O, acidified with 4 M HCl, and extracted with light petroleum. The extracts were dried (Na_2SO_4) and evaporated. The residue (190 g) was fractionally distilled to give methyl 8-nonenoate, b.p. 48°/13 Pa, n_D^{25} 1.4311, yield 58.8 g (35% of theory), and methyl 10,10-dimethoxy decanoate, b.p. 93–95°/6.7 Pa, n_D^{25} 1.4360 [lit.[16] b.p. 137–138°/33 Pa], yield 87.0 g (35% of theory). NMR δ 2.30 (tr, J = 7.5, 2H, $-CH_2CO-$); 3.31 (s, 6H, CH_3-O-C); 3.66 (s, 3H, ester $-OCH_3$); 4.36 (tr, J = 6.0, 1H, $-CH(O-)_2$). The solid residue in the distillation flask was crystallised from MeOH, giving dimethyl 1,18-octadecanedioate, m.p. 58–59° (lit.[17] m.p. 57°), yield 8.9 g (3% of theory). Methyl 8-nonenoate; IR (film): 1740 cm^{-1} (C=O), 3071 cm^{-1} (vinyl C—H), 1637 cm^{-1} (C=C), 996 and 909 cm^{-1}. NMR: δ 1.36 (complex, 8H, $-(CH_2)_4-$); 2.11 (complex, 4H, $-CO\cdot CH_2-$ and $-CH_2-C{=}C$); 3.60 (s, 3H, CH_3-O); 4.81 (complex, 2H, $=CH_2$); 5.78 (complex, 1H, $-CH{=}C-$). The complexes at δ 5.78 and 4.81 had the typical $-CH_2-CH{=}CH_2$ pattern.

Alternatively, methyl 10-undecenoate (270 g, 1.36 mol) in 2.7 l optical grade light petroleum was treated with a stream of O_3 in O_2 until reaction was complete (external cooling with an ice bath). The solvent was evaporated (2 kPa, 30°) on a rotary evaporator, and the ozonides dissolved in 200 ml MeOH. This soln was poured with stirring into a freshly prepared soln of 270 g $FeSO_4\cdot 7H_2O$ (0.97 mol) in 4 l MeOH to which 405 g cupric acetate (2.03 mol) had been added. The mixture came gradually to reflux temp, and after 30 min reaction was complete. MeOH was evaporated off, and some water and 6 M HCl added. The mixture was extracted with light petroleum, and the extract washed, dried and evaporated. The residue (260 g) was fractionally distilled, giving methyl 8-nonenoate, b.p. 51°/8.0 Pa, n_D^{20} 1.4336, yield 106.5 g (46% of theory) and methyl 10,10-dimethoxy decanoate, b.p. 107°/53 Pa, n_D^{25} 1.4388, yield 73.8 g (22% of theory). The distillation residue was 32 g.

Methyl 7-octenoate (from methyl oleate). Methyl oleate (92% by GLC, 162 g corresponding to 0.5 mol) in 1.6 l MeOH was treated with O_3 in O_2 as above until reaction was complete. MeOH was then removed under reduced pressure till the final volume was about 0.5 l. The residual oil was poured into a freshly prepared mixture of 105 g $FeSO_4\cdot 7H_2O$ (0.38 mol) and 150 g cupric acetate hydrate (0.75 mol) in 1.5 l MeOH in a 5 l Erlenmeyer flask and swirled till homogeneous. The product was worked up as above by concentrating the MeOH soln, adding water and 6 M HCl, and extracting with light petroleum. The extract was washed, dried and evaporated, leaving 138 g product as an oil. A part of this oil (120 g) in 100 ml EtOH was saponified with 40 g NaOH dissolved in 200 ml aqueous EtOH (50%) by warming on a steam bath for 2 hr. The mixture was cooled and extracted with 4 × 100 ml ether to remove neutral material, of which 63 g were recovered on washing, drying and evaporating the ether extract. This product contained nonanal. The aqueous layer was made slightly acid by adding 6 M HCl, and extracted with 4 × 100 ml ether. The combined extracts were washed, dried and evaporated, leaving 37.5 g of an oil. This was re-esterified with ethereal diazomethane and the product fractionally distilled to give methyl 7-octenoate, b.p. 80–82°/2 kPa; GLC 95%. Yield 18.5 g (22% of theory). IR: 1740, 1435, 1250, 1200, 1170, 1115 cm^{-1} (methyl ester); 3075, 1640, 1418, 995 and 912 cm^{-1} (vinyl).

NMR: δ 1.2–1.5 (complex, 4H, $-(CH_2)_2-$); 1.64 (quintet, J = 7.5, 2H, $-CH_2-$); 2.05 (quartet, J = 6.7, 2H, $C{=}C-CH_2-$); 2.31 (tr, J = 7.5, 2H, $-CH_2-CO$); 3.67 (s, 3H, OCH_3); 4.94 (br d, J = 10.3, 1H, $HC{=}C$); 4.99 (br d, J = 16.8, 1H, $HC{=}C$); 5.80 (d of d of tr, J = 16.8, 10.3, 6.6, 1H, $C{=}CH-C$).

Methyl 11-dodecenoate (from methyl erucate). 35.2 g (0.1 mol) Methyl erucate (methyl (*Z*)-13-docosenoate) was suspended in 250 ml MeOH and ozone was passed in, as above. During the ozonolysis the mixture became homogeneous. The soln was partly evaporated, and the residue slowly added to a soln of 28 g $FeSO_4\cdot 7H_2O$ (0.1 mol) and 40 g (0.2 mol) $Cu(OAc)_2\cdot H_2O$ in 400 ml MeOH. GLC of the end-products versus standards showed the presence of 1-octene, nonanal, nonanal dimethyl acetal, methyl 11-dodecenoate, C_{13} aldoester and its dimethyl acetal. The mixture was separated partially by column chromatography on silicagel, and the apolar eluates were fractionally distilled, giving 5.0 g methyl 11-dodecenoate, b.p. 106–108°/133 Pa, n_D^{25} 1.4410. Yield 24% of theory based on methyl erucate.

When the ozonolysis was carried out in light petroleum and the ozonides reacted as above, the final mixture contained only 1-octene, nonanal, methyl 11-dodecenoate and the C_{13} aldoester (GLC). The aldehyde groups were reduced with excess $NaBH_4$ in methanol and the mixture of products was readily separated by column chromatography on silicagel as above. The apolar fraction was distilled to give pure methyl 11-dodecenoate. IR: 1740, 1435, 1250, 1200, 1170, 1115 cm^{-1} (methyl ester); 3075, 1640, 1418, 995 and 912 cm^{-1} (the vinyl intensities were different from those of methyl 7-octenoate).

NMR: δ 1.2–1.5 (complex, 12H, $-(CH_2)_6-$); 1.62 (br quintet, J = 7.0, 2H, $-CH_2-$); 2.04 (quartet, J = 6.6, 2H, $C{=}C-CH_2$); 2.30 (tr, J = 7.5, 2H, $-CH_2-CO$); 3.66 (s, 3H, OCH_3); 4.93 (br d, J = 10.3, 1H, $HC{=}C$); 4.99 (br d, J = 17.0, 1H, HC=C); 5.81 (d of d of tr, $J = 16.8, 10.3, 6.6$, 1H, C=CH—C).

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