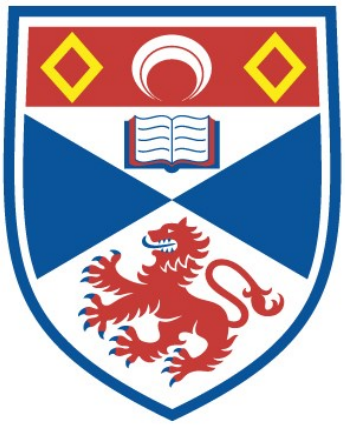
SYNTHESIS OF LONG-CHAIN FATTY ACIDS AND SOME DERIVATIVES

Hannah Sumathi Vedanayagam

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1975

In deep gratitude

to

my husband B. J. Vedanayagam

my daughters Nandu & Chitra

my sisters Dr. E. S. Ebenezer & Dr. L. N. Ebenezer

and my brother Sam Ebenezer

SYNTHESIS OF LONG-CHAIN FATTY ACIDS AND SOME DERIVATIVES

being a thesis

presented by

(Mrs.) Hannah Sumathi Vedanayagam

to the

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SUMMARY

An attempt has been made to compare anodic synthesis, malonation, and chain-extension with enamines as procedures for converting readily-available acids to higher homologues.

Anodic synthesis was successfully employed to prepare esters of several olefinic acids (20:1 11c, 22:1 13c, 20:2 11c 14c, 22:2 13c 16c, 20:3 8c 11c 14c), acetylenic acids (18:1 16a, 18:1 17a), and saturated acids of 'odd' chain length (13:0, 15:0, 17:0, 19:0, 21:0). The desired esters were recovered from the reaction products by column chromatography and further purified when necessary by crystallisation. Yields were usually in the range 40-50%.

Some difficulty was encountered with acids having $\Delta 5$ and $\Delta 6$ unsaturation and this made the chain-extension of γ -linolenic acid by this procedure unsatisfactory. A possible reason for this is descussed.

An electrolytic procedure for converting long-chain acids (RCO_2H) to their nor-alcohols (ROH) has been examined : oleic, linoleic, and ricinoleic acid were converted to the corresponding C_{17} alcohols.

Oleic, linoleic, α -linolenic and γ -linolenic acids were successfully converted to their C_{20} homologues in 70-80% yield by an improved malonation procedure which was recently described. In one case the malonation was repeated to give a C_{22} acid.

The enamine chain-extension procedure was briefly examined using cyclopentanone and cyclohexanone to furnish heneicosanoic and eicosanoic acids respectively.

The ^{13}C NMR spectra of the starting materials and products have been recorded. It has proved possible to allocate the observed resonances (with greater or lesser certainty) to all the constituent carbon atoms and some interesting generalisations are presented.

* * * *

A minor study was concerned with the preparation of long-chain hydroperoxides and peroxides by reaction of the mesylates of some primary alcohols (stearyl, oleyl, linoleyl) with hydrogen peroxide and t-butyl peroxides. Some secondary peroxides were formed by a similar reaction with allylic bromides.

Declaration

I hereby declare that this thesis is a record of the results of my own experiments, that it is my own composition, and that it has not previously been presented in application for a higher degree.

The research was carried out in the Department of Chemistry, United College of St. Salvator and St. Leonard, University of St. Andrews, under the supervision of Professor F. D. Gunstone, D. Sc., F. R. I. C.

Certificate

I hereby certify that Hannah Sumathi Vedanayagam has completed twelve terms of research work under my supervision, has fulfilled the conditions of the Resolution of the University Court 1967, No. 1 (St. Andrews) and that she is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Research Supervisor.

University Career

After obtaining the Senior Cambridge Certificate in Hyderabad, I graduated in 1959 from Osmania University, Hyderabad with the degree of Bachelor of Science. In 1967 I obtained the Associateship to the Institute of Chemists' (India) from the Calcutta University.

I was admitted as a research student in the United College, University of St. Andrews in October 1972, with a grant provided by the Department of Chemistry and The British Council.

Acknowledgements

I thank Professor F.D. Gunstone for accepting me as a research student. I am deeply indebted to him for his sincerity and kindness in helping and guiding me through the entire period of this research work. He is an excellent supervisor. Inspite of his busy schedule he has devoted many an hour to discussing the progress of my work. I have thoroughly enjoyed working with him.

I take this opportunity to thank the members of my family who have played a vital role in the fulfilment of this work. I thank my husband, B. J. Vedanayagam and our two small daughters Rachel Nandita and Ruth Suchitra for their patience and endurance in all that my absence from home has involved. To my sisters Dr. Sarojini Ebenezer and Dr. Lily Ebenezer and brother Sam Ebenezer I owe a large debt of gratitude since I could not possibly have ventured to come to St. Andrews without their caring for my children.

I wish to thank Dr. C. M. Scrimgeour for his advice and help on several occasions. I thank all the other research workers in the 'Lipid group' who have been of great help to me. I have enjoyed their company very much. I thank Mike Pollard for 'enduring' my company at the work bench!

I thank Mrs. M. Smith and Mr. C. Millar, for running the NMR and mass spectra. I wish to thank all my other friends in the Chemistry department who have on several occasions gone out of their way to help me especially Mr. Andrew Watson, Mr. N.G. West, Mr. Jim Rennie, Mr. J. Ward and Mrs. Sheila Johnson.

I thank Professors Lord Tedder and P. A. H. Wyatt for making available the grant from the Chemistry Department, for my stay in St. Andrews. I also thank the British Council for undertaking the payment of fees for this degree and Dr. G. S. Sidhu, the Director of Regional Research Laboratory, Hyderabad for the sanction of study leave.

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CONTENTS

EXPERIMENTAL

THE PREPARATION OF SOME LONG CHAIN HYDROPEROXIDES AND t - BUTYL PEROXIDES

PART II

Abbreviations

DEGS	diethylene glycol succinate
DMF	dimethylformamide
DMSO	dimethylsulphoxide
E	ether
ECL	equivalent chain length
GLC	gas-liquid chromatography
IR	infrared
Me	methyl
NMR	nuclear magnetic resonance
CMR	^{13}C magnetic resonance
P	petroleum ether
TLC	thin layer chromatography
TMS	trimethylsilyl/tetra methylsilane in nuclear magnetic resonance
UV	ultraviolet
W	omega

An abbreivated form for systematic names of fatty acids and their methyl esters is frequently used. For example, octadec-cis-9-enoic acid, ie. oleic acid is abbreviated as 18:1 (9c). The numbers 18 and 1 give the number of carbon atoms and the number of unsaturated centres, respectively. The expression in parenthesis (9c) indicates that the unsaturated centre is located between C(9) and C(10) and is a cis double bond; "t" denotes a trans double bond and "a" stands for an acetylenic bond.

SUMMARY

An attempt has been made to compare anodic synthesis, malonation, and chain-extension with enamines as procedures for converting readily-available acids to higher homologues.

Anodic synthesis was successfully employed to prepare esters of several olefinic acids (20:1 11c, 22:1 13c, 20:2 11c 14c, 22:2 13c 16c, 20:3 8c 11c 14c), acetylenic acids (18:1 16a, 18:1 17a), and saturated acids of 'odd' chain length (13:0, 15:0, 17:0, 19:0, 21:0). The desired esters were recovered from the reaction products by column chromatography and further purified when necessary by crystallisation. Yields were usually in the range 40-50%.

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PART I

SYNTHESIS OF LONG-CHAIN FATTY ACIDS AND SOME DERIVATIVES

INTRODUCTION

INTRODUCTION

NATURAL ACIDS

Although a wide variety of fatty acids occur naturally, particularly in the vegetable kingdom, the greater part of the total fatty acids in nature is accounted for by a small number of acids, such as oleic, linoleic, palmitoleic, palmitic and a few others[1]. These are all straight-chain saturated or unsaturated (olefinic) acids. Three types of long-chain acids may be distinguished according to their structure and the extent to which they occur : those which are widespread and are major constituents of natural lipids, those of similar structure which are generally minor constituents, and those of unusual structure whose occurrence is limited to a few sources, where however they may account for a large proportion of the fatty acids present. These acids, whether "major", "minor" or "rare" accumulate as end-products of metabolic processes, and may be extracted, investigated and utilized by man.

MAJOR FATTY ACIDS

The major fatty acids are all saturated or unsaturated monocarboxylic acids with a straight, even-numbered carbon chain; the reason for this structure rests on their biosynthesis. The saturated homologues, lauric (dodecanoic), myristic (tetradecanoic), palmitic (hexadecanoic) and stearic (octadecanoic) acids are present in most vegetable fats but even more abundant are the unsaturated analogues oleic (octadec-cis-9-enoic), linoleic (octadeca-cis-9, cis-12-dienoic) and α-linolenic (octadeca-cis-9, cis-12, cis-15-trienoic) acids. These seven acids were said to account for 94% of

all those in the world's commercial vegetable fats in 1969[2]. In general they are widely distributed throughout plant lipids often with palmitate, oleate and linoleate predominating. These unsaturated fatty acids illustrate the general ubiquity of the cis double bond in the 9- position and of the 1,4-diene or "methylene interrupted" structure (·CH : CH·CH_2·CH : CH·) in the polyenoic acids.

MINOR SATURATED ACIDS

The lower fatty acids (C_4-C_{10}) occur mainly in milk fats and a few seed fats. Cow milk fat contains butanoic acid (10%) with smaller amounts of the C_6, C_8, C_{10} and C_{12} acids ; sheep and goat milk fats contain these same acids with decanoic in greatest amount (up to 10%). The C_{10} acid is a major component (60%) in the seed fat of the elm, and the C_8 and C_{10} acids (each 5-10%) accompany the higher proportion of lauric acid in coconut oil and to a lesser extent, in palm kernel oil both of which are readily available. Long-chain acids (up to C_{38}) are present in waxes as esters of long-chain alcohols, but they are most conveniently obtained by synthetic procedures[1].

The higher fatty acids (C_{20}-C_{24}) are major components in only a few uncommon seed fats.

Fatty acids of odd carbon atoms are minor components. Early reports of natural odd acids were generally invalidated by subsequent investigation. The C_{17} acid, for example, was generally a mixture of C_{16} and C_{18} acids. More recently, however, there has been incontravertible evidence of odd acids as trace or minor components. Traces of pentadecanoic and heptadecanoic acids are present in leaves (Stumpf and

James 1963)[3]. Saturated odd acids have been identified in animal fats (C_1-C_{23}), wool wax and sebum lipids (C_7-C_{21}), fish oils (C_{13}-C_{19}), some vegetable fats (C_9-C_{23}), and some micro-organism lipids (C_9-C_{19})[1]. In only a few cases do the odd acids exceed 1-2% of the total and generally they are much less than this.

MINOR UNSATURATED ACIDS

Hexadec-cis-9-enoic acid is a constituent of nearly all fats but a major component only in fish oils and a few seed oils. The 3t isomer has been discovered in a number of sources and the 11c acid is a major component of one seed oil (Doxantha unguis-cati)[2].

Among C_{20} and C_{22} acids, erucic (22:1;13c) is best known as the chief acid in many seed oils of the Cruciferae and Tropaeolaceae (e.g. mustard 30% , rape 40%) where it is usually accompanied by smaller proportions of a C_{20} acid (20:1;11c). Isomers of these two acids (20:1;9c and 22:1;11c) are important constituents of many marine oils and the two 5c isomers (C_{20} and C_{22}) are present in a seed oil (Limnanthes douglasii)[2].

Arachidonic acid (20:4 5c8c11c14c) is the best known of the higher, polyunsaturated fatty acids because of its widespread occurrence in animal lipids, as a trace component in some glycerides and a minor or major component in phosphoglycerides. It is frequently accompanied by 20:5, 22:5 and 22:6 acids.

RARE ACIDS

The unusual structural feature of rare acids is generally a

substituent/or an unsaturated bond in an abnormal position. These acids may be conveniently divided into six groups :

i) Non-conjugated polyene acids: Non-conjugated polyethenoid acids of which many are known to occur in animals, plants and micro-organisms. The majority of these acids belong to the C_{16}, C_{18}, C_{20} and C_{22} series though they contain mainly 2-4 double bonds penta- and hexa-enoic acids are known. These are commonly found in fish oils and in animal phospholipids.

ii) Conjugated polyene acids : Practically all are C_{18} compounds and almost one-half of them contain an additional oxygenated function which is often attached to a carbon atom adjacent to the unsaturated system. Many of the acids contain an additional isolated double bond in the terminal position. The conjugated systems usually contain two or three unsaturated centres and start at C(2), C(8), C(9) or C(10).

iii) Acetylenic acids : such as tariric (18:1 6a) and stearolic (18:1 9a) are known. Poly-ynoic acids are mainly conjugated acids, occur most commonly in seed oils from two families Olacaceae and Santalaceae[1].

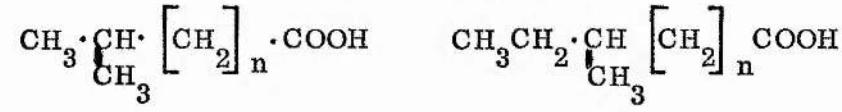
iv) Substituted acids : Ricinoleic acid [D-(+)-12-hydroxyoctadec-cis-9-enoic acid] is the major acid in castor oil. Related acids include (1) 17-hydroxyoleic acid which accompanies 17-hydroxystearic acid in an extracellular oil formed during fermentation of a strain of Torulopsis magnoliae 11) 9-hydroxy-octadec-12-enoic acid present in Strophanthus seed oils 111) Lesquerolic acid [D-(+)-14-hydroxyeicos-cis-11-enoic] which is the C_{20} homologue of ricinoleic acid present in most Lesquerella

seed oils[1]. Lower homologues of ricinoleic acid (unsaturated C_{16}, C_{14} and C_{12} and saturated C_{10} and C_8 hydroxy acids) are present in the fat of rats fed on castor oil. 18-Fluoro-oleic acid is the poisonous principle of some unusual seeds. There exists also an interesting series of C_{18} epoxy acids which may be derived from oleic, linoleic and linolenic acids[1].

These hydroxy and epoxy acids are present in glycerides of certain fungi and some seed oils and include 9, 10-epoxy stearic, 9, 10-epoxyoctadec-12-enoic (coronaric), 12, 13-epoxyoleic (vernolic) and 15, 16-epoxylinolenic acids.

v) Branched-chain acids : Though a great majority of fatty acids are straight-chain compounds, others have a branched-chain or contain a cyclic group. The most widely distributed branched-chain acids have a single methyl substituent attached to the penultimate (iso) or antepenultimate (anteiso) carbon atom[1].

The latter are generally dextrorotatory and belong to the L-series.



iso-acids (mainly even) anteiso-acids (mainly odd)

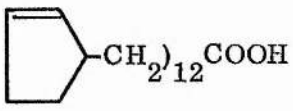
Acids of these two series accompany n-acids in most waxes. Sometimes the α-hydroxy (D-series) and w-hydroxy acids of all three series are also present.

A group of New Zealand workers, led by Hansen and Shorland, found a more limited range of odd acids (C_{13}-C_{17}) as trace constituents of many animal fats[1].

In addition to the iso- and anteiso-acids other branched-chain acids are known in which the methyl group occupies a more central position [such as D-(-)-10-methylstearic acid (tuberculostearic)] or in which there are several methyl groups on alternate carbon atoms usually close to the CO_2H group (eg. C_{24}-mycosanoic acid $CH_3[CH_2]_{17}\cdot CHMe\cdot CH_2\cdot CHMe\cdot CO_2H$, C_{27}-phthienoic acid $CH_3\cdot[CH_2]_{17}\cdot CHMe\cdot CH_2\cdot CHMe\cdot CH{=}CMe\cdot CO_2H$) 3,7,11,15-tetramethylhexadecanoic acid and 2,6,10,14-tetramethylpentadecanoic acid, are thought to be derived from the diterpene phytol by partial oxidation[1].

vi) Acids containing cyclic systems : Hofmann and Lucas (1950)[4] isolated from the lipids of Lactobacillus ararbinosus an unusual fatty acid which they later found to be 10-(2-hexylcyclopropyl)-decanoic acid, $CH_3(CH_2)_5\text{-}CH\text{-}CH\text{-}(CH_2)_9CO_2H$ (with CH_2 bridging the two CH). Nunn[4] obtained a more unusual fatty acid, 'Sterculic acid' $CH_3(CH_2)_7\text{-}C{=}C\text{-}(CH_2)_7CO_2H$ (with CH_2 bridging the two C) from the seed oil of Sterculia foetida. Christie[4] has reviewed the occurrence, structure and biogenesis of the cyclopropane and cyclopropene acids.

Cyclopent-2-ene acids : chaulmoogra and related seed oils of the family Flacourtiaceae contain acids having a cyclopent-2-ene group such as



11-Cyclohexylundecanoic acid is a trace component (0.01%) of butter fat and is suggested to occur in the bovine rumen bacteria[4].

Availability of pure fatty acids

When a fatty acid is required for study attention has to be given to three possible sources. Some acids, such as oleic and linoleic, occur in such large amounts in readily available sources, that they can be isolated from these in a pure state (>99%). Other acids, which do not occur in nature or are extremely rare, can only be conveniently obtained by complete synthesis. Yet a third group are most easily obtained by modification of the readily available acids.

There follows a review of the major chain-extension procedures by which readily - available fatty acids may be converted to their higher homologues.

Preparation of saturated and unsaturated fatty acids by chain-extension

1. Addition of one carbon atom

The conversion of an acid to its homologue with one additional carbon atom has been classically effected by a series of steps in which the important one is the conversion of an alkyl halide to a cyanide. The complete sequence is :

$$RCO_2Me \longrightarrow RCH_2OH \longrightarrow RCH_2Cl \longrightarrow RCH_2CN \longrightarrow RCH_2CO_2Me$$

In a recent modification of this Baumann and Mangold[5] treated an alkyl methanesulphonate (obtained from the alcohol) with potassium cyanide to give a nitrile.

None of the reactions affect olefinic groups so that this reaction sequence may be safely applied to saturated and unsaturated acids. It is

very commonly used to produce isotopically labelled acids with the assistance of labelled cyanide.

2. Addition to two carbon atoms by Malonation

The malonic ester synthesis constitutes another classical method for increasing the chain-length of aliphatic compounds. This has been applied to the synthesis of a variety of long-chain acids. The reaction involves the following steps :

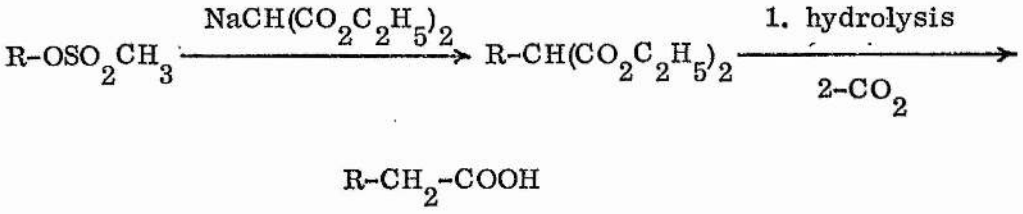
$$CH_2(CO_2Et)_2 \xrightarrow{NaOEt} \bar{C}H(CO_2Et)_2 \xrightarrow{RX} RCH(CO_2Et)_2$$

$$\longrightarrow RCH(CO_2H)_2 \longrightarrow RCH_2CO_2H$$

Bleyberg and Ulrich[6] applied the malonic ester synthesis to the preparation of the C_{20}, C_{22}, C_{24}, C_{26} and C_{30} alkanoic acids. Longer acids up to C_{38} were prepared by Francis et al[7].

Branched-chain acids can also be obtained by chain-extension of secondary alkyl bromides.

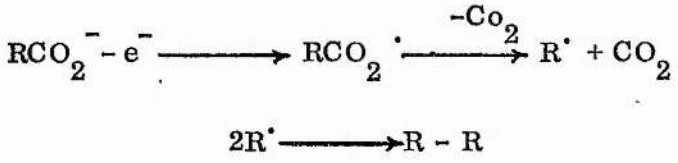
A recently described improvement of the method involves the use of a mesylate rather than a bromide as alkylating agent (in many cases both would be obtained from the corresponding alcohol). In ethanol saturated ethyl ethers are formed as by products so Marcel and Holman[8] substituted benzene for ethanol and carried out the reaction in a sealed ampoule at 100° for 5hr with yields around 50% . Spener and Mangold[9] have further improved the reaction. A mesylate is used to alkylate the diethyl malonate carbanion in xylene; saponification of the diethyl alkylmalonate and decarboxylation of the corresponding acid are carried out following established procedures.



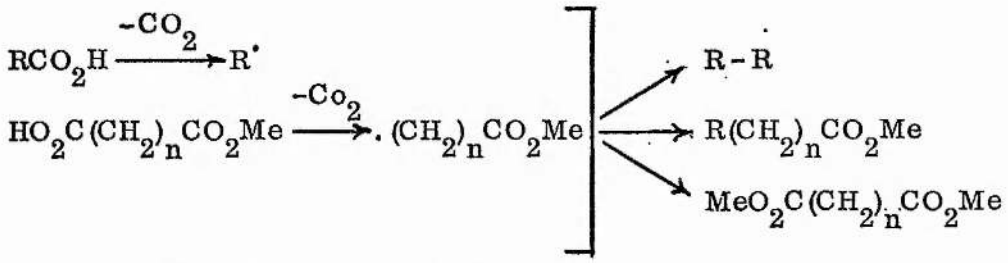
Using this improved synthetic procedure Spener and Mangold prepared eicosenoic acid (20:1, 11c) from octadec-cis-9 enoic acid in 85 - 95% yield.

3. Addition of two or more carbon atoms by Anodic Synthesis

Kolbe electrolysis is one of the earliest reactions applied in organic synthesis for the formation of dimeric products from the oxidation of carboxylic acid salts.



In 1895 von Miller and Hofer[10] introduced a method for the synthesis of fatty acids consisting of electrolysing a mixture of a monocarboxylic acid and a half-ester (crossed coupling).



The use of anodic synthesis for the preparation of long-chain acids was improved and exploited by Linstead and Weedon who, with their colleagues, published from 1950 onwards a series of papers on the subject[11]. Reaction with the half-ester of succinic acid (C_4) results in the addition of

two carbon atoms and the easily available C_5, C_6, C_8, C_9 and C_{10} dibasic acid derivatives lead to chain extension by 3, 4, 6, 7 and 8 carbon atoms respectively.

This procedure has been applied to saturated acids and, more usefully, to a limited range of unsaturated acids or to suitable precursors. By crossed coupling with an appropriate half-ester, oleic acid, for example, has been converted into three comparatively rare acids viz, eicos-cis-11, enoic acid (1, n=2), a constituent of the unique liquid seed wax jojoba oil,

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH + HOOC(CH_2)_nCO_2Me \xrightarrow[(2)\ \text{hydrolysis}]{(1)\ \text{electrolysis}}$$

$$CH_3(CH_2)_7CH{=}CH(CH_2)_{7+n}COOH$$
(I)

erucic acid (22:1,13c) (1, n=4), a characteristic constituent of Cruciferae fats, and nervonic acid (24:1,15c) (1, n=6), the principal unsaturated acid of the cerebrosides and a constituent of shark and ray liver oils. No stereomutation of the double bonds was observed in any of these syntheses[12].

Another route to unsaturated acids is provided by the anodic chain extension of acetylenic acids and half-esters. Coupling of stearolic acid with adipic half-ester yielded behenolic acid which could then be reduced to erucic acid[12].

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH + HOOC(CH_2)_4COOCH_3 \xrightarrow[(2)\ \text{hydrolysis}]{(1)\ \text{electrolysis}}$$

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_{11}COOH \xrightarrow{H_2/Pd\text{-}Pb} CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOH$$

The following synthesis of oleic acid illustrates how flexible is this route to unsaturated fatty acids. By coupling the acetylenic half-ester (2, n=4) or its lower homologue (2, n=3) with a monobasic acid, and then coupling the resulting acetylenic acid with a suitable half-ester (3), stearolic acid was obtained. This on partial reduction over the Lindlar catalyst gave oleic acid[12].

$$CH_3(CH_2)_{7-n}COOH \xrightarrow{\text{(i)}} CH_3(CH_2)_7C{\equiv}C(CH_2)_nCOOH$$

(ii) (iii)

$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH$

stearolic acid

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$

Oleic acid

(i) electrolysis with $HO_2C(CH_2)_nC{\equiv}C(CH_2)_nCO_2Me$(2) followed by hydrolysis.

(ii) electrolysis with the half-ester $HO_2C(CH_2)_{7-n}CO_2Me$ (3, n=3 or 4) followed by hydrolysis.

(iii) Reduction with H_2/Pd-Pb (Lindlar catalyst).

Another example of successful anodic syntheses affords (+)- and (-) - tuberculo stearic acids. Electrolysis of mixtures of (+) - and (-) - methyl hydrogen β -methylglutarate (4) with octanoic acid led to (+) - and (-) - 3 - methylundecanoic acids (5). (+) - and (-) - Tuberculostearic acids (6) were then obtained by further reaction with methyl hydrogen azelate[12].

$$HO_2CCH_2CHMeCH_2CO_2Me \xrightarrow{\text{(i)}} Me(CH_2)_7CHMeCH_2CO_2H$$

(4) (5)

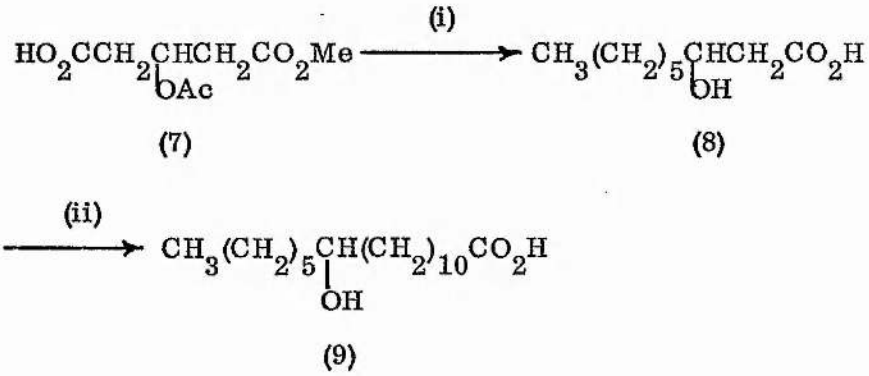
$$\xrightarrow{\text{(ii)}} Me(CH_2)_7CHMe(CH_2)_8CO_2H$$

(6)

(i) electrolysis with octanoic acid followed by hydrolysis.

(ii) electrolysis with methyl hydrogen azelate followed by hydrolysis.

The preparation of D-(+)-12-hydroxystearic acid with known absolute configuration illustrates the use of the anodic synthesis method to establish stereochemical relationships. This was achieved by coupling of hexanoic acid with (-) - methyl hydrogen β -acetoxyglutarate (7) followed by a second anodic synthesis with methyl hydrogen undecanedioate. The product was of opposite configuration from ricinoleic acid.



(7) (8)

(9)

(i) Electrolysis with hexanoic acid followed by hydrolysis.

(ii) Acetylation followed by a second anodic synthesis with methyl hydrogen undecanedioate. As the configuration of the starting material is known, that of ricinoleic acid is now established[12].

Some disadvantages in the use of the anodic synthesis method will be reported in the Discussion of our results.

Addition of five or six carbon atoms using cyclic compounds

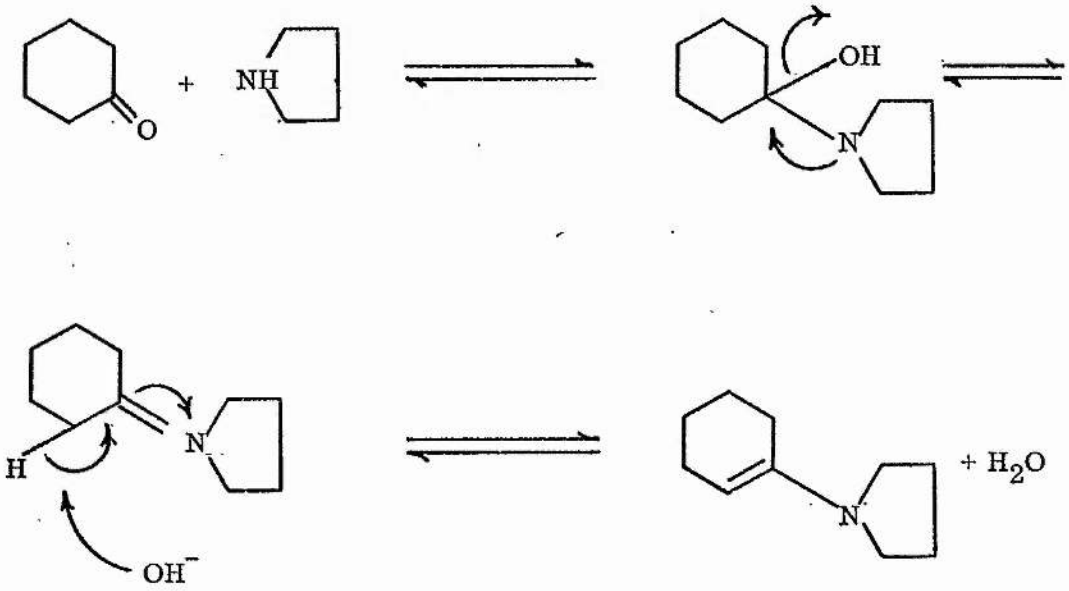
(i) The Enamine route

The term "enamine" was coined by Wittig and Blumenthal[13] in 1927 in order to indicate a general structural feature in which a nitrogen

atom replaces an oxygen atom in the familiar "enol".

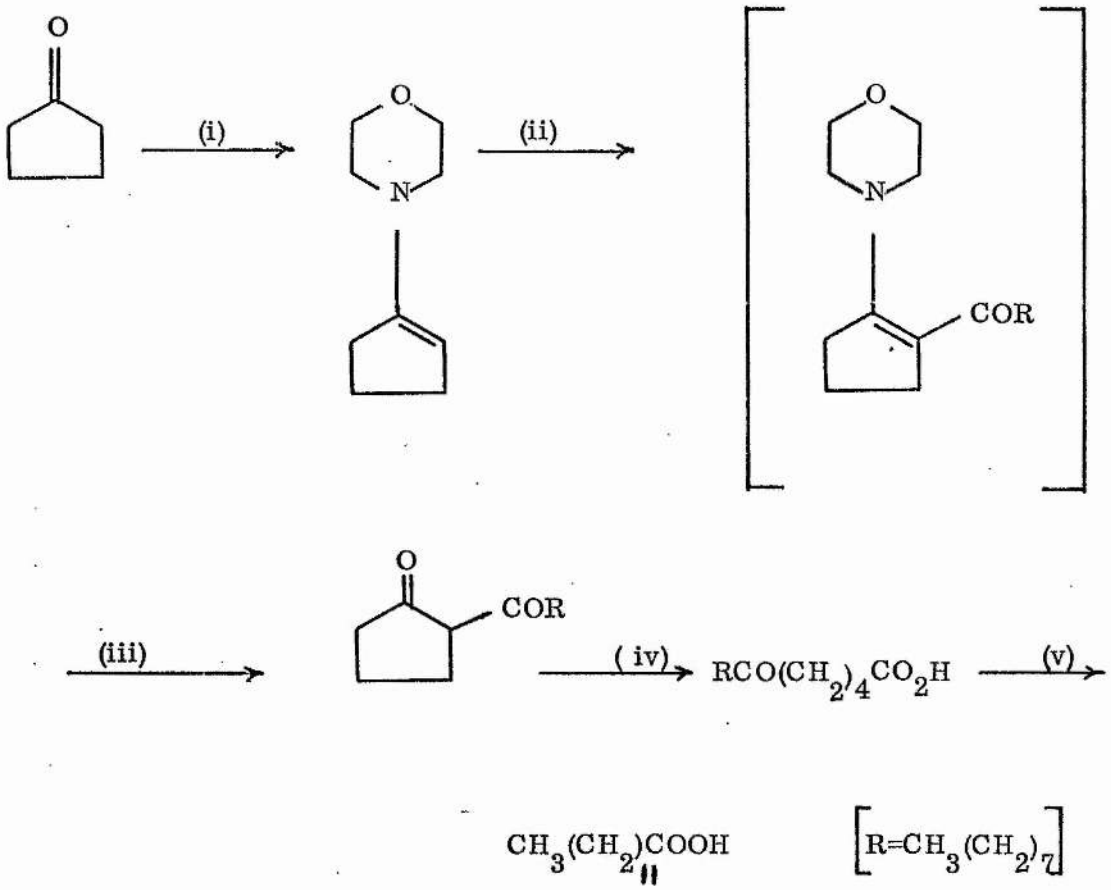
enol enamine

Herr and Heyl[14] introduced a procedure in which a carbonyl compound and an excess cyclic secondary amine in benzene was refluxed under nitrogen (with a water separator) to give an enamine.



Ketones from enamines which can be readily alkylated or acylated and reaction with the enamine derived from cyclopentanone or cyclohexanone has been employed as a route to fatty acids with five or six additional carbon atoms. The complete reaction scheme involves acylation of the enamine in the presence of triethylamine followed by acid hydrolysis to give 1,3 - diketones, ring opening to give an oxo-acid and reduction to the alkanoic acid. This is illustrated in the synthesis of tridecanoic acid from octanoic

acid and an enamine of cyclopentanone.



$CH_3(CH_2)_{11}COOH$ $\quad [R=CH_3(CH_2)_7]$

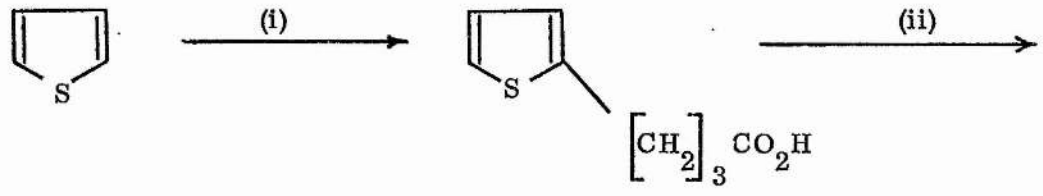
Tridecanoic acid

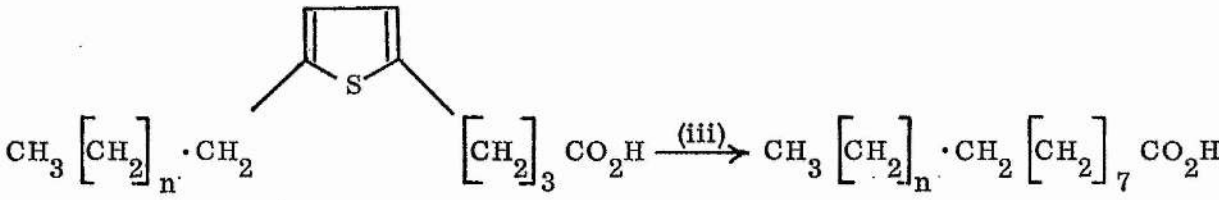
Chain-extension of octanoic acid to tridecanoic acid : (i) reaction of cyclopentanone and morpholine, with a catalytical amount of p-toluene sulphonic acid to give 1-morpholino-1-cyclopent-1-ene, (ii) Acylation of the enamine with octanoyl chloride (iii) hydrolysis to give a β -diketone and (iv) alkaline hydrolysis to give 6-oxo-tridecanoic acid and (v) reduction to give tridecanoic acid.

The addition of six carbon atoms can be achieved using cyclohexanone. Some limitations of this method will be discussed later.

(ii) Other methods

a) The use of thiophene for chain-extension depends on its ability to undergo Fridel-Crafts acylation at the 2- and 5- position. This reaction is followed by reduction of carbonyl groups and hydrogenolysis of the heterocyclic ring with nickel. The following preparation of C_{10}, C_{16}, and C_{18} acids is typical[1].





n = 0, 6 or 8

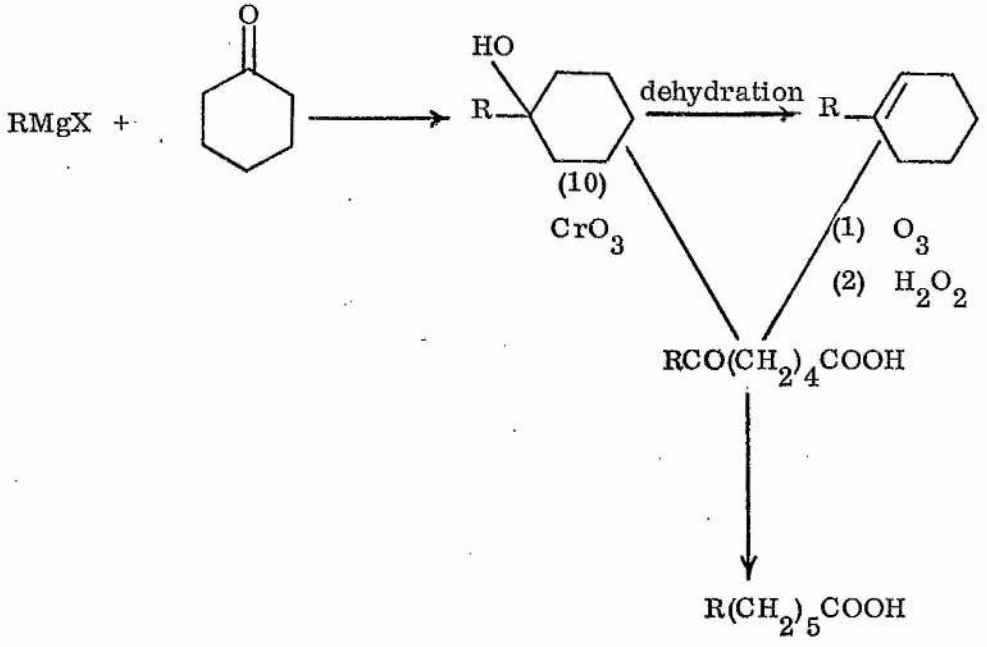
(i) $ClCO[CH_2]_2 CO_2Me/SnCl_4; N_2H_4, KOH$

(ii) $MeOH, H^+; CH_3 [CH_2]_n COCl/SnCl_4; N_2H_4, KOH$

(iii) hydrogenolysis of the heterocyclic ring with nickel.

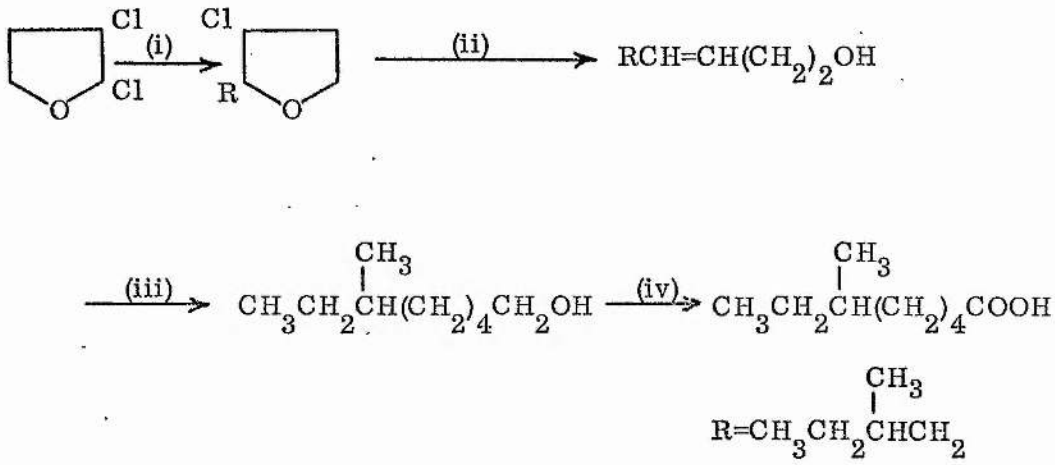
b) Alkyl magnesium halides add to cyclic ketones such as cyclohexanone, to form 1-alkyl-1-hydroxy-cycloalkanes (10). These may be

oxidised with chromic oxide in acetic acid[15] or, after dehydration to the alkyl cycloalkene, with ozone and peroxide to form acyclic keto acids which may be reduced by the Wolff - Kishner method to long-chain acids.



Fieser and Szmuszkovicz[16] prepared tetracosanoic acid, $CH_3(CH_2)_{22}COOH$ in this way and Keskin[17] prepared hexadecanoic acid $CH_3(CH_2)_{14}COOH$, starting with octadecyl bromide and decyl bromide respectively. Nunn[18] synthesised a series of keto and "anteiso" aliphatic acids by the above method.

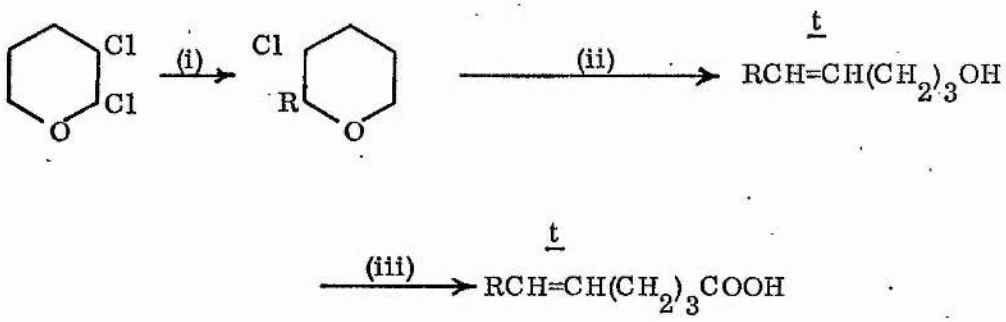
c) 2,3-Dichlorotetrahydrofuran reacted with a Grignard reagent to yield a mixture of cis and trans acids. Crombie and Harper[19] used this method to prepare dextrorotatory 6-methyl-octanoic acid.



(i) RMgBr (ii) Na, (iii) H_2/Pt and (iv) $KMnO_4$ oxidation.

This method is useful only for saturated acids since the intermediate alkenoic acid is a mixture of cis and trans isomers.

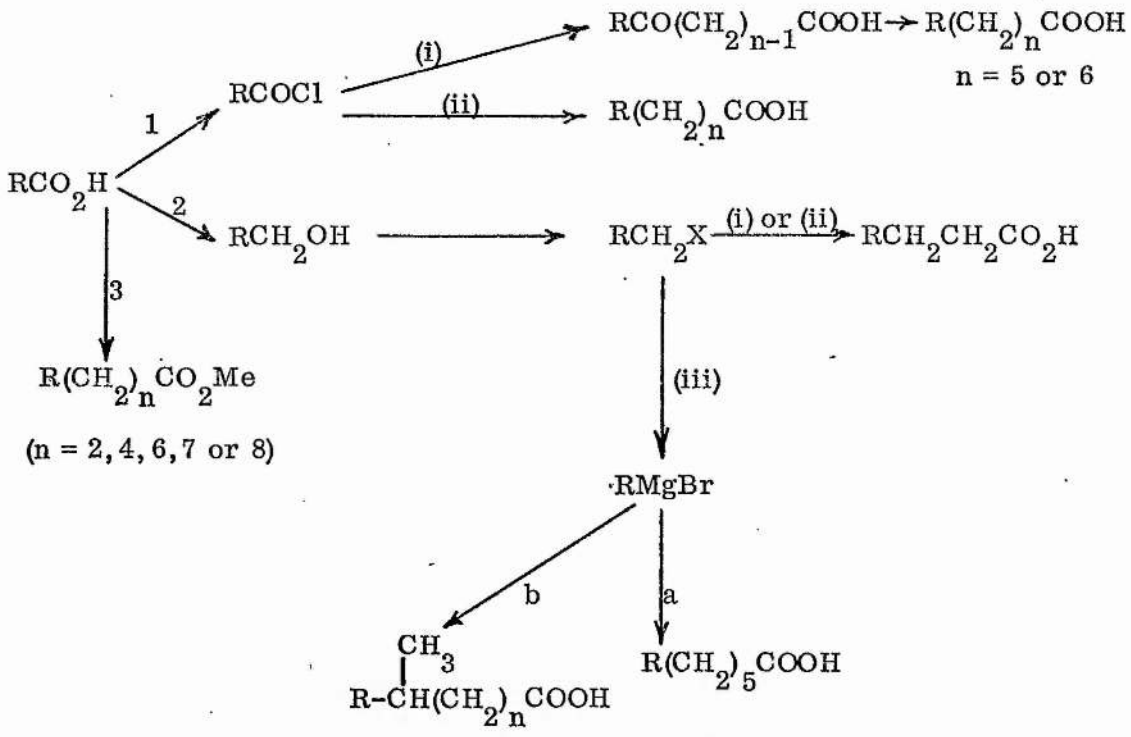
d) If the above reagent is replaced with 2,3-dichlorotetrahydropyran, the chain can be extended by five carbon atoms.



(i) RMgBr (ii) Na (iii) via bromide and derived Grignard reagent[20]

The intermediate appears to maintain the 5t structure which may be of value for its own sake.

The procedures leading to chain-extension by one or more carbon atoms are summarised in Scheme 1.



1 (i) the enamine route

(ii) with the use of thiophene

2 (i) or (ii) the malonic ester synthesis via the halide or mesylate.

(iii) the reaction of alkyl magnesium halides
- a) with cyclic ketones
- b) with 2, 3-dihalogenated furans or pyrans to give branched-chain acids (could be used to prepare optically active acids)

3 anodic synthesis with half-esters.

DISCUSSION

DISCUSSION

Some of the common fatty acids are most easily obtained by isolation from natural sources. This applies to many of the saturated acids (especially C_{12}, C_{14}, C_{16} and C_{18}) and to some unsaturated acids such as oleic, linoleic, α -linolenic, and arachidonic and when these acids are purchased from chemical suppliers they are almost centainly of natural origin. The most economic routes to oleic and linoleic acids have recently been studied in St. Andrews[21].

The 'unnatural' unsaturated acids (i.e. isomers of natural acids) and many of the rare natural acids can only be obtained by synthesis and a large number of these have been prepared in St. Andrews during the last decade.[22]

Yet a third group of acids, many of which occur naturally but generally only as minor components in complex mixtures, are best prepared by a modification of a more common natural acid. Gunstone and Jacobsberg[22] have described the preparation of several, 9,12-diunsaturated C_{18} acids starting from crepenynic acid (18:2 9c 12a) and from vernolic acid (12,13-epoxy 18:1 9c).

The purpose of the present investigation was to examine and compare a number of chain-extension procedures by which oleic, linoleic and linolenic acids could be converted to their higher homologues. In addition, a few acetylenic acids and some saturated acids of less common chain length have also been prepared. The methods employed include anodic synthesis, malonation and the use of enamines prepared from cyclopentanone

and cyclohexanone.

In anodic syntheses involving oleic acid and the C_2 and C_3 chloro, hydroxy and acetoxy acids we got hydrocarbons, ethers and alcohols as products. Unexpectedly most of these products had one carbon atom less than the starting material. We developed this reaction into a new procedure for converting unsaturated fatty acids to their nor-alcohols[23]. This in fact links up with the early work of Hofer and Moest (1902)[24] who described the formation of alcohols by anodic oxidation of carboxylates (customarily called the Hofer - Moest reaction).

ANODIC SYNTHESIS

General Considerations

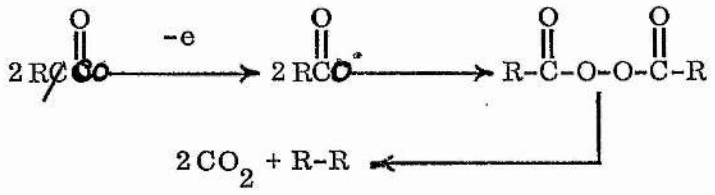
Mechanism :

In early work on the Kolbe reaction, a dimeric product was usually explained as arising from radical intermediates. However the nature of the intermediates was then uncertain. The evolution of the mechanism of the Kolbe electrolysis is described briefly below :

Formation of Acyl Peroxides

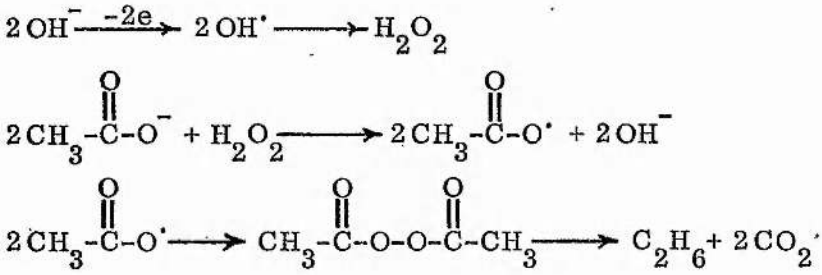
The oxidation of acids was originally thought to proceed through acyl peroxides, resulting from the union of two acyl peroxy radicals and loss of carbon dioxide.

This suggests that under special conditions (e.g., low temperatures) the isolation of the peroxide might be possible. Failure to detect any appreciable amounts of such peroxides has produced some doubt about the validity of this theory.



Formation of Hydrogen Peroxide

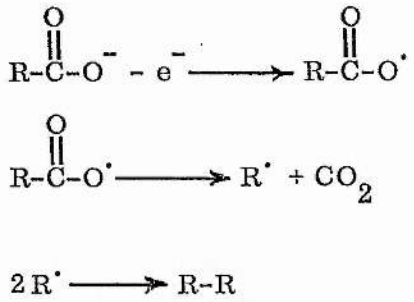
Glasstone and co-workers[25,26] advanced another mechanism for the Kolbe reaction which involves the formation of hydrogen peroxide in aqueous solutions and as intermediate in the formation of acyl peroxides.



However, the following observations make it doubtful whether this mechanism is operative to a great extent : (i) attempts to detect any amounts of hydrogen peroxide during the reaction were not successful, (ii) addition of hydrogen peroxide to acetate solutions produces only trace amounts of hydrocarbons and (iii) the Kolbe synthesis is quite efficient in nonaqueous media, such as DMF[27,28].

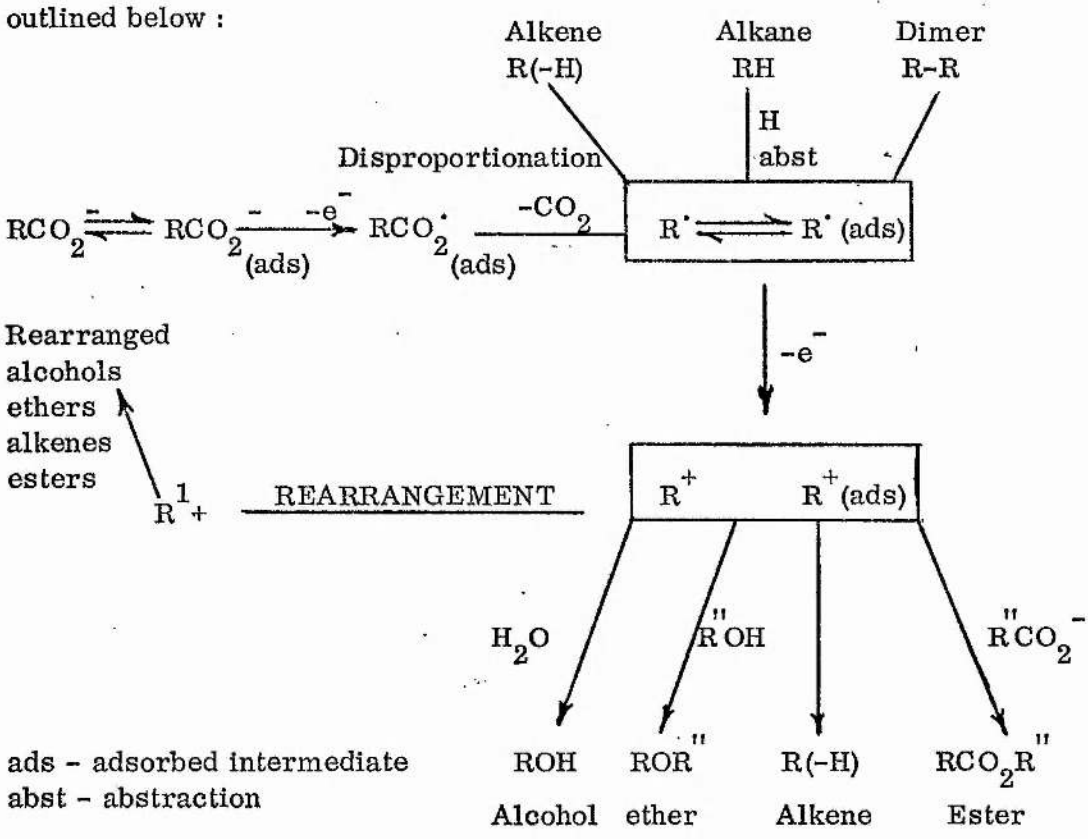
Formation of Radicals

The formation of radical intermediates in the Kolbe reaction was first advanced by Crum-Brown and Walker and was later developed by Walker and co-workers[29].



While evidence for the formation of radical intermediates in the Kolbe reaction has been advanced[30], very little is known about the nature of these radicals. Although there is no ESR evidence to support the existence of radicals it is possible that they cannot be detected in this way because they are absorbed on the surface of the electrode. This concept is discussed by L. Eberson[31].

A useful mechanistic scheme on which to base a discussion is outlined below :



SCHEME 2

Experimental variables

Concentration and pH :- Kolbe dimerisation is favoured by high concentrations of carboxylate ion, low pH and high current densities. In practice the first two requirements may be attained by using nonaqueous solvents in which high concentrations of carboxylic acid are partly neutralised (about 10%) with base. As electrolysis proceeds the alkali metal discharged at the cathode continuously neutralises the acid and the electrolyte does not become alkaline until all the carboxylic acid has been consumed. Alternative methods of operating at low pH and high concentration include the use of tetra-alkylammonium carboxylates instead of the usual but less soluble alkali metal salts, and electrolysis of alkali metal carboxylates in the Dinh-Nguyen cell[32]. In this cell (Fig. 3, page 71) the cathode is a pool of mercury and the alkali metal discharged during electrolysis becomes amalgamated and the electrolyte remains neutral. In this way completely neutralised acid may be used as starting material.

In our work we used two kinds of cells (1) with two platinum electrodes and (2) the Dinh-Nguyen cell. The concentration of carboxylic acid ranged from 8 to 60% which was neutralised (2-10%) by added base (sodium hydride 50% dispersion in oil).

Cross-Coupling

The preparation of cross-coupled products by electrolysis of different alkanoate ions can be efficient and often provides the simplest route to important fatty acid derivatives. Utley[33] states that from the general case for co-electrolysis of the ions $R^1CO_2^-$ and $R^2CO_2^-$, assuming

the radical intermediates combine rapidly and at comparable rates, it follows that

$$\frac{d\left[R^1 . R^1\right]}{dt} \propto \left[R^1\right]^2,$$

$$\frac{d\left[R^2 . R^2\right]}{dt} \propto \left[R^2\right]^2,$$

and

$$\frac{d\left[R^1 . R^2\right]}{dt} \propto \left[R^1\right] . \left[R^2\right]$$

If the relative concentrations of radicals are roughly proportional to the relative concentrations of carboxylate the conversion of $R^1CO_2^-$ into the cross-coupled product is therefore increased by having R^2CO_2 in high concentration. In practice this works well and is particularly important where one component is not readily available. The results of one of the few systematic studies[34] of this feature are illustrated in Table 1.

TABLE 1

Optimum conditions for cross-coupling of $CH_3(CH_2)_4CO_2H$(A) and $HO_2C(CH_2)_4CO_2Me$(B) to give $CH_3(CH_2)_8CO_2Me$ (C)

Concentration Ratio A : B	% Yield of C in Methanol	% Yield of C in aqueous Methanol
1:1	36	12
1:2	49	39
1:6	58	48

We checked this conclusion with oleic acid and methyl hydrogen succinate (see Table 2).

TABLE 2

Optimum conditions for cross-coupling of
Oleic acid (18:1 9c) A and $HO_2C(CH_2)_2CO_2Me$ B
to give 20:1 ester

Concentration Ratio A:B	% Yield 20:1 (in Methanol)
1:3	28
1:4	36
1:6	48

The two components may be of quite dissimilar molecular weights without severly reducing the efficiency of cross-coupling. For the preparation of a given fatty acid by this method it is often best to select components of different sizes so that the products of crossed-coupling are most easily separated from those resulting from symmetrical coupling.

The ratio of 1:6 was therefore preferred. Attempts to supply the half-ester in two portions at the beginning and half way through the reaction did not improve the yield of our product.

Co-electrolysis of a monocarboxylate and a half-ester is a very convenient method for the chain extension of a carboxylic acid. As the stereochemistry of the components is preserved during such reactions the method has also been used for the synthesis of naturally occurring optically active acids and for the establishment of stereochemical relationships.

Weedon and his co-workers have developed and used the method with considerable success (as detailed in Introduction).

Solvents

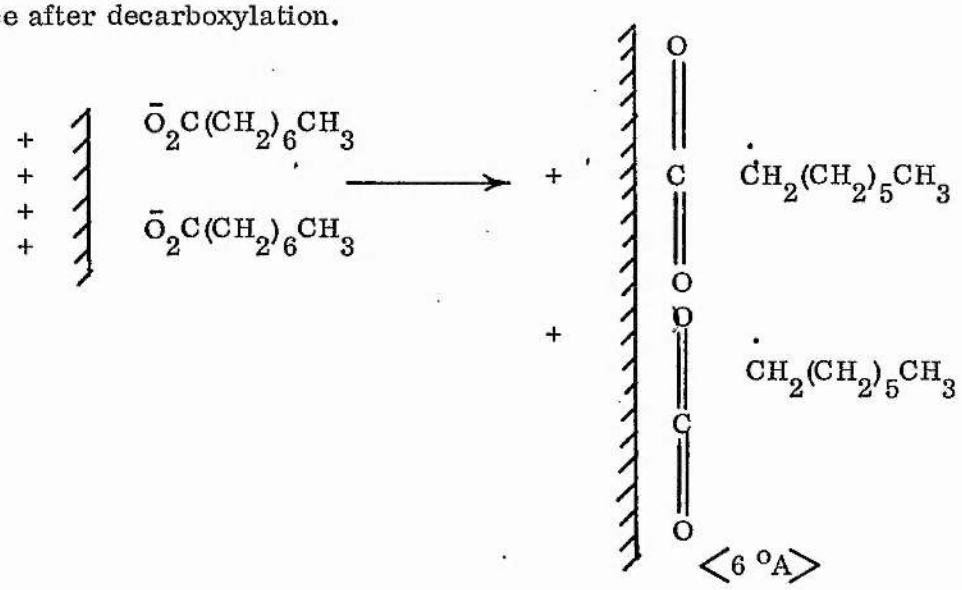
Of the nonaqueous solvents available methanol is the most used. Utley[33] reports that good yields associated with electrolysis in methanol were not reduced by the addition of small amounts of water that serve to increase the solubility of the electrolyte. Other solvents may have advantages that have not yet been fully explored. For instance in methanol the diphenylacetate ion is oxidised almost exclusively to the relatively stable diphenylmethyl cation but in dimethylformamide tetraphenylethane has been obtained in 24% yield[27]. One possible reason why DMF has not been more widely used is that it is itself fairly easily oxidised. Acetonitrile, an aprotic solvent of high dielectric constant, also offers attractive possibilities as a solvent for Kolbe coupling and it has already been used successfully[35,36a,b]. It is reported that in some oxidations, the carbonium ions produced react with acetonitrile and subsequent hydrolysis of the nitrilium ion leads to interesting products. When carbonium ions are intermediates in the Kolbe reactions, the products are alcohols, ethers or alkenes.

In the present work methanol, DMSO and acetonitrile were used as solvents in trial experiments. Methanol was found to give the best results and was therefore preferred for all electrolyses.

Nature of the electrode

The reason why different electrodes have various effects on the course of reactions is not always clear. Several explanations have been

advanced mostly related to the surface of the electrodes (perhaps specific adsorption, catalysis etc.) for example Kolbe coupling was claimed to have been achieved with a carbon electrode. Muck and Wilson[37] consider that stacking of alkyl chains resulting from lateral attraction (as shown below) favours dimerisation and at the same time slows diffusion to the electrode surface after decarboxylation.



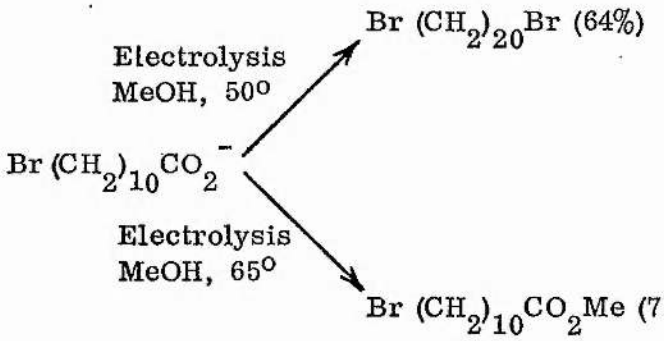
In the oxidation of sodium acetate in the presence of aromatic compounds, the use of a graphite anode produced mainly methylated products with some acetoxylation, while the use of a platinum anode afforded the acetoxylated products exclusively[38]. Koehl[39] has shown that the use of graphite as anode in the oxidation of simple aliphatic acids failed to produce dimeric products. This is presumably due to the formation of reactive carbonium ions, which react immediately to form olefins or undergo chemical rearrangement. Thus, while there is no rule as to which anode will give a specific intermediate, the use of carbon generally favours carbonium ions, while the use of platinum favours the radical intermediate.

In the present work a platinum anode was used.

Temperature

Low temperature (25-35°C) is generally held to favour the coupling process although there has been little systematic study of the aspect. In principle an optimum temperature would be expected as temperature affects key factors in various directions. For instance, high concentrations of carboxylate are better achieved at high temperatures as are the high rates of diffusion necessary for high current densities. On the other hand, it can be argued that at high temperatures the diffusion of the radical intermediates away from the elctrode environment is encouraged and that the subsequent dilution of such species favours competing unimolecular reactions. Alternatively higher temperatures would be expected to increase the rate of side reactions but have little effect upon the rate of the diffusion - controlled radical dimerization.

The Kolbe reaction is not generally sensitive to temperature change especially in nonaqueous solvents. In one case however, a large effect has been reported[40]:



In the present work a temperature of 25-30° was steadily maintained

with the use of Apparatus 2.

Structure of Acid

It was shown ny Fichter and co-workers[41] that Kolbe synthesis does not take place in aqueous solution when a double bond is too close to the carbonyl group. In fact, appreciable coupling was not found until the double bond was in the γ - position or further from the carboxyl group. Similarly, no coupling product was observed from benzoic and phenylacetic acid. However, the oxidation of phenylacetic acid in DMF was shown to afford 1,2-diphenylethane in 88% yield.

The presence of substituents α - to the carboxyl group suppresses the formation of coupled products. Thus, little or no such products were observed for most α -alkyl, methoxy-, hydroxy-, halogeno-, keto-, cyano- and amino groups.

In the present work coupling took place with most of the acids used. C_2 chloro and hydroxy acids however, when coupled with oleic acid did not give the desired product. γ -Linolenic acid with methyl hydrogen succinate gave the expected C_{20} ester along with some side products. Though not fully identified it is thought that these could result from interaction of the radical at C(2) with the double bond at Δ.6.

Apparatus 1.

In the first few experiments an apparatus similar to that described by Weedon[11] was used (page 70). The cell was a small beaker or cylindrical vessel with two parallel pieces of platinum foil as electrodes. To avoid overheating the distance between the electrodes was reduced to at

least 3 mm. As electrolysis proceeded carboxylate ions were converted into product at the anode, sodium liberated at the cathode reacted with the solvent, and the resulting alkali neutralised more acid. The process continued in this way until all the acids had been consumed and the electrolyte turned alkaline.

The equipment was subject to two disadvantages. Heat generated during the reaction was not easily dissipated and it proved difficult to keep the reaction temperature below 50^{o}, especially around the electrodes. With saturated acids the solid product tended to come out of solution and to coat the electrodes. Against this however, there was some advantage in that the current could be reversed periodically. This helped to remove hydrocarbon and other products which tended to deposit on the anode.

Apparatus 2

Nguyen Din-Nguyen[32] reported the advantages of using a mercury cathode and a platinum anode in the Kolbe electro-syntheses. We prefer this apparatus and have used it to prepare olefinic, acetylenic and saturated fatty acids and also some nor-alcohols.

We found that this cell with a platinum anode and a mercury cathode had the following advantages.

1. It was possible to maintain a lower, steady temperature ($25-30^{o}C$) during the reaction because of the double walled vessel with continuous cold water circulation.

2. The revolving anode produced efficient mixing of the reactants.

3. Since sodium liberated at the mercury cathode is held as an

amalgam it is possible to use more base. Because of the higher ion concentration larger currents can be employed thereby reducing the reaction time. The current falls when the carboxylate ion concentration is reduced and the end of the experiment is readily detected.

During some electrolyses (in both cells) of unsaturated acids in particular, an isoluble polymer was formed on the electrodes causing the current to drop. Using apparatus 1, these deposits could be dislodged by reversing the direction of the current from time to time by means of the commutator. With apparatus 2 it was necessary to interrupt the electrolysis at intervals and clean the electrode.

PREPARATION OF ALKENOIC ACIDS

Several alkenoic acids were prepared from C_{18} acids by anodic synthesis. The results are summarised in Table 3 (overleaf).

(i) Eicos-cis-11-enoic acid

Oleic acid, electrolysed with methyl hydrogen succinate using apparatus 1, gave a 46% yield of methyl eicosenoate (20:1 11c, 96%pure). When this experiment was repeated using apparatus 2, a 50% yield of the ester (98% pure) was obtained. For these reasons and those detailed in sections titled "Apparatus 1 and 2", the subsequent preparations were carried out using apparatus 2.

(ii) Docos-cis-13-enoic acid

Oleic acid was reacted with methyl hydrogen adipate to give 22:1 (13c) in a 6 % yield. This poor yield was obtained because the half-ester was contaminated with a large amount of diester. This preparation

was not repeated but there is no reason to doubt that the ester could be obtained in 40-50% yield.

TABLE 3

1. ALKENOIC ACIDS

	Monobasic acids	Half-ester $HOOC(CH_2)_nCO_2Me$	Product* yield
i)	18:1 (9c)	n = 2	20:1 (11c) 46%, 50%
ii)	18:1 (9c)	n = 4	22:1 (13c) 6%
iii)	18:2 (9c12c)	n = 2	20:2 (11c14c) 37%
iv)	18:2 (9c12c)	n = 4	22:2 (13c, 16c) 38%
v)	18:3 (6c9c12c)	n = 2	20:3 (8c11c14c) 21%
vi)	18:1 (5c)	n = 2	20:1 (7c) 17%
vii)	18:1 (6c)	n = 2	20:1 (8c) 3%

* Some side products such as hydrocarbons and diesters were formed in all preparations but the monoester could be easily separated from the mixture by column chromatography (silica).

(iii) and (iv) Eicosa-cis-11, cis-14-dienoic and Docosa-cis-13, cis-16-dienoic acids

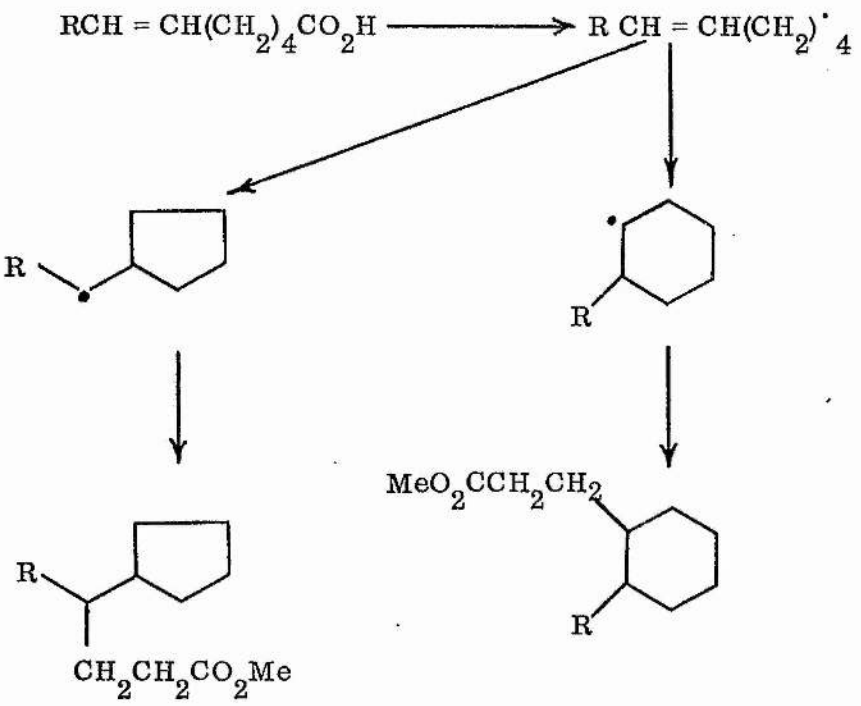
Linoleic acid was similarly converted to 20:2 and 22:2 acids with slightly lower yields.

In all these preparations there was no evidence of double bond migration or steromutation on the basis of von Rudloff oxidation and NMR spectra of the products. The yield of chain-extended product ranged from 37 to 50%.

v) Eicos-cis-8, cis-11, cis-14-trienoic acid

With γ -linolenic acid the reaction took a different course. The major product (20%) was 20:3 (8c 11c 14c) as judged by its NMR and IR spectra but this was accompanied by a minor component. The GLC of the monoester showed a major peak of ECL 21.5 with a shoulder at ECL 21.2.

We have not been able to identify fully this minor product. The fact that it has a higher Rf on the Ag^+ plate and the absence of trans unsaturation (IR spectrum) led us to believe that it might be a cyclic compound having only 2 unsaturated centres. Cyclisation of the initially formed radical could lead to a 5 or 6 membered ring compound thus :



$R=CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2$

The NMR signals of this product showed a complex pattern of multiplets in the region 1.53 and 1.62 δ in addition to the usual signals. An attempt was made to identify this component by gas chromatograph, mass spectrometry but the fragmentation expected of a five or six membered ring could not be detected.

There have been two earlier reports of unidentified components obtained from chain elongation of γ -linolenic acid. Struijk, Beerthuis, Pabon and von Dorp[42] report chain extension of γ -linolenic acid with monomethyl glutarate in methanol at 35-40°. The monoester obtained by counter current distribution (86%pure by GLC) had to be further purified by TLC on silica plates impregnated with silver nitrate but still contained $\sim$ 10% of a trans compound.

Klenberg[43] also reports the chain-extension of γ -linolenic acid with the half ester of glutaric acid and of β , β -dimethylglutaric acid in methanol. The products obtained were purified by column chromatography (silica) then through a silicic acid/25% $AgNO_3$ column and finally, after hydrolysis, through a silicic acid column. He states "the wrong isomers produced in the electrosynthesis" had slightly shorter retention times than the desired acids, which was also observed by us. He claims that 20-35% of an isomer was obtained in which the first double bond had shifted three carbon atoms further from the carboxyl group than in the acid desired.

We think it most unlikely that there has been a shift of the triene system by three carbon atoms but prefer the idea that the double bond

nearest to the carboxyl group no longer exists so that unsaturation starts three carbons further along the chain.

vi) Eicos-cis-7, enoic acid

Because of the difference in behaviour between γ -linolenic (Δ 6, 9, 12) on the one hand and oleic (Δ9) and linoleic (Δ 9, 12) acids on the other we examined the electrolysis of the Δ 5 and Δ 6 18:1 acids. With octadec-5-enoic acid two monoesters were again obtained. The major component was the expected methyl eicos-cis-7-enoate on the basis of its NMR signals and had a lower Rf on a silicic acid TLC plate impregnated with silver nitrate. The minor component which accompanied this ester had a higher Rf and was not fully identified.

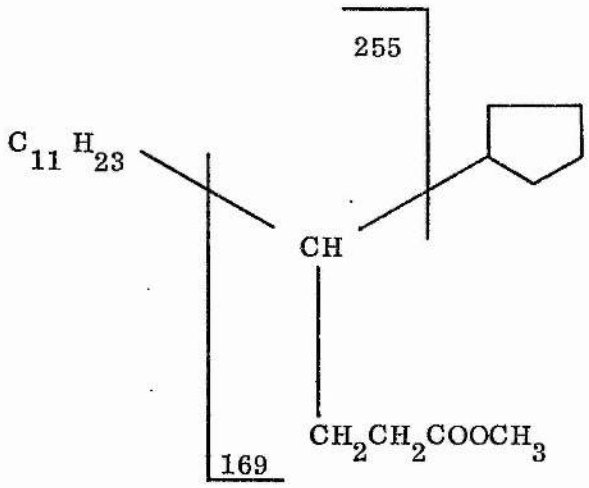
Gas chromatograph mass spectrometry analysis of both the major product and component 1 did not give meaningful results.

vii) Eicos-cis-8, enoic acid

With octadec-cis-6-enoic acid two monoesters were similarly obtained. The major product was the expected methyl eicos-cis-8-enoate on the basis of its NMR signals and had a lower Rf on a silver nitrate TLC plate. In this preparation however the minor component was well separated and had a higher Rf than the expected chain extended product. Although we were unable to completely identify this compound its NMR spectra showed no evidence of olefinic protons.

Gas chromatograph mass spectrometry of the minor product showed peaks at m/e 255, 169, and 137 (169-32) which result from the

fragmentation shown :



2. PREPARATION OF ALKYNOIC ACIDS

The synthesis of alkenoic acids with the double bond far away from the carboxyl function presents some difficulties when the intermediates required to produce the corresponding alkynoic acids are insoluble in the reaction solvent. Gustone and Ismail[44] strove to overcome this difficulty by preparing 12:1 acids and extending them to 18:1 acids by chain extension with the enamine of cyclohexanone. There was, however, some evidence of double bond migration during the Wolff-Kishner reduction which occurs under fairly strong alkaline conditions. It seemed worthwhile, therefore, to see whether this chain extension could be more satisfactorily effected by anodic synthesis.

We found that 12:1 (10a) and 11:1 (10a) could be satisfactorily chain extended to 18:1 (16a) and 18:1 (17a) by reaction with the half ester of suberic and azelaic acids respectively. Products of ~ 95% purity were obtained in a 50% yield as shown in Table 4 .

TABLE 4

2. ALKYNOIC ACIDS

Monobasic acid	Half-ester $HO_2C(CH_2)_nCO_2Me$	Product (yield %)	Purity %	m.p. as ester
12:1 10a	n = 6	18:1 16a (51)	94	-
11:1 10a	n = 7	18:1 17a (53)	96	32°

The NMR signals of 18:1 16a methyl ester gave the necessary evidence of a W 2 triple bond - 0.94 δ ($C\underline{H}_3C\equiv C$-) and a triplet at

2.15 δ (-C≡C-$\underline{CH}_2$-) and that of 18:1 17a gave NMR signals at 1.78 ($\underline{CH}$≡C-) and 2.15 δ (CH≡CC$\underline{H}_2$-) confirming the presence of a terminal actelynic group.

These acids could be partially hydrogenated to get the corresponding alkenoic acids, quite easily.

3. PREPARATION OF SATURATED ACIDS

'Odd' acids occur naturally only as very minor components and these acids (often used as GLC standards) are therefore more readily available by synthesis or by modification of the more easily available 'even' acids.

We prepared the C_{13}, C_{15}, C_{17}, C_{19} and C_{21} acids by Kolbe electrolysis in yields ranging from 56-95%. The reaction product was a mixture of solids but the monoester was isolated quite easily by column chromatography (sorbsil).

TABLE 5

PREPARATION OF 'ODD' ACIDS

Monobasic acid	Half-ester $HO_2C(CH_2)_nCO_2Me$	Product, yield* 1 and 2	Purity* by GLC %	m.p. as* acid(lit)[1] °C
11:0	n = 2	13:0 52, 44	94	41-42(41.8)
11:0	n = 4	15:0 77, 69	97	52-53(52.5)
10:0	n = 7	17:0 85, 68	83	61-62(61.3)
12:0	n = 7	19:0 84, 74	90	69-70(69.4)
14:0	n = 7	21:0 1) 79 -	94	
		2) 92, 78	94	75-75.5(75.2)

* Yield 1 relates to that obtained initially by column chromatography (sorbsil). The esters were then crystallised from petrol (Yield 2) to the 99%purity level (by GLC).

The C_{13} to C_{19} esters were crystallised at 0^{o} and the C_{21}, ester at room temperature to a level of 99% purity. The melting points were obtained on the pure samples. Literature values are given in parentheses.

4. PREPARATION OF NOR-ALCOHOLS

We re-examined the electrolysis of oleic acid with chloro, hydroxy and acetoxy C_2/C_3 acids because we hoped that the products would be useful precursors for other acids by oxidation or via the nitrile.

$$RCO_2H + HO_2C(CH_2)_nX \longrightarrow R(CH_2)_nX \longrightarrow \text{Other acids}$$

$n = 1$ or 2

$X = Cl$, OH, OAc

This hope was not fulfilled though our results became of interest in another way.

With 3-chloropropionic acid oleic acid gave heptadecenyl chloride (30%), nonadecenyl chloride (20%) and heptadecenol (20%). With chloroacetic acid heptadecenyl chloride (20%) was the only identified product.

Hydroxyacetic acid furnished a mixture of heptadecenol (11%) and octadecenol (3%), whilst 3-hydroxypropionic acid gave heptadcenol (14%) and nonadecenol (7%).

Electrolysis of acetoxyacetic acid with oleic acid gave a mixture of heptadecenyl and octadecenyl acetates.

These results are very different from those described earlier between half-esters and oleic acid. Independantly of whether the electrolysis is carried out in the presence of an acetic acid or propionic acid derivative

the major products are C_{17} compounds and we think these may be products of a reaction occurring via carbonium ions thus :

$$RCO_2^- \longrightarrow RCO_2^{\cdot} \longrightarrow R^{\cdot} \longrightarrow R^+ \begin{cases} \xrightarrow{\bar{O}H} ROH \\ \xrightarrow{Cl^-} Rcl \end{cases}$$

Because the C_{17} chloride and alcohols could be usefully employed as precursors of labelled acids by the reaction sequence shown below we have examined this reaction further and improved it.

$$RCO_2^- \longrightarrow ROH \xrightarrow{MsCl} ROMS \xrightarrow{K^+CN} R^+CN \xrightarrow{MeOH, H^+}$$

$$R^+ CO_2Me$$

Heptadec-cis-8-enol : Oleic acid was electrolysed (Apparatus 2) with excess alkali (sodium hydride) in aqueous methanol to obtain heptadec-cis-8-enol (34%). Repeated with excess sodium hydroxide the reaction gave a slightly increased yield of alcohol (44%). The alcohol was identified by its TLC and GLC behaviour in comparison with a sample of oleyl alcohol, its IR spectrum (strong OH absorption at 3340 cm^{-1}), its NMR spectrum (particularly the triplet signal at 3.15 δ for CH_2-OH) and by von Rudloff oxidation to nonanoic acid and 8-hydroxyoctanoic acid. The 17:1 alcohol was accompanied by a hydrocarbon (25%) and a methyl ether thought to be methyl heptadec-cis-8-enyl ether (7%).

Heptadec-cis-8, cis-11-dienol

Linoleic acid reacted in a similar way and furnished a C_{17} alcohol in slightly lower yield (21%) along with some hydrocarbon (2%) and a methyl

ether (8%) probably methyl heptadec-cis-8, cis-11-dienyl ether. The alcohol was considered to be heptadeca-cis-8, cis-11-dienol on the basis of its GLC behaviour and its infrared and NMR spectra.

Heptadec-cis-8-en-1,11-diol

Electrolysis of ricinoleic acid furnished heptadec-cis-8-en-1,11 diol (17%) accompanied by a smaller amounts of a monohydroxy compound, and a monohydroxy monomethoxy compound shown to be 1-methoxy heptadec-cis-8-en-11-ol. The diol and the hydroxy methoxy derivatives were identified by their GLC behaviour (as TMS ethers) and by their IR and NMR spectra.

The TMS ether of the 17:1 diol was compared (GLC) with that of 18:1 diol as authentic sample. The IR and NMR spectra of 18:1 diol were also compared.

Products of the electrolysis of γ-linolenic and α-linolenic acid in alkaline medium

The two trienoic acids, γ-linolenic and α-linolenic, failed to produce the desired nor-alcohols.

The products obtained were mixtures of hydrocarbons, methyl ethers and alcohols but these mixtures could not be satifactarily separated by prep. TLC on silica nor silica impregnated with silver nitrate.

^{14}C-Carboxy- labelled fatty acids and their esters (13) are usually prepared by interaction of an appropriate halide (12) or equivalent substrate (mesylate, tosylate) with K^{14}CN followed by hydrolysis or methanolysis. For saturated acids the halide (12) is easily obtained from the unlabelled

acid (11) by Hunsdiecker decarboxylation or an equivalent process[45]. This procedure is less suitable for unsaturated acids though labelled oleic and linoleic acids were first made in this way after protection of the double bond(s)

$$RCO_2H \longrightarrow RBr \xrightarrow[MeoH, H^+]{K^{14}CN} R\,^{14}CO_2Me$$

(11) (12) (13)

by bromination . This approach is less satisfactory with more highly unsaturated acids and with the improvement of synthetic procedures the required nor-halides are more frequently obtained by synthesis using acetylenic intermediates or the Wittig reaction[46]. Nevertheless there remains a need for a general procedure by which (natural) unsaturated acids (11) can be converted into their ^{14}C-carboxy-labelled forms and we here report a new method of preparing nor-alcohols from carboxylic acids. The former can be oxidised by chromic acid to the unlabelled nor-acid[47] or can be converted via the mesylate and nitrile into labelled ester or acid with the same number of carbon atoms as the starting acid[8,47,48].

CHAIN-EXTENSION BY MALONATION

Use and preparation of mesylates

A number of alkylating agents, such as alkyl halides, toluene-sulphonates (tosylates) and methanesulphonates (mesylates) are used in syntheses of both aliphatic and carbocyclic compounds. Mesylates have been shown to be especially effective alkylating agents owing to their ability to produce carbonium ions and have been applied with great success in the synthesis of several long-chain compounds. Unsaturated mesylates can

be prepared without isomerisation of double bonds.

An improved procedure for the preparation of mesylates however, has been published recently[50] which makes use of triethylamine instead of pyridine. We have used the procedure described by Baumann and Mangold[49] (see Experimental section, General procedures).

The long-chain mesylates prepared from the 18:0, 18:1, 18:2, γ 18:3 and α 18:3 alcohols were characterised by their IR spectra which showed a strong band around 1175 cm^{-1} for the S-O symmetric stretching frequencies in the SO_2 group. The NMR spectrum showed a sharp singlet at 2.88 δ (OSO_2-CH_3) and a triplet (J = 6Hz) at 4.12 δ ($-CH_2OSO_2CH_3$).

SYNTHESIS OF 20:1, 20:2, 22:2, 20:3 (11c 14c 17c) and 20:3 (8c 11c 14c) acids

C_{20} unsaturated acids have been prepared by chain extension of methyl oleate, linoleate, α -linolenate and γ -linolenate under conditions recommended by Spener and Mangold[9].

The C_{18} esters ($>$99% pure) were reduced to the corresponding alcohols and then converted to mesylates by reaction with methanesulphonyl chloride in cold pyridine. Interaction of each mesylate with the sodium derivative of diethyl malonate gave the alkylated malonate which was hydrolysed, decarboxylated and methylated to give the C_{20} esters. The ester obtained in 84 to 96% yield was usually 94 to 99% pure though dark in colour. A colourless acid was obtained by elution from a column (silica) which was topped with a mixture of silica and charcoal. Yields were then 49 to 79% of 99% pure material. The 20:2 and 22:2 acids were

further purified by low temperature crystallisation (-78°) to obtain a level of 99% purity. The yields of these acids then fell to 66 and 41% respectively.

TABLE 6

ALKENOIC ACIDS PREPARED BY MALONATION

SUMMARY OF YIELDS

ACID	1[a] Yield	1[a] Purity (GLC)	2[b] Yield	2[b] Purity (GLC)	3[c] Yield	3[c] Purity (GLC)
20:1 (11c)	84	99	75	99	-	
20:2 (11c 14c)	88	95	79	98	66	99
22:2 (13c 16c)	83	90	49	97	41	99
20:3 (11c 14c 17c)	96	94	75	99	-	-
20:3 (8c 11c 14c)	86	97	72	99	-	-

a. the yield of acid initially obtained

b. yield after purification by column chromatography (silica)

c. yield after low temperature crystallisation.

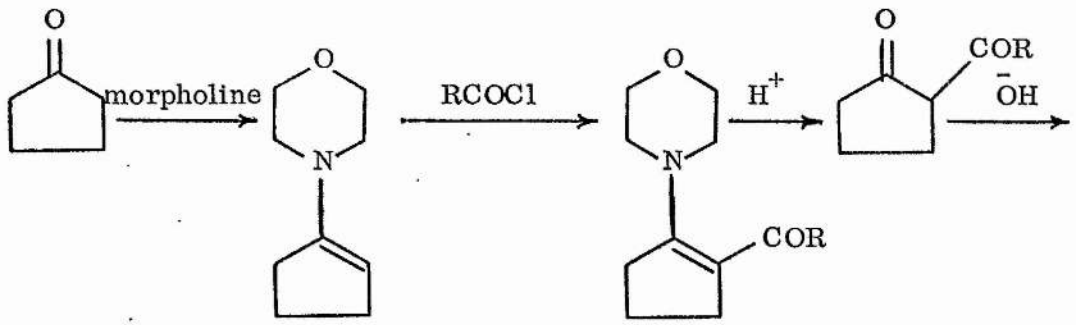
The yields are based on the corresponding mesylate (as starting material).

Each ester was characterised by its spectroscopic and chromatographic properties. GLC showed the product to be homogeneous. Infrared spectra confirmed the absence of trans unsaturation, u v spectra the absence of conjugated unsaturation and the NMR spectra had the expected signals. von Rudloff oxidation confirmed double bond positions.

CHAIN-EXTENSION VIA ENAMINES

Enamines, which are readily prepared from the cyclic ketones cyclopentanone and cyclohexanone, are activated molecules which can

readily be acylated by acid chlorides. After acidic hydrolyses, the product is a β -diketone which can be hydrolysed by alkali to an oxo acid. This may be reduced to an alkanoic acid having 5 or 6 carbon atoms more than the original acid chloride.



$$RCO(CH_2)_4CO_2H \xrightarrow{\text{Reduction}} R(CH_2)_{n+5}CO_2H$$

This procedure was examined briefly. Tetradecanoic acid was converted to eicosanoic acid (47%) by reaction with the enamine from cyclohexanone and hexadecanoic acid was extended to heneicosanoic acid (56%) by chain-extension with cyclopentanone.

COMPARISON OF CHAIN-EXTENSION PROCEDURES

Three chain-extension procedures have been examined and it remains to consider the advantages and disadvantages of each. The enamine synthesis procedure is a convenient method which can be handled on a moderately large scale but is not appropriate for unsaturated compounds because double bond migration occurs when the carboxyl group of the intermediate oxo-acid is reduced.

Malonation can be applied to saturated and unsaturated acids. The method gives good yields and products are of high quality. The disadvantage however, is that only two carbon atoms can be added in each cycle.

Anodic synthesis seems to be the most flexible method for it can easily be used to add two, four, six or seven carbon atoms. It can be used to prepare both saturated and unsaturated acids. In the case of unsaturated acids there is no double bond migration or steromutation in the final product. The method involves few stages but gives moderate yields.

There are however, some disadvantages in that it is a slow reaction and cannot be easily applied on a large scale. Also the purification of acids can involve some problems. Although the monoester can be easily isolated from the expected mixture of hydrocarbon, monoester and diester purification of acids which are extended by only two or three carbon atoms can be tedious because small quantities of starting material are esterified during the reaction and separation of the desired acid from its homologues differing by two or three carbon atoms can be difficult.

Because of our interest in producing unusual fatty acids for sale we had hoped to "cost" each of our preparations with a view to estimating their relative efficiency on a cost basis. This was not possible in any accurate way and we have confined ourselves to comparing the time taken to obtain the pure product in each of our synthetic procedures. This is valid

because labour costs are very much higher than material costs. The figures to be quoted are very approximate and are given in terms of hours of labour per gram of product. A real comparison is difficult because (a) the several experiments were carried out on different scales and (b) these values are very dependant on the yield and we were unable in the time available to repeat each experiment sufficiently to optimise the yield.

Anodic synthesis carried out on 10g of long-chain acid gave a product at the rate of 1g per 17 hours, malonations carried out on 20g of long-chain ester gave a product at the rate of 1g per 8 hours, and chain extension with enamines carried out on 65g of long-chain acid gave product at the rate of 1g per 3 hours. These cost considerations must of course be modified by the chemical advantages and disadvantages of each procedure which have already been elaborated.

^{1}H - Nuclear magnetic resonance (PMR)

^{1}H NMR spectra have been used throughout this study and it seems convenient to summarise our observations (δ values obtained at 100 MHz on a Varian HA 100 spectrophotometer).

TABLE 7

	1	2	3	4
Olefinic esters	CH_3	$-(CH_2)_n-$	$-CH_2COOCH_3$	$-COOCH_3$
20:1 7c	0.88	1.26	2.22	3.58
20:1 8c	0.88	1.25	2.22	3.58
20:1 11c	0.88	1.28	2.21	3.57
20:2 11c 14c	0.91	1.29	2.22	3.58
20:3 8c 11c 14c	0.89	1.32	2.22	3.58
Acetylenic esters				
18:1 16a	0.94	1.24	2.22	3.58
18:1 17a	-	1.27	2.22	3.58
Olefinic Alcohols	CH_3	$-(CH_2)_n-$	$-CH=CHCH_2-$	$-CH=CH-$
17:1 8c 10H	0.88	1.27	1.96 - 2.01	5.27
17:2 8c 11c 10H	0.90	1.32	2.00 - 2.05	5.28
17:1 8c 1, 11 diol	0.90	1.34	2.04 - 2.24	5.43
18:1 9c 1, 12 diol	0.90	1.32	2.02 - 2.16	5.42

continued overleaf

Table 7 continued.

	5	6	7
Olefinic esters	-CH=CHC$\underline{H}_2$-	-C$\underline{H}$=C$\underline{H}$-	=CHC$\underline{H}_2$CH=
	1.96 - 2.02	5.26	-
	1.96 - 2.02	5.26	-
	1.96 - 2.01	5.26	2.72
	2.00 - 2.06	5.28	2.76
	2.00 - 2.07	5.30	2.76

Acetylenic esters	C$\underline{H}$≡C-	CH≡CC$\underline{H}_2$	
	-	2.15	
	1.78	2.15	

Olefinic Alcohols	C$\underline{H}_2$OH	C$\underline{H}$OH	O$\underline{H}$	=CHC$\underline{H}_2$CH=
	3.51	-	2.71	-
	3.51	-	3.60	2.72
	3.53	3.36	-	-
	3.58	3.40	-	-

^{13}C Nuclear magnetic resonance (CMR)

Bloch[51] and Purcell[52] were the first to realise the experimental applications of ^{13}C NMR spectroscopy (1945). By the mid 1960s, Grant and his co-workers had succeeded in studying many classes of organic compounds with this technique[53]. It is hoped that CMR spectra, which are sensitive to small changes in the structure of molecules, will afford maximum information in the study of fatty acids and their derivatives.

Frost and Gunstone[54] have studied the shielding and deshielding effects of certain commonly occurring functional groups in natural and synthetic long-chain acids by ^{1}H NMR spectroscopy and a similar study of the ^{13}C NMR spectra of acetylenic, olefinic, and oxygenated long-chain acids (esters) is now being undertaken. A paper on alkanoic and alkynoic acids has already been prepared and the results reported here will, along with others, make up a paper on olefinic acids and esters.

Gunstone et al.[55] report that with the ^{13}C NMR facilities available in St. Andrews they were able to distinguish five signals for alkanes, eleven for alkanoic acids, and twelve for methyl alkanoates. These resonance signals averaged over the range C_8 to C_{21} for the acids and esters, were allocated as follows :

alkanes

C	C	C	C	(C)$_n$	C	C	C	C
14.14	22.85	32.14	29.58	29.90	29.58	32.14	22.85	14.14

alkanoic acids

ROOH—C—C—C—C—C—(C)$_n$—C—C—C—C

180.60 34.23 24.80 29.22 29.38 29.56 29.80 29.49 32.06 22.79 14.12

methyl alkanoates

CH_3OOC—C—C—C—C—C—(C)$_n$—C—C—C—C

51.26 174.04 34.18 25.11 29.36 29.45 29.64 29.84 29.53 32.10 22.83 14.1

The C_{13}, C_{15}, C_{17}, C_{19}, C_{20} and C_{21} alkanoic acids prepared during the course of this research project were used in this survey.

From their study of C_8-C_{20} acids with one or two acetylenic centres they were able to assign quantitative values to the influence of COOH, CH_3 and C≡C group on neighbouring carbon atoms. A similar survey of olefinic acids/esters is now being undertaken.

The results obtained for the olefinic acids (esters) used or prepared in this synthetic study are set out in Table 8 . The allocations are made on the following basis.

(i) The distinctive signals for C(1), C(2), C(3), W1 W2 and W3 are readily assigned. This is true also for the olefinic carbon atoms (for detailed assignment see below) and for the allylic carbon atoms which are reported by others[56] to give resonance signals around 27.32 ppm.

(ii) On this basis all the signals for 18:3 (6,9,12) were easily assigned and it was then not difficult to assign a signal to the W4 carbon atom in all the W6 acids/esters. (Although acids and esters do not give identical signals they are unlikely to be significantly different for the

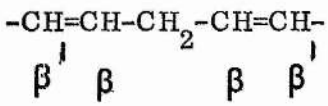
W1-W4 carbon atoms). It is then possible, from these four acids/esters to get a rough value for the influence of a cis double bond on the β, γ, δ and ϵ carbon atoms and to use these along with values previously observed for stearic acid, arachidic acid and their methyl esters to determine the remaining assignments. Once this has been done more refined values for the influence of the double bond on neighbouring carbon atoms can be measured and these are given in Table 9. It is of interest to compare these with values for the effect of a triple bond (Table 9). The triple bond exerts an ' α effect' of -10.96 while that of the double bond is only -2.51. The subsequent effects on β, γ, δ and ϵ carbon atoms are also correspondingly lower for the double bond.

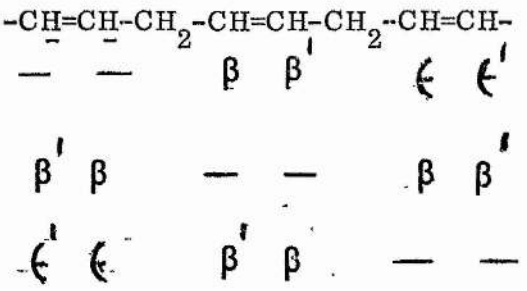
(iii) To allocate the olefinic signals between the olefinic carbon atoms it is necessary to use information from the series of octadecenoic acids (Charles M. Scrimgeour - private observation). With these acids there are two olefinic signals except for the Δ12 (129.94 ppm) and Δ13 (129.90 ppm) acids. Using the mean value (129.92) the other olefinic signals can be given a value representing the difference between the observed value and the mean value (129.92) which must represent the olefinic signal undistrubed by COOH or CH_3.

Isomer	Δ 6	Δ 7	Δ 8	Δ 9	Δ 10	Δ 11	W 3
C(n)/Wm	-0.91	-0.47	-0.27	-0.14	-0.09	-0.03	+1.62
C(n + 1)Wm + 1	+0.71	+0.39	+0.25	+0.17	+0.08	+0.04	-0.53

In addition, following the successful treatment of the acetylenic

acids, we assigned terms such as those shown below to indicate the influence of a double bond on nearby olefinic carbon atoms.





For example the signals for the olefinic carbons in linoleic acid will be given by :

C(9) $129.92 - 0.14 + \beta'$

C(10) $129.92 + 0.17 + \beta$

C(12) $129.92 + 0.00 + \beta$

C(13) $129.92 + 0.00 + \beta'$

Since these have to fit the observed values of 128.08, 128.24, 130.01 and 130.20 ppm it is possible to derive values of β and β^1. These values obtained from our six polyenoic acids are summarised in Table 10 .

TABLE 8 Allocation of resonance signals (ppm downfield from TMS) for olefinic acids (esters)

Acids	1*	2	3	4	5	6	7	8	9	10
18:1 (W9)	180.55	34.24	24.80	29.22	29.22	29.22	29.83	27.31	129.78	130.09
18:2 (W6)	180.56	34.24	24.78	29.21	29.21	29.21	29.72	27.32	130.01	128.24
18:3 (W3)	180.39	34.20	24.79	29.23	29.23	29.23	29.71	27.32	130.17	127.94
20:3 (W6)	179.87	34.04	24.66	28.92	28.92	29.38	27.22	130.14	127.94	25.69

Acids	11	12	13	14	15	16	17	18	19	20
18:1 (W9)	27.31	29.83	29.47	29.68	29.47	32.06	22.80	14.13	-	-
18:2 (W6)	25.77	128.08	130.20	27.32	29.48	31.67	22.69	14.08	-	-
18:3 (W3)	25.75	128.33	128.33	25.68	127.28	131.88	20.67	14.31	-	-
20:3 (W6)	128.26	128.38	25.69	127.71	130.43	27.22	29.38	31.56	22.59	14.04

* Nos. 1-20 are carbon numbers

contd. overleaf.

TABLE 8 contd.

Methyl Esters	1*	2	3	4	5	6	7	8	9	10
18:1 (W9)	173.88 51.21	34.12	25.08	29.28	29.28	29.28	29.90	37.32	129.78	130.02
18:3 (W6)	173.83 51.31	33.99	24.70	29.23	26.96	129.60	128.38	25.74	128.14	128.45
20:1 (W9)	173.93 51.22	34.12	25.09	29.46	29.46	29.46	29.59	29.46	29.91	27.34
20:2 (W6)	174.06 51.29	34.13	25.04	29.38	29.38	29.51	29.51	29.38	29.75	27.31
20:3 (W3)	173.84 51.19	34.09	25.09	29.42	29.42	29.60	29.60	29.42	29.79	27.37

Methyl Esters	11	12	13	14	15	16	17	18	19	20
18:1 (W9)	27.32	29.83	29.46	29.68	29.46	32.07	22.79	14.11	-	-
18:3 (W6)	25.74	127.74	130.42	27.33	29.44	31.64	22.66	14.07	-	-
20:1 (W9)	129.88	129.88	27.34	29.91	29.46	29.59	29.46	32.08	22.81	14.12
20:2 (W6)	130.13	128.07	25.73	128.07	130.13	27.31	29.51	31.64	22.66	14.08
20:3 (W3)	130.28	127.87	25.74	128.33	128.33	25.74	127.31	131.86	20.66	14.30

* Nos. 1-20 are carbon numbers

TABLE 9

Changes in chemical shift of CH_2 groups (29.80 in acids and 29.84 in esters) produced by functional groups

**		α	β	γ	δ	ϵ
CH_3 (14.13)		- 7.01	+2.26	-0.31	-	-
COOH (180.60)		+ 4.43	-5.00	-0.58	-0.42	0.24
$COOCH_3$ (174.04) 51.26		+ 4.34	-4.73	-0.48	-0.39	-0.20
-C≡C- (80.19)		-10.96	-0.56	-0.84	-0.53	-0.16
	*	-10.73	-0.30	-0.65	-0.49	-0.09
-CH=CH- (129.92)		- 2.51	-0.05	-0.40	-0.20	-0.05
	*	- 2.14	-0.19			0.05

** These values are quoted from the paper by Gunstone et al except for the last line which is based on our assignments in Table 8. These are subject to correction on the basis of additional information being gathered on other olefinic acids (esters).

* The upper line refers to CH_2 and lower line to CH_3.

TABLE 10

Effect of (cis) olefinic centres on the resonance signals of other olefinic carbon atoms

	β	β'
18:2 W6	-1.85	+0.23
	-1.84	+0.28
20:2 W6	-1.85	+0.21
	-1.89	+0.24
AVGE	-1.86	+0.24
	ϵ	ϵ'
18:3 W6	-0.39	+0.35
	-0.32	+0.26
20:3 W6	-0.37	+0.25
	-0.35	+0.27
AVGE	-0.36	+0.38
18:3 W3	-0.29	+0.15
	-0.25	+0.10
20:3 W3	-0.23	+0.15
	-0.22	+0.08
AVGE	-0.25	+0.12

EXPERIMENTAL

EXPERIMENTAL

1. GENERAL PROCEDURES

(i) Solvents

All solvents were reagent grade. Petrol ether was distilled and the fraction boiling between 40° and 60°C was used. Benzene, carbon tetrachloride, acetone, methanesulphonyl chloride, triethylamine and thionyl chloride were redistilled before use.

Methanol was dried by Vogel's method . Diethyl ether and xylene were dried by (i) standing over calcium chloride overnight, (ii) decanting and distilling and (iii) storing over sodium wire. Chloroform was refluxed for one hour with phosphorous pentoxide and then distilled. Pyridine was refluxed for two hours with potassium hydroxide pellets before distillation and then the dry pyridine stored over potassium hydroxide.

(ii) Melting points

Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

(iii) Chromatographic procedures

Thin layer chromatography (TLC)

Analytical TLC was carried out on glass plates coated with 0.25 mm layer (wet thickness) of silica gel G. For silver ion TLC silver nitrate (15% W:W) was added to silica gel G. The plates were activated for 1 hr at 120°C. For separation on a preparative scale, plates (20 cm x 20 cm) with a silica gel layer of 1 mm (wet thickness) were activated for 2 hr at 120°C.

Mixtures of petroleum and diethyl ether were used as developing solvents. Abbreviations such as PE 20 indicate mixtures of petroleum and ether in a ratio of 80 to 20 (v:v).

Components separated on analytical TLC plates were generally detected by spraying with an ethanolic solution of phosphomolybdic acid (10%) followed by heating for ca. 10 min at 120°C.

Preparative plates were sprayed with an ethanolic solution of 2^1, 7^1- dichlorofluoroscein (0.2%) and viewed under ultraviolet light. Bands were marked and scraped off, extracted with ether and filtered. The ether was evaporated and the weight of each residue was recorded. The order of the separated bands is designated 1, 2, 3 etc. according to their decreasing Rf values.

Column Chromatography

Compounds were purified by column chromatography whenever necessary using columns of appropriate dimension (40 x 1" for 2-5g, 48 x 2" for 10-20g quantities). The stationary phase was sorbsil and petroleum-ether mixtures were used as eluting solvents. The columns were packed in the presence of solvent.

Gas liquid chromatography (GLC)

Gas liquid chromatography was carried out with a Pye 104 chromatograph fitted with a flame ionisation detector. The columns used were of stainless steel or glass (1.52 m x 4.75 mm id) and contained diethylene glycol succinate (DEGS 20%) coated on Chromosorb AW - DMCS (dimethyl chlorosilizane) 80-100 mesh. The number of theoretical plants

was about 1700 which deteriorated slightly with use. Nitrogen was used as carrier gas. The flow rate was usually 60 ml/min. The normal oven temperature was 180-190°C. The operating conditions were varied according to the nature of the substance under consideration.

The composition of a mixture was estimated on the basis of peak heights and retention distances. Saturated straight chain methyl esters were used as external (or internal) standards for the determination of ECL (equivalent chain length). Apparent inconsistencies in ECL values reported in the text were due to deterioration of the polar liquid phase with use. Whenever possible the GLC behaviour of a reaction product was compared with that of an authentic sample run consecutively.

(iv) Spectroscopic procedures

Infrared (IR)

IR spectra were recorded on Perkin-Elmer 237 and 257 spectrometers. Samples were run either as films between sodium chloride discs or as ca. 1% solutions in carbon tetrachloride or carbon disulphide using sodium chloride cells of 1 mm path length.

Nuclear magnetic resonance (NMR) (^{1}H)

Spectra were recorded at 100 MHz on a Varian HA 100 instrument using ca. 15% solutions in carbon tetrachloride which contained 3% tetramethylsilane as internal standard.

All shift values are given in ppm downfield from tetramethylsilane (δ=0). Coupling constants are given in Hz. The following

abbreviations are used for describing the appearance of NMR signals : s(singlet), b.s. (broad singlet), app.d. (apparent doublet), t(triplet), and m(multiplet).

Nuclear magnetic resonance (NMR) (^{13}C)

Spectra were recorded at a field of 18.7 KG on a Varian CFT - 20 ^{13}C NMR spectrometer. 1M solutions in $CDCl_3$ (10 mm tubes) with TMS as internal standard were used. The spectra were noise decoupled and were run in the range 0.200 ppm and, in some cases, 0-50 ppm to give an expansion of the 29 ppm region.

(v) Mass Spectrometry (MS)

Mass spectra were recorded with direct-probe insertion of samples into the source of an AE1 MS 902 mass spectrometer. The source pressure was 2×10^{-7} torr and the temperature about $200^{o}C$. The ionisation potential was 17 or 70 ev with respective ion currents of 100 and 500 uA.

Gas chromatograph mass spectrometry was used whenever necessary.

(vi) GENERAL CHEMICAL PROCEDURES

Esterification

(a) From acids

For small scale methylation the fatty acid (50 mg) was refluxed for 30 min with a 2% solution of sulphuric acid in dry methanol (2 ml). A 2% solution of boron trifluoride-methanol complex in dry methanol (10 ml) was also sometimes used. The cooled reaction mixture was poured into

brine (2 ml) and extracted with ether (2 x 2 ml). The ether extracts were pooled and dried.

Large scale methylation (20g) was carried out by refluxing the acid for 1 hr with methanolic sulphuric acid (75 ml, 0.5 M). The cooled reaction mixture was poured into brine (40 ml) and extracted with ether (2 x 100 ml). The ether extracts were washed with aqueous sodium hydrogen carbonate (5%, 2 x 20 ml) and brine (2 x 20 ml), combined and dried.

b) From triglycerides

Small scale transesterifications of triglycerides were carried out using the same procedure as for the small scale esterifications of acids, except that the triglyceride was dissolved in dichloromethylene (1 ml) and refluxed for 2 hr with methanolic sulphuric acid (2% sulphuric).

Hydrolysis

Small scale hydrolyses of esters (1g) were carried out with ethanolic potassium hydroxide (10 ml, KOH 0.56g, water 0.5 ml and ethanol 9.5 ml) for 1 hr at reflux temperature. The reaction mixture was poured into sulphuric acid (4 ml, 0.5M) and brine (20 ml, 5%) and the acid was extracted with petrol (3 x 20 ml). The combined petrol layers were washed with water (20 ml) and dried.

Large scale hydrolysis was carried out in the following manner : a mixture of the oil (500g), potassium hydroxide (115g), water (125 ml) and ethanol (400 ml) was prepared in a flask (2 l) and refluxed for 1 hr. The flask was then set aside to cool in ice. During the reflux sulphuric acid

solution [20%, 200 ml conc. sulphuric added to crushed ice and water (1 l)] was prepared. The reaction mixture, followed by the acid solution (600 ml), was added in to crushed ice (500 ml) in a separating funnel (2 l). The mixture was shaken thoroughly to ensure all the potassium salts were neutralised, and the two layers were allowed to separate. The lower layer was drawn off into another separating funnel and extracted with ether (200 ml). The ether extract was added to the organic layer from the first separation and the mixture extracted with water (2 x 100 ml). The organic phase was transferred to a weighed rotary evaporator flask and benzene (200 ml) was added (this was done in a fume cupboard). The solvent was removed on a rotary evaporator and the weight of the acids obtained were recorded.

Trimethylsilylation

The hydroxy compound (5 mg), dissolved in dry pyridine (1 ml) was stirred (magnetic stirrer) for 1 min with hexamethyldisilizane (0.2 ml) and trimethylchlorosilane (0.1 ml). The solution was allowed to stand for 5 min and then poured into petrol (2 ml). This mixture was washed with water (4 x 2 ml). The petrol layer was then dried and evaporated for examination by GLC.

Preparation of methanesulphonates (mesylation)

A dry pyridine solution (500 ml) of alcohol (20g), usually prepared by reduction of the corresponding pure (99%) methyl ester, was placed in a three necked flask (500 ml) equipped with a mechanical stirrer and dropping funnel and was chilled in an ice-bath during the slow addition of

methanesulphonyl chloride (20g, 1:2 mole ratio of alcohol to mesyl chloride) over 1 hr. After stirring for a further 2 hr at room temperature, ice and hydrochloric acid (2 M, 200 ml) were added slowly and the mesylate (26g, 90%) was recovered from an ether extract (3 x 150 ml) which had been washed with sulphuric acid (1M, 150 ml), water (100 ml), potassium hydrogen carbonate (1% aqueous, 200 ml) and water (100 ml).

An IR spectrum of the mesylate confirmed the absence of the O-H stretching at 3340 cm^{-1} and the presence of bands at 1125, 1290 and 1315 cm^{-1} associated with S=O stretching.

Reduction with lithium aluminium hydride

The ester (20g) in dry ether (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (4g) in dry ether (250 ml) in a 3 necked flask (1 l). After stirring for a further 30 min the excess of hydride was carefully destroyed with wet ether (200 ml) followed by water (200 ml). After addition of sulphuric acid (1M, 300 ml), the product was extracted with ether (3 x 150 ml).

Reduction of oxo esters to hydroxy esters with sodium borohydride

Sodium borohydride (30 mg) was added to a stirred solution of the methyl oxo ester (30 mg) in methanol (3 ml) and left to react at room temperature. After 30 min the mixture was diluted with water, acidified with hydrochloric acid (2M, 2 ml) and the product was extracted with ether (2 x 2 ml).

von Rudloff oxidation

A stock aqueous solution of sodium metaperiodate (20.86 g,

0.0975 M) and potassium permanganate (0.4g; 0.0025 M) and another of potassium carbonate (2% or 2.5g/l) were prepared.

The potassium carbonate solution (5 ml) and the oxidant solution (30 ml) were added to the unsaturated material (100 mg) dissolved in distilled t-butanol* (10 ml). The mixture was stirred overnight at room temperature. After the excess oxidant had been destroyed with sulphur dioxide the solution was made alkaline (aq. KOH) and butanol was removed carefully under vacuum. The residue was acidified (2 M Hcl), saturated with sodium chloride solution and extracted with ether (3 x 25 ml). The combined ether layers were then washed (2 x 20 ml) and dried and the resulting monobasic and dibasic acids were esterified (boron trifluoride methanol) for GLC examination.

*Commercial t-butanol (700 ml) was first oxidised with aqueous potassium permanganate (6%, 50 ml) by stirring together at 60°.

2. Chain-extension by anodic synthesis.

2.1. Preparation of starting materials.

Pure (99%) decanoic, undecanoic, dodecanoic, tetradecanoic, undec-10-ynoic, dodec-8-ynoic, octadec-cis-5-enoic, octadec-cis-6-enoic, octadeca-cis-9, cis-12-dienoic (linoleic), octadeca-cis-6, cis 9, cis-12-trienoic (γ-linolenic) and octadeca-cis-9, cis-12, cis-15-trienoic (α-linolenic) acids were available in the laboratory.

(i) Pure oleic acid

Technical oleic acid (380g, 75% was purified by the following processes : (i) interaction with urea (200g) and methanol (600 ml) to remove an adduct rich inpalmitic acid, (ii) interaction with urea (850g) and methanol (2 l) to obtain an adduct rich in oleic acid (84%) (iii) recrystallisation of the adduct from methanol (1 l), (iv) interaction of the product (180g, 89%) with urea (100g) and methanol (500 ml) to give oleic acid (95%) in the mother-liquor and (v) final crystallisation from petrol (10 vol) at -32° to give pure oleic acid (50g, 100%).

(ii) Methyl hydrogen succinate

Succinic anhydride (>99% pure as diester by GLC, 100g, 1 mole) was refluxed with methanol (80 ml) for 45 min. The excess methanol was removed on a rotary evaporator and the residue taken up in a petroleum ether/ether (1:1) mixture. Crystals of methyl hydrogen succinate which separated at room temperature were filtered and dried (76g, 58%, m.p. 55°-57°, lit 58° [57]). On TLC (petroleum ether, ether, acetic acid 50:50:1)

this product showed up as a brown spot with iodine vapours and there was no evidence of any diester. The half-ester gave NMR signals at 2.64 [4H, m-$(CH_2)_2$-], 3.70 [3H, s, -$COOCH_3$] and 11.5 δ [1H, s, -COOH].

(iii) Methyl hydrogen adipate[58]

A mixture of adipic acid (99% pure, 146g, 1 mole), dimethyl adipate (100g, 0.58 mole), di-n-butyl ether (50 ml), conc. hydrochloric acid (25 ml) and methanol (60 ml) was refluxed for 4 hr with no second addition of methanol as recommended in the original method. After removing excess solvent under water pump pressure the mixture was distilled using a short Vigreux column under oil pump pressure. After recovering dimethyl adipate (167g, b.p. 90-100°C/4 mm), a mixture of diester and half-ester (100g, b.p. 100-140°) was obtained. This was redistilled to obtain pure methyl hydrogen adipate (90g, 56%, b.p. 125-135°C/0.8 mm, lit[59], 158°/10 mm). It was checked for purity by TLC (see methyl hydrogen succinate).

Methyl hydrogen adipate gave NMR signals at 1.64, J=4Hz [4H, m, -$(CH_2)_2$-], 2.28 [2H, app. d, -CH_2COOCH_3], 2.34 [2H, app. d, $HOOCCH_2$-], 3.60 [3H, s, -$COOCH_3$] and 11.6 δ [1H, br. s, -COOH] and dimethyl adipate at 1.62, J=4Hz [4H, m, -$(CH_2)_2$-], 2.28 [4H, m, $H_3COOCCH_2$-] and 3.62 [6H, s, -$COOCH_3$].

(iv) Methyl hydrogen suberate

Suberic acid (200g) was heated with di-n-butyl ether (70 ml) and conc. hydrochloric acid (30 ml). After all the acid had dissolved, the mixture was cooled and methanol (60 ml) was added and refluxed. This

mixture was stirred for more efficient esterification whilst it was refluxed (4 hr, oil bath). The half-ester was isolated by distillation (see methyl hydrogen adipate). Dimethyl suberate (75g, b.p. 120-140°/8 mm, lit. 120°/6 mm[59]), a mixture of diester and half-ester (37g, b.p. 140-160°) and methyl hydrogen suberate (76g, 40%, b.p. 160-170°/3 mm, lit. 185-186°/18 mm[60]) were obtained.

The half-ester showed NMR signals at 1.38 and 1.64 [8H, m, $-(CH_2)_4-$], 2.31 [2H, m, $-CH_2COOCH_3$], 2.35 [2H, m, $-CH_2COOH$], 3.66 [3H, s, $-COOCH_3$] and 11.20 δ [1H, b.s, $-COOH$].

(v) Methyl hydrogen azelate

Techincal azelaic acid (450g, 50% pure), crystallised three times from acetone at room temperature, gave the pure acid (130g, 99% pure by GLC, ECL of diester 17.3).

Pure azelaic acid (188g, 1 mole), dimethyl azelate (100g, 0.58 mole), di-n-butyl ether (50 ml) and conc. hydrochloric acid (20 ml) were refluxed till the mixture was homogeneous. The mixture was cooled, methanol (60 ml) added, and the mixture refluxed for 4 hr. The half-ester was then isolated by distillation (see methyl hydrogen adipate). Dimethyl azelate (110g, b.p. 140°/12 mm, lit.[59] 128°/5 mm) was obtained first followed by the half-ester (90g, 40%, b.p. 155°-160°/oil pump lit.158-159.5/3 mm)[61] TLC showed this to be free of diester.

2.2. Apparatus and General procedure

Apparatus 1 (fig 1 page 70) consisted of a cylindrical glass cell (two sizes were used : 15 and 6 cm in height with a diameter of 3 cm), containing two parallel platinum-foil electrodes (2.0 x 1.5 cm) kept 3 mm apart. The cell was cooled in ice-water and a thermometer suspended with the bulb near to the plates measured the internal temperature, which was kept below 50°. When stirring of the electrolyte was necessary (especially when solid esters were formed in the reaction) a glass stirrer was used.

Each electrode was spot-welded to a short piece of platinum wire sealed into the end of a length of glass tubing. Electrical contact was made by dipping two copper leads into the two tubes through small pools of mercury. The power was supplied from a 180 volt D.C. source (Fig 2).

The solvent used was methanol, containing enough sodium hydride (a 50% dispersion in oil MW 48 instead of metallic sodium) to neutralise 2% of the acids. Electrolysis was continued until the electrolyte became distinctly alkaline (pH 8-9).

During electrolysis the direction of the current was reversed periodically, and especially when the current began to fall towards the end of the reaction. An insoluble product usually formed on the electrodes, in varying amounts depending on the acids used. This was not always completely removed by reversing the current, and cleaning of the electrodes failed to make any appreciable difference, so that for the last 20% of an electrolysis the current had to be reduced to keep the cell temperature down to below 50°.

APPARATUS 1

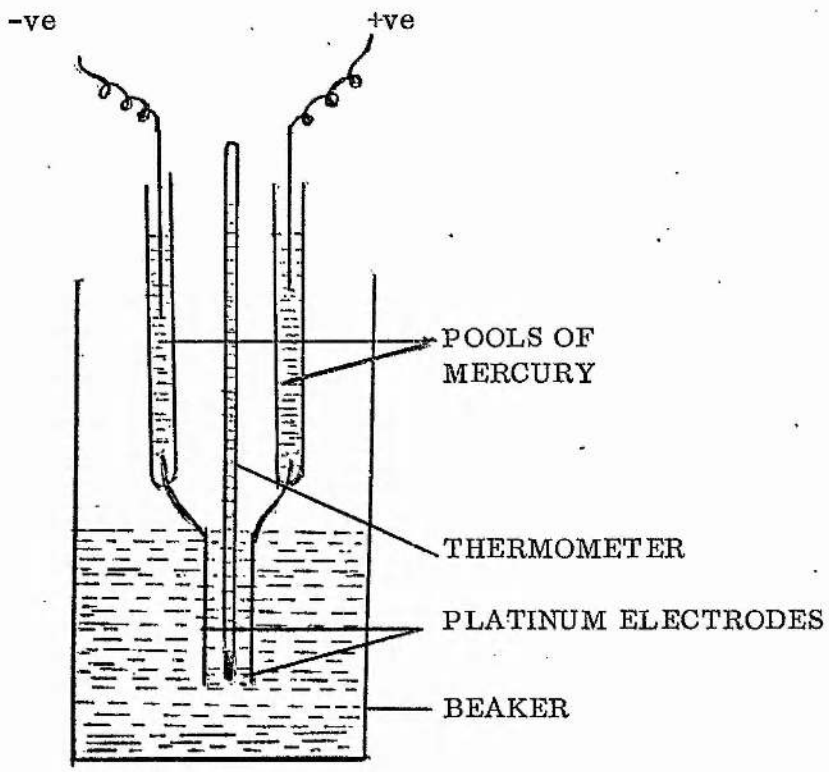


FIG.1. ELECTROLYSIS CELL

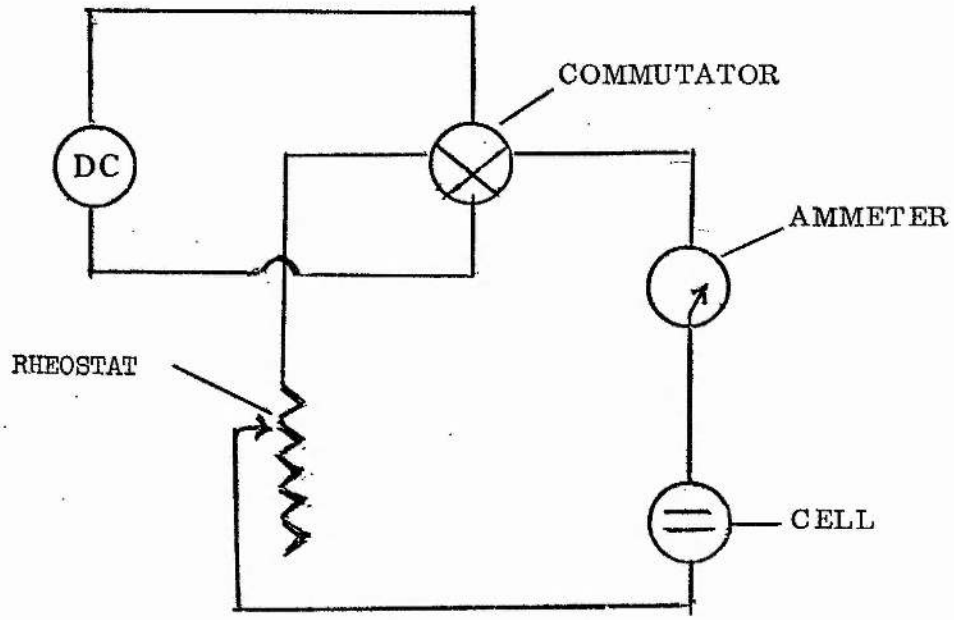


FIG. 2. ELECTRICAL CIRCUIT

APPARATUS 2

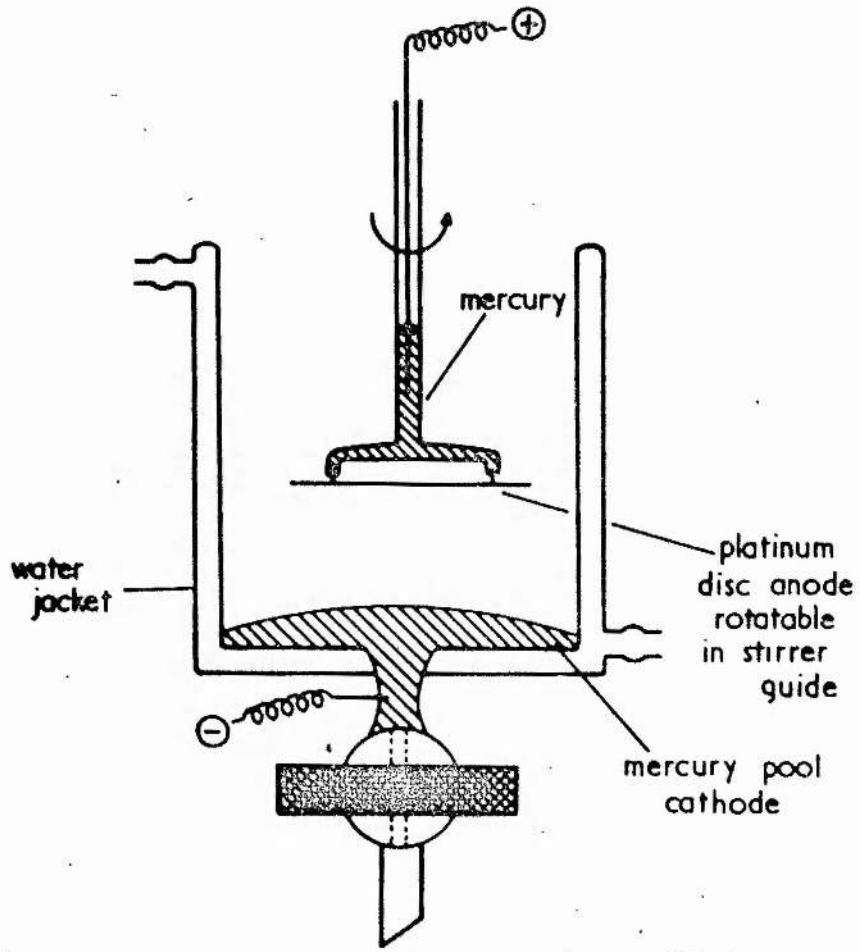


FIG. 3 THE DINH-NGUYEN CELL.

After electrolysis, the insoluble product was filtered off, the filtrate neutralised with a few drops of acetic acid, most of the methanol removed under reduced pressure and the residue purified by column chromatography. Sorbsil (200g) was sufficient for 5g of reaction product. Hydrocarbons were eluted with PE 2 followed by nonoester eluted with PE 5 or PE 10 and diester eluted with ether.

Apparatus 2 (Fig 3 page 71) consisted of a cylindrical double-walled glass vessel (with an inlet and outlet for water circulation) containing mercury at the bottom which served as the cathode, and a stirrer (a glass tube filled with mercury and open on top) with two arms below. A platinum sheet $1\frac{1}{4}$ x 1" (0.005" thick) was mounted horizontally by spot-welding, to two short pieces of platinum wire sealed into the two arms of the stirrer. Electrical contact was made with the anode with a lead dipping into the mercury in the stirrer and with the cathode through a platinum wire into the stem of the vessel (which was filled with mercury) just above the tap. The anode was placed at a distance of 1 cm above the level of mercury. The stirrer was attached by a pulley to an electric motor which was controlled by a variac. The power was supplied from a 180 volt D.C. source with an ammeter which read up to 1 amp.

The solvent was methanol or aqueous methanol, to which sodium hydride (a 50% dispersion in oil MW 48) was added to neutralise 10% of the acids. Electrolysis was continued until the current fell from 0.7 amp to 0.2 amp. The anode was rotated at a fairly high speed to bring about efficient stirring.

During the electrolysis an insoluble product usually formed on the anode (as in apparatus 1) in varying amounts depending on the acids used. Sometimes it became necessary to stop the electrolysis and clean the anode.

After electrolysis, the insoluble product was filtered off and the filtrate neutralised with a few drops of acetic acid, most of the methanol removed under reduced pressure and the residue purified by column chromatography (as detailed in apparatus 1).

2.3. ANODIC SYNTHESES

(i) Methyl eicos-cis-11-enoate

(a) Pure oleic acid (1.5g, 5 mmoles), methyl hydrogen succinate (4.0g, 30 mmoles) and sodium hydride (35 mg of a 50% dispersion in oil equivalent to 2% of total acid) in methanol (30 ml) were electrolysed (Apparatus 1, current 0.4-0.5 amp) with frequent inversion of polarity for 4.5 hr at 40-50°C. The electrolysis was stopped when the solution became distinctly alkaline. The reaction mixture was acidified (acetic acid) and excess methanol distilled off. The residue (4g) was purified by column chromatography (25 cm column of Sorbsil). The products were (i) hydrocarbon [(250 mg ; probably a mixture of 17:2 (1,8) and 34:2 (9,25)], (ii) methyl eicosenoate (700 mg, 46%, 96% pure, ECL 20.4) and (iii) diester (2g, a mixture of dimethyl succinate and adipate).

The 20:1 ester gave NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.28 [-$(CH_2)_n$-], 1.96-2.01 [4H, app. d, -CH=CHCH_2-], 2.21 [2H, t, -CH_2 $COOCH_3$], 3.57 [3H, s, -$COOCH_3$] and 5.26 δ [2H, m, -CH=CH-].

(b) Oleic acid (1.43g, 5.0 mmoles) and methyl hydrogen succinate (4.0g, 30 mmoles), sodium hydride (168 mg) were electrolysed in methanol (45 ml) for 3.5 hr (Apparatus 2, at a current of 0.7 amp falling to 0.2 amp after 3 hr). Methanol was removed as before after the solution had been acidified with acetic acid. The residue was purified by column chromatography and the products were again (i) hydrocarbon (150 mg) (ii) methyl eicosenoate (800 mg, 50%, 98%pure) and (iii) diester (3.7g).

Oxidative cleavage (von Rudloff oxidation, see general chemical procedures) confirmed the position of the double bond at $\triangle$11. The cleaved ester gave two peaks on GLC which corresponded to methyl nonanoate and dimethyl undecanedioate.

(ii) Methyl docos-cis-13-enoate

Oleic acid (1.5g, 5.0 mmoles) and methyl hydrogen adipate (4.8g, 30 mmoles) were electrolysed for 3.5 hr in methanol as detailed in the preparation of the 20:1 ester (Apparatus 2). The following products were separated by column chromatography; (i) hydrocarbon (400 mg), (ii) methyl docos-cis-13-enoate (100 mg, 6%, Ecl 22.4) and (iii) diester (2.5g).

(iii) Methyl eicosa-cis-11, cis-14-dienoate

Linoleic acid (10.9g, 35 mmoles, > 99% pure) and methyl hydrogen succinate (22.0g, 140 mmoles) were electrolysed in methanol (100 ml) for 54 hr (Apparatus 2) using the same conditions as for the 20:1 ester. The total product (27g) when purified by column chromatography gave (i) hydrocarbon (2.5g) (ii) methyl docosa-cis-11, cis-14-dienoate (4.5g, 37%, 84% pure, ECL 23.0) and (iii) diester (13.2g). The 20:2 ester was contaminated with some methyl linoleate.

Methyl docosa-cis-11, cis-14-dienoate gave NMR signals at 0.91 [3H, t, CH_3CH_2-], 1.29 [-$(CH_2)_n$-], 2.00-2.06 [4H, app. d, -CH_2CH=CH-], 2.22 [2H, t, -CH_2COOCH_3], 2.72 [2H, t, =CHCH_2CH=], 3.58 [3H, s, -$COOCH_3$] and 5.28 δ [4H, m, -CH=CH-].

(iv) Methyl docosa-cis-13, cis-16-dienoate

Linoleic acid (4.2g, 15 mmoles) and methyl hydrogen adipate (9.6g, 60 mmoles) were electrolysed (Apparatus 2) in methanol (90 ml) for 18.5 hr. The total product (15g) on column purification yielded (i) hydrocarbon (1.0g), (ii) methyl docosadienoate (3.0g, 58%, 95% pure, ECL 23.0) and (iii) diester (4.0g).

This preparation was repeated on a larger scale when linoleic acid (11.5g, 40 mmoles) and methyl hydrogen adipate (25.7g, 160 mmoles) were electrolysed in methanol (120 ml) for 42 hr. The product yielded (i) hydrocarbon (2.4g), (ii) methyl docosa-cis-13, cis-16-dienoate (6.4g, 50%, 94% pure, Ecl 23.0) and (iii) diester (6.9g).

This 22:2 ester gave the same NMR signals as the 20:2 ester already reported.

(v) Methyl eicosa-cis-8, cis-11, cis-14-trienoate

γ-Linolenic acid (5.3g, 19 mmoles) and methyl hydrogen succinate (10.0g, 76 mmoles) were electrolysed for 27 hr (Apparatus 2). Purified by column chromatography the total product gave (i) hydrocarbon (655 mg) (ii) monoester (1.4g) and (iii) diester (5.7g).

GLC of the monester (ECL 21.5) indicated that it was not homogeneous. The main component had an ECL of 21.5 and a shoulder peak at 21.2. On prep TLC (PE 20) two merging bands were observed but these were better separated with silver ion chromatography to give component 1 (233 mg, ECL 21.1) and component 2 (911 mg, 20% yield based on γ 18:3 ; ECL 21.4).

Component 1 (possibly a cyclised product) gave NMR signals at [0.88 t, CH_3CH_2-], 1.30 [-$(CH_2)_n$-] 1.53 and 1.62 [2 sets of m], 2.00-2.06 [app. d, -CH=CHCH_2-], 2.23 [m, CH_2COOCH_3], 2.74 [t, -CH=CHCH_2CH=CH-], 3.16 [s], 3.26 [m], 3.58 [s, -COOCH_3] and 5.32 δ [m, -CH=CH-].

The IR spectrum showed no evidence of a trans double bond.

Component 2 is probably the expected 20:3 (8c 11c 14c) ester on the basis of its NMR signals at 0.89 [3H, t, CH_3CH_2-], 1.32 [-$(CH_2)_n$-], 2.00-2.07 [4H, app. d, -CH=CHCH_2-], 2.22 [2H, t, -CH_2COOCH_3], 2.76 [4H, t, -CH=CHCH_2CH=CH-], 3.58 [3H, s, -COOCH_3] and 5.30 δ [6H, m, -CH=CH-].

This spectrum was similar to that of the 18:3 (6c 9c 12c) ester. The ir spectrum showed no evidence of a trans double bond.

(vi) Methyl eicos-cis-7-enoate

Octadec-cis-5-enoic acid (1.5g, 5.3 mmoles) and methyl hydrogen succinate (4.0g) were electrolysed in methanol for 10 hr (Apparatus 2). The total product (3.0g), purified by column chromatography, gave (i) hydrocarbon (260 mg) (ii) monoester (350 mg, 21%) and (iii) diester (2.5g).

The monoester was homogeneous on GLC (ECl 20.3) and gave one band on prep TLC, but on silver ion plate two merging bands were observed. Component 1 (90 mg, ECL 20.2 which may be a cyclised product gave NMR signals at 0.88 [t, CH_3CH_2-], 1.26 [-$(CH_2)_n$-], 1.64 [m] 1.97-2.02

[app. d, CH_2-CH=CH-], 2.22 [m, CH_2COOCH_3], 3.12 and 3.26 [2 sets of m] and 3.58 [3H, s, -$COOCH_3$], and 5.28 δ [m, -CH=CH-].

An IR spectrum of this component did not show any evidence of a trans double bond.

Component 2 (280 mg, 17%, ECL 20.3) was probably the expected methyl eicos-cis-7-enoate on the basis of its NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.26 [-$(CH_2)_n$-], 1.96-2.02 [4H, app. d, -CH=CHCH_2-], 2.22 [2H, t, -CH_2COOCH_3], 3.58 [3H, s, -$COOCH_3$] and 5.26 δ [2H, m, -CH=CH-].

An IR spectrum of the monoester did not show any evidence of a trans double bond.

(vii) Methyl eicos-cis-8-enoate

Octadec-6-enoic acid (1.7g, 6 mmoles) and methyl hydrogen succinate (4.1g, 28 mmoles) were electrolysed in methanol (30 ml) for 11 hr (Apparatus 2). The total product, purified by column chromatography gave (i) hydrocarbon (205 mg), (ii) monester (372 mg) and (iii) diester (2.0g).

The monester did not separate on prep TLC, but gave two clear bands on a silver ion plate. Component 1, possibly a cyclic product, (105 mg, ECL 20.3) gave NMR signals at 0.88 [t, CH_3CH_2-], 1.25 [-$(CH_2)_n$-], 2.20 [m, -CH_2COOCH_3] 3.24 [m] and 3.58 δ [3H, s, -$COOCH_3$]. There was no evidence of olefinic protons.

Component 2 (58 mg, 3%, ECL 20.5) was probably the expected 20:1 (7c) ester and gave NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.25

$\left[-(CH_2)_n-\right]$, 1.96-2.00 $\left[4H,\ app.\ d,-CH=CHCH_2-\right]$, 2.22 $\left[2H,t,-CH_2COOCH_3\right]$, 3.58 $\left[3H,s,-COOCH_3\right]$ and 5.26 δ J=6Hz $\left[2H,m,-CH=CH-\right]$.

An IR spectrum showed no evidence of a trans double bond.

(viii) Methyl octadec-16-ynoate

Dodec-10-ynoic acid (2.4g, 12.4 mmoles) and methyl hydrogen suberate (9.4g, 50 mmoles) were electrolysed in methanol (50 ml) for 18 hr (Apparatus 2). The total product (12.7g) when purified by column chromatography yielded (i) hydrocarbon (774 mg) (ii) monoester (1.86g, 51%, ECL 21.3 94% pure) and (iii) diester (4.0g).

Methyl octadec-16-ynoate gave NMR signals at 0.94 $\left[3H,s,CH_3-\right]$, 1.24 $\left[-(CH_2)_n-\right]$, 2.15 $\left[2H,m,-C\equiv CCH_2-\right]$, 2.22 $\left[2H,t,-CH_2COOCH_3\right]$, and 3.58 δ $\left[3H,s,-COOCH_3\right]$.

(ix) Methyl octadec-17-ynoate

Undec-10-ynoic acid (10g, 55 mmoles) and methyl hydrogen azelate (44.4g, 220 mmoles) were electrolysed in methanol (120 ml) for 40 hr (Apparatus 2). The total product when purified by column chromatography yielded (i) hydrocarbon (4.3g), (ii) methyl octadecynoate (8.6g, 53%, ECL 21.5 96% pure) and (iii) diester (21.4g). The monoester (8.4g) was crystallised from petrol to give pure ester (5.2g, 99%, m.p. 32°.

The monoester gave NMR signals at 1.27 $\left[-(CH_2)_n-\right]$, 1.78 $\left[1H,t,CH\equiv C-\right]$, 2.15 $\left[2H,m,CH\equiv CCH_2-\right]$, 2.22 $\left[2H,t,-CH_2COOCH_3\right]$ and 3.58 δ $\left[3H,s,-COOCH_3\right]$.

Undec-10-ynoic acid gave NMR signals at 1.34 $\left[-(CH_2)_n-\right]$,

1.77 [1H, t, $CH\equiv C-$] , 2.14 [2H, m, $CH\equiv CCH_2-$] , 2.31 [2H, m, CH_2COOH] and 12.03 δ [1H, s, $-COOH$] .

(x) Methyl tridecanoate

Undecanoic acid (9.6g, 52 mmoles) and methyl hydrogen succinate (27.5g, 208 mmoles, added in 2 lots, 13.7g at the start of experiment and 13.8g after 38 hr of electrolysis) were electrolysed for a total period of 76 hr (Apparatus 2) in methanol (120 ml). The total product (36.8g) when purified by column chromatography gave (i) hydrocarbon (2.3g) (ii) monoester (6.2g, 52%, ECL 13.0, 94% pure) and (iii) diester (19.7g). The monoester when crystallised from petrol (0^{o}) was 99% pure (5.2g, 44%, m.p. 41-42^{o} as acid, lit[1] 41.8)

(xi) Methyl pentadecanoate

Undecanoic acid (9.0g 48 mmoles) and methyl hydrogen adipate (37.5g, 234 mmoles) were electrolysed in methanol (120 ml) for 54 hr (Apparatus 2). The total product when purified by column chromatography gave (i) hydrocarbon (1.6g), (ii) monoester (9.4g, 77%, ECL 15.0, 97% pure) and (iii) diester (14.0g). The monoester on crystallisation from petrol (0^{o}) was 99% pure (8.4g, 69%, m.p. 19-19.5^{o}, lit[1] 19.1^{o}, 52.5^{o} as acid).

(xii) Methyl heptadecanoate

Decanoic acid (4.6g, 26 mmoles) and methyl hydrogen azelate (11.3g, added in two lots as in the preparation of methyl tridecanoate) were electrolysed in methanol (70 ml) for 42 hr (Apparatus 2). The total product (29g) on purification by column chromatography gave

(i) hydrocarbon (1.2g) (ii) monoester (6.2g, 85%, ECL 17.0, 83% pure containing methyl decanoate 17%) and (iii) diester (14.0g). The monoester was crystallised in petrol (0^{o}) to obtain a 99% pure sample (5.0g, 68%, m.p. 28-29^{o}, lit[1] 29.7^{o}).

(xiii) Methyl nonadecanoate

Dodecanoic acid (4.5g, 23 mmoles) and methyl hydrogen azelate (18.2g, 90 mmoles, added in two lots as in the preparation of methyl tridecanoate were electrolysed in methanol (80 ml) for 20 hr (Apparatus 2). The total product purified by column chromatography gave (i) hydrocarbon (1.3g) (ii) monoester (5.8g, 84%, ECL 19.0, 90%pure) and (iii) diester (13.6g). The monoester was further purified by crystallisation from petrol at 0^{o} to a level of 99% purity (5.0g, 74%, m.p. 38-39^{o}, lit[1] 38.5^{o}).

(xiv) Methyl heneicosanoate

a) Tetradecanoic acids (1.14g, 5 mmoles) and methyl hydrogen azelate (5.1g, 20 mmoles) were electrolysed in methanol (30 ml) for 5.5 hr (Apparatus 1). The total product when purified by column chromatography gave (i) hydrocarbon (80 mg), (ii) monoester (1.3g, 79%, ECL 21.0, 94% pure) and (iii) diester (3.2g).

b) Tetradecanoic acid (9.52g, 40 mmoles) and methyl hydrogen azelate (32.73g, 160 mmoles) were electrolysed in methanol (120 ml) for 48 hr (Apparatus 2). The total product when purified by column chromatography gave (i) hydrocarbon (3.0g), (ii) monoester (12.0g, 92%, ECL 21.0, 94% pure) and (iii) diester (15.4g). The monoester was crystallised in petrol at room temperature and a purity of 99% was obtained

(10.2g, 78%, m.p. 75-75.5° as acid, lit[1] 75.2°).

(xv) Anodic syntheses involving oleic acid and $X(CH_2)_nCOOH$ X=Cl, OH or OAc, n=1 or 2

Oleic acid (2.8g, 10mmoles and W-chloro, hydroxy and acetoxy alkanoic acids (1:4 molar ratio) were each electrolysed in methanol (30 ml) for 15-20 hr (Apparatus 2). The reaction products (diluted with water (5 ml) and extracted with petrol (3 x 30 ml) were purified by prep TLC (petrol). Any polar bands obtained were rechromatographed (PE 30). Details of the products are summarised in Table 11 and its footnotes.

TABLE 11

PRODUCTS OF ANODIC SYNTHESES INVOLVING OLEIC ACID AND $X(CH_2)_nCOOH$

X = Cl, OH or OAc, n = 1 or 2

X	ACETIC ACID DERIVATIVES	PROPIONIC ACID DERIVATIVES
Cl	(i) Alkenyl chloride (17:1)[a] (ii) Unidentified polymeric material	(i) Alkenyl chlorides (17:1 and 19:1)[b] (ii) alkenol (17:1)[c]
OH	(i) hydrocarbon (ii) alkenols (17:1 and 18:1)[d]	(i) hydrocarbon (ii) methyl alkenyl ether (17:1)[e] (iii) alkenols (17:1 and 19:1)[f]
OAc	(i) hydrocarbon (ii) alkenyl acetates (17:1 and 18:1)[g] (iii) alkenols (17:1 and 18:1)[h]	-

a. Possibly heptadec-cis-8-enyl chloride (20%, Ecl 15.9)

b. Heptadec-cis-8-enyl chloride (30%, Ecl 15.8) and nonadec-cis-10-enyl chloride (20%, Ecl 17.7), NMR signals at : 0.88 [3H, t, CH_3CH_2-], 1.28 [-$(CH_2)_n$-], 1.96-2.00 [4H, app. d, -CH_2CH=CH-], 3.45 [2H, t, -CH_2Cl] and 5.26 δ [2H, m, -CH=CH-].

c. Heptadec-cis-8-enol (20%, ECL 18.5 ECL of TMS ether 15.6), infrared band at 3640 cm^{-1} (O-H stretching)

d. Heptadec-cis-8-enol (11%, ECL 18.4) and octadec-cis-9-enol (3%, ECL 19.4), ECL of TMS ethers 15.6 and 16.8, infrared band at 3640 cm^{-1} (O-H stretching), NMR signals at : 0.88 [3H, t, CH_3CH_2-], 1.28 [-$(CH_2)_n$-], 1.96-2.00 [2H, app. d, -CH_2CH=CH-], 3.53 [2H, t, CH_2OH], 4.68-4.72 [1H, b. s, -OH] and 5.27 δ [2H, m, -CH=CH-].

e. Methyl heptadec-cis-8-enyl ether (12%, ECL 14.2) NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.28 [-$(CH_2)_n$-], 1.98-2.04 [4H, app. d, -CH_2CH=CH-], 3.23 [3H, S, -OCH_3] and 5.28 δ [2H, m, -CH=CH-].

f. Heptadec-cis-8-enol and nonadec-cis-10-enol (ECL 18.5 and 20.5 respectively). NMR signals similar to those detailed for product 'd'.

g. Heptadec-cis-8-enyl acetate (ECL 18.2; 18.5 after hydrolysis to the corresponding alcohol) and octadec-cis-9-enyl acetate (ECL 19.0 identical with an authentic sample).

h. Heptadec-cis-8-enol (ECL18.5) and octadec-cis-9-enol (ECL19.5). NMR signals similar to those reported for product 'd'.

2.4. Preparation of nor-alcohols from unsaturated fatty acids

(i) Heptadec-cis-8-enol

a) Oleic acid (1.0g) was electrolysed in methanol (30 ml) with sodium hydride (1.2g) (Apparatus 2). The current started at 0.8 amp and fell rather quickly (1 hr) to 0.2 amp. Hence at the end of every hour the electrolysis was stopped for 0.5 to 0.75 hr and then continued for a further hour. The total electrolysis time was 4.5 hr. Aliquots (1 ml) were taken hourly, esterified (2% methanolic sulphuric acid) to check the amount of unreacted oleic acid left in the mixture by analytical TLC (PE 10) and GLC (Ecl 18.5). Finally the reaction mixture was acidified (AcoH), methanol evaporated, water (10 ml) added and the total product (1.4g), extracted with a petroleum ether/ether mixture (PE 20). When purified by prep TLC (PE 30) it gave (i) hydrocarbon (273 mg, possibly a C17 compound on the basis of its GLC behaviour (ii) methyl ether (230 mg, Ecl 14.1) (ii) heptadec-cis-8-enol (302 mg, 34%, ECL 19.4,* TMS ether ECL 16.1*)

An authentic sample of octadec-cis-9-enol gave an ECL of 20.4* and its TMS ether 17.1.

The heptadec-cis-8-enol gave NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.27 [-$(CH_2)_n$-], 1.96-2.01 [4H, app. d, -CH_2CH=CH-], 2.71 [1H, s, -OH], 3.51 [2H, t, CH_2OH] and 5.27 δ, J=6Hz [2H, m, -CH=CH-].

* Higher values of ECL than those reported earlier because GLC column was replaced with a freshly prepared one.

An IR spectrum showed a strong O-H stretching absorption at 3642 cm^{-1} and no evidence of a trans double bond in the region 975 cm^{-1}.

von Rudloff oxidation of the unsaturated alcohol gave (after esterification) methyl nonanoate and methyl 8-hydroxyoctanoate. These conclusions were based on a comparison of GLC behaviour of the products of oxidation of oleyl alcohol viz methyl nonanoate and methyl 9-hydroxynonanoate.

b) The preparation of heptadec-cis-8-enol was repeated when oleic acid (1.01g) was electrolysed with sodium hydroxide (1.23g, dissolved in water 1 ml) in methanol (30 ml) for a total electrolysis time of 6.5 hr. The reaction product (obtained from the mixture as reported earlier) when esterified (2%H_2SO_4, MeOH) and purified by prep TLC (PE 30) gave (i) hydrocarbon (230 mg, 25%), (ii) a mixture (341 mg) of a methyl ether thought to be methyl heptadec-cis-8-enyl ether (7%, Ecl 14.1) and methyl oleate (14%) and (iii) heptadec-cis-8-enol (473 mg, 44%, Ecl 19.3).

An IR spectrum of the heptadec-cis-8-enol showed strong O-H absorption (3340 cm^{-1}) and no evidence of a trans double bond. Its NMR signals were similar to those reported for the earlier preparation of the 17:1 alcohol.

(ii) Heptadeca-cis-8, cis-11-dienol

Linoleic acid (543 mg) was electrolysed with sodium hydroxide (554 mg dissolved in 1 ml water) in methanol (20 ml) (Apparatus 2) for a total electrolysis time of 5.75 hr. The total product (521 mg), obtained as in the experiment with oleic acid, gave on purification by prep TLC (i) hydrocarbon (56 mg) (ii) a mixture (243 mg) of a methyl ether probably

methyl heptadeca-cis-8, cis-11-dienyl ether (ECL 14.5) and methyl linoleate and (iii) heptadeca-cis-8, cis-11-dienol (101 mg, 21%, Ecl 20.0, ECL of TMS ether 16.2).

The 17:2 alcohol gave NMR signals at 0.90 [3H, t, CH_3CH_2-], 1.32 [-$(CH_2)_n$-], 2.00-2.05 [4H, app. d, -CH_2CH=CH-] 2.72 [2H, t, -CH=CHCH_2CH=CH-], 3.51 [2H, t, -CH_2OH], 3.60 [1H, S, -OH] and 5.28 δ [4H, m, -CH=CH-].

An IR spectrum showed no evidence of trans absorption.

(iii) Heptadeca-cis-8-en-1, 11-diol

Ricinoleic acid (1.08g) was electrolysed with sodium hydroxide (1.0g dissolved in water (1 ml) in methanol (30 ml) for a total electrolysis time of 5 hr. The total product (1.0g extracted with ether 4 x 20 ml) purified by prep TLC (PE 1:1) gave (i) a monohydroxy compound (79 mg), (ii) a monohydroxy monomethoxy compound (95 mg, possibly 1-methoxy-heptadec-cis-8-en-11-ol) with NMR signals at 0.90 [3H, t, CH_3CH_2-], 1.28 [-$(CH_2)_n$-], 2.00-2.22 [m, -CH_2CH=CH-], 3.24 [3H, S, -OCH_3], 3.48 3.60 [m, CH_2OCH_3 and -CHOH] and 5.42 δ [2H, m, -CH=CH-] and (iii) heptadec -cis-8-en-1, 11-diol (109 mg, 17%, ECL of TMS ether 19.3) with NMR signals at 0.90 [3H, t, CH_3CH_2-], 1.34 [-$(CH_2)_n$-], 2.04-2.24 [4H, m, -CH_2CH=CH-], 3.36 [1H, m, CHOH], 3.53 [2H, t, CH_2OH], 4.10 [2H, b.s, -OH] and 5.43 δ [2H, m, -CH=CH-].

For comparison methyl ricinoleate was reduced to octadec-cis-9-en-1, 12-diol (ECL of TMS ether 20.4) which showed NMR signals at 0.90 [3H, t, CH_3CH_2-], 1.32 [-$(CH_2)_n$-], 2.02-2.16 [4H, m, -CH_2CH=CH-],

3.40 and 3.58 [3H, m, CH_2OH and -CHOH] and 5.42 δ [2H, m, -CH=CH-].

Infrared spectra of the C_{17} and C_{18} diols showed strong OH absorption at 3360 and no evidence of trans absorption at 975 cm^{-1}.

(iv) Products of the electrolysis of γ-linolenic and α-linolenic acid in alkaline medium

γ-Linolenic acid (1.14g, 4.1 mmoles) and α-linolenic acid (1.21g, 4.4 mmoles) were each electrolysed in methanol (30 ml) with sodium hydroxide (1.2g dissolved in water, 1 ml) for 3 hr (Apparatus 2). The reaction mixtures were made acidic (AcoH), methanol evaporated, esterified (2% H_2SO_4, MeOH) and extracted (1.1g and 1.0g respectively) as reported for heptadec-cis-8-enol.

Details concerning the products are summarised in Table 12.

TABLE 12

Products of electrolysis of γ-linolenic and α-linolenic acids in alkaline medium

Nature of product	from 18:3 (6,9,12)(1.14g) ECL (mg)	from 18:3 (9,12,15)(1.3g) ECL (mg)
hydrocarbons	12.5 (105 mg)	12.0 and 12.5 (85 mg)
methyl ethers	14.0 and 14.5 (129 mg)[a]	14.5 and 15.0(185 mg)[c]
alcohols	19.0, 20.2, 20.3 (71.6 mg)[b]	19.4, 21.1, 21.8 (100 mg)[d]
	(TMS ethers 16.6, 18.3)	(TMS ether 13.7, 15.0 and 15.8)

a-d. None of these mixtures could be separated by prep TLC on silica nor

silica impregnated with silver nitrate.

a) This mixed product gave NMR signals at 0.90 [t, CH_3CH_2-], 1.05-1.13 [m], 1.28-1.46 [m, -$(CH_2)_n$-], 1.46-1.63 [m], 2.00-2.06 [m, CH_2CH=CH-], 2.76 [t, -CH=CHCH_2CH=CH-], 3.16 [s, -OCH_3] 3.30 [t, CH_2OCH_3], and 5.30 δ [m, -CH=CH-].

b) The mixed product gave NMR signals at 0.90 [t, CH_3CH_2-], 1.06-1.50 [m], 2.00-2.06 [m, -CH_2CH=CH-], 2.78 [t, -CH=CHCH_2CH=CH-], 3.22-3.28 [m], 3.56 [t, -CH_2OH], 3.62 [s, -OH] and 5.30 δ [m, -CH=CH-].

c) This mixed product gave NMR signals at 0.95 [t, CH_3CH_2-], 1.02 [m], 1.26-1.34 [m, -$(CH_2)_n$-] 2.00-2.06 [m, -CH_2CH=CH-], 2.76 [t, -CH=CHCH_2CH=CH-], 3.14 [s, -OCH_3], 3.22 [m] and 5.30 δ [m, -CH=CH-].

d) This mixed product gave NMR signals similar to those reported for 'b' with multiplets at 3.21, 3.34 and a singlet at 3.58 δ -OH.

3. CHAIN EXTENSION BY MALONATION

General procedure

Methanesulphonates were prepared from methyl esters via the alcohols, following the procedures reported on page 63 and 64. ^{13}C NMR data are summarised on page 54-55.

(i) Eicos-cis-11-enoic acid

A suspension of sodium (850 mg, 37 mmoles) in dry xylene (400 ml) was prepared in a three-necked flask (250 ml) equipped with a reflux condenser and calcium chloride tube, stirrer and dropping funnel with nitrogen inlet tube. The contents of the flask were stirred vigorously for 5 to 10 min at 115°C and then allowed to cool to room temperature without further stirring. Diethyl malonate (3.12g, 20 mmoles) was added at once and allowed to react overnight when a white precipitate of sodium diethyl malonate formed in a clear colourless solution.

This mixture was heated to 110° and stirred continuously during the slow addition of octadec-cis-9-enyl mesylate (5.2g) in dry xylene (30 ml) over one hour and for a further four hours. The reaction mixture was cooled, transferred to a round bottom flask, and the solvent distilled off on a rotary evaporator.

The residue was refluxed and stirred with ethanolic potassium hydroxide (80 ml, 5% potassium hydroxide in 80% aqueous ethanol) for 1 hr (at 80°C). At the same temperature, sulphuric acid (1M, 60 ml) was added dropwise to the solution (until acidic) and stirring continued for 30 min.

Most of the ethanol was carefully distilled off under reduced pressure, water (150 ml) was added, and octadec-cis-9-enyl malonic acid (4.9g) was extracted with ether (3 x 100 ml). The combined ether phases were washed with water (until neutral) and dried. The solution was reduced to about 15 ml, transferred to a 250 ml two-necked flask and the residual solvent evaporated in a stream of nitrogen.

The flask containing the sample was connected to a water pump while a gentle stream of nitrogen was allowed to pass through the vessel. The flask was placed in an oil bath preheated to 125°C and the temperature was raised to 165°. Decarboxylation was observed by the effervescence, which ceased after 1.5 to 2 hr. The flask was cooled and eicos-cis-11-enoic acid (3.9g, 84%ECL of ester 20.6, 99% pure by GLC was obtained. The highly coloured acid (3.9g) purified by passage through a column of sorbsil (150g) topped with a mixture of sorbsil (25g) and charcoal (5g) gave colourless C_{20} acid (3.5g, 75% eluted with 2 l of PE 5).

The 20:1 methyl ester gave an NMR spectrum similar to that already reported (page 74). An IR spectrum did not exhibit any absorption in the trans region. von Rudloff oxidation gave nonanoic and undecanedioic acids.

(ii) Eicosa-cis-11, cis-14-dienoic acid

Octadeca-cis-9, cis-12-dienyl mesylate (25.5g) subjected to malonation as described gave eicosa-cis-11, cis-14-diene-1,1-dioic acid (31.5g) which was decarboxylated to eicosa-11, 14-dienoic acid (20.1g, 88%, ECL of ester 21.1, 95% pure by GLC.

The highly coloured product (20.1g) purified by passage through a column of sorbsil (400g) topped with a mixture of sorbsil (50g) and charcoal (10g) gave octadecadienyl chloride (1.4g eluted with 1 l of petrol) and colourless C_{20} acid (18.0g, 79% eluted with 4 l of PE 5, 98% pure by GLC). It was further purified to the 99% level (15.2g, 66%) by crystallisation from petrol (150 ml), at -78°C. The NMR spectrum of its methyl ester was similar to that already reported and the IR spectrum showed complete absence of trans isomer.

(iii) Docosa-cis-13, cis-16-dienoic acid

Eicosa-cis-11, cis-14-dienyl mesylate (11.6g) was submitted to malonation. The diacid (13.5g) first obtained was decarboxylated to give docosa-cis-13, cis-16-dienoic acid (8.6g, 83% 90% pure ECL of methyl ester 23.1) which was further purified by column chromatography (200g sorbsil topped with sorbsil (50g) and charcoal (10g) as detailed for the 20:2 acid). Docosadienyl chloride (0.9g) was eluted first followed by the 22:2 acid (5.2g, 49% 97% pure as methyl ester). The acid was converted to its methyl ester (5.4g) and was further purified by low temperature cyrstallisation (-78°C from petrol 30 ml) when a precipitate (4.3g, 41.0%, 99% pure) of methyl docosa-cis-13, cis-16-dienoate was obtained.

An IR spectrum of the ester did not show any evidence of trans absorption at 975 cm^{-1} and gave NMR signals similar to those reported earlier for methyl eicosa-cis-11, cis-14-dienoate (page 75).

(iv) Eicosa-cis-8, cis-11, cis-14-trienoic acid

Octadeca-cis-6, cis-9, cis-12-trienyl mesylate (23.5g) subjected to

malonation as described earlier gave the diacid (34.2g) which on decarboxylation gave eicosa-cis-8, cis-11, cis-14-trienoic acid (18.0g, 86%, ECL of ester 22.2, 97.6% pure). The highly coloured acid was further purified as its methyl ester by column chromatography (sorbsil and charcoal) to give colourless 20:3 ester (16g, 72 %, 99% pure).

An IR spectrum did not show any evidence of a trans double bond. The NMR signals were similar to those reported earlier (page 77).

(v) Eicosa-cis-11, cis-14, cis-17-trienoic acid

Octadeca-cis-9, cis-12, cis-15-trienyl mesylate (5.7g) was malonated as before. On decarboxylation the diacid (12.3g) gave eicosa-11, 14, 17-trienoic acid (4.9g, 96%, ECL of ester 20.7, 94% pure). The acid as its methyl ester was further purified by column chromatography (sorbsil and charcoal) when eicosatrienyl chloride(0.4g) and methyl eicosa-11, 14, 17-trienoate (4.0g, 75%, 99%pure) were obtained.

An IR spectrum of the ester did not reveal any trans absorption. The NMR signals were similar to those of methyl octadec-cis-9, 12, 15-trienoate as follows : 0.97 [3H, t, CH_3CH_2-], 1.32 [-$(CH_2)_n$-], 2.00-2.05 [4H, app.d., -CH=CHCH_2-], 2.22 [2H, t, -CH_2COOCH_3], 2.76 [4H, t, =CHCH_2CH=], 3.58 [3H, s, -COOCH_3] and 5.31 δ [6H, m, -CH=CH-],

4. Chain-extension by enamine synthesis

General procedures

1-Morpholino-1-cyclopentene

A solution of cyclopentanone (128g, 1.5 moles), morpholine (158g, 1.8 moles*) and p-toluenesulphonic acid (1.7g) in toluene (300 ml) was heated to boiling in a 1 l flask, to which a water separator under a reflux condenser was attached. The separation of water began at once and ceased after five to six hours. The excess toluene was distilled off at atmospheric pressure using an indented claissen stillhead. 1-Morpholino-1-cyclopentene was then distilled under reduced pressure (115g, b.p. 70^{o}/1.2 mm, lit[57] b.p. $105-106^{o}$/14 mm) as a colourless liquid**.

1-Morpholino-1-cyclohexene

A solution of cyclohexanone (150 g, 1.51 moles), morpholine (157g, 1.80 moles) and p-toluenesulphoric acid (1.5g) in toluene (300 ml) were reacted as detailed earilier to give colourless 1-morpholino-1-cyclohexene (145g, b.p. $90-92^{o}$/1.8 mm, lit[62]).

* An excess of morpholine is required, because the water that is removed during the reaction always contains a considerable amount of the base.

** 1-Morpholino-1-cyclopentene is very easily hydrolysed. Accordingly care was taken to keep moisture out. On long standing in a refrigerator, the compound generally becomes yellow in colour but this does not affect its usefulness in subsequent reactions.

Tetradecanoyl chloride

Tetradecanoic acid (99% pure as methyl ester, 65g, 0.3 moles) was refluxed with redistilled thionyl chloride (78g, 0.6 moles) for 30 min. The reaction mixture was distilled under reduced pressure when tetradecanoyl chloride (56g, 77%, b.p. 125-128°/1.7 mm, lit[59] 174°/10 mm) was obtained.

Hexadecanoyl chloride

Hexadecanoic acid (99% pure as its methyl ester, 70g, 0.27 moles) was converted to its acid chloride (50g, 67%, b.p. 140°/0.8 mm, lit[59] b.p. 145°/18 mm) by reaction with thionyl chloride (78g, 0.6 moles) as already described.

(i) Eicosanoic acid

2-Tetradecanoylcyclohexanone

Tetradecanoyl chloride (53g, 0.21 moles) in dry chloroform (140 ml) was added over ninety minutes to a stirred solution of 1-morpholino-1-cyclohexene (55g) and redistilled triethylamine (40 ml) in dry chloroform (200 ml) maintained at 35°. The reaction mixture was stirred for a further 2 hr. Next day concentrated hydrochloric acid (46 ml) in water (23 ml) was added and the mixture refluxed for 5 hr. The mixture (2 layers) was transferred to a separating funnel, the chloroform layer was drawn off and set aside. The aqueous layer was extracted with chloroform (2 x 70 ml) which was then combined with the chloroform layer obtained earlier. The pooled extracts were concentrated to give crude 2-tetradecanoylcyclohexanone (57g).

6-oxo-eicosanoic acid

The diketone (57g), sodium hydroxide (10g) and water (100 ml) were refluxed for 4 hr. The mixture was poured into ice and acidified (conc. Hcl), extracted with ether (4 x 100 ml) to give crude 6-oxoeicosanoic acid (48g). A sample (2.0g) of this acid was converted to its methyl ester and purified by prep. TLC to give Methyl 6-oxo-eicosanoate (95% pure by GLC).

Eicosanoic acid

The crude 6-oxo-eicosanoic acid (43g) was refluxed with ethanolamine (225 ml), hydrazine hydrate (99-100%, 20g) and potassium hydroxide (8g) for 1 hr at 150°. The reflux condenser was then replaced by a claisen stillhead, potassium hydroxide (40g) and ethanolamine (225 ml) were added and the mixture was distilled until the contents of the flask attained a temperature of 175°. A jet of nitrogen was directed towards the contents to break up the foam which formed. The condenser was then replaced and the mixture was refluxed again for 1 hr. The product was poured into ice, acidified (conc. Hcl) and extracted with chloroform (4 x 100 ml) to give crude eicosanoic acid (44g, 47%, 85%pure as methyl ester). It contained 15% of unreacted tetradecanoic acid as impurity. Hence it was crystallised from ethanol (5 vol) at 0° to give two crops of crystals. The still brown acid, recrystallised from ethanol (5 vol) in the presence of charcoal (~1g) gave pure eicosanoic acid (36g, 37% m.p. 46-47°, as ester, lit[1] 46.4°) 99% pure as methyl ester by GLC).

HENEICOSANOIC ACID

2-Hexadecanoylcyclopentanone

Hexadecanoyl chloride (65g, 0.24 moles) in dry chloroform (250 ml) was reacted with 1-morpholino-1-cyclopentene (55g, 0.36 moles) and triethylamine (55 ml) in dry chloroform (300 ml) as already described, to give the crude diketone (60g).

6-Oxoheneicosanoic acid

The crude diketone (60g) was hydrolysed with sodium hydroxide (15g) and water (250 ml) for 4 hr at 150° to give crude 6-oxo-heneicosanoic acid (55g).

Heneicosanoic acid

The crude oxo-heneicosanoic acid (55g) was refluxed for 1 hr with hydrazine hydrate (99-100%, 30 ml) and potassium hydroxide (10g) in diethylene glycol* (150 ml). The reflux condenser was removed and more potassium hydroxide (40g) and diethylene glycol (150 ml) were added and the mixture processed in the same manner as described earlier, to give crude heneicosanoic acid (48g, 56% containing 8% unreacted hexadecanoic acid as impurity). The acid was crystallised from ethanol (5 vol at 0°) to give pure heneicosanoic acid (40g, 44% 99% pure as methyl ester by GLC, ECL 21.0, m.p. 75-75.5°, lit[1] 75.2°)

* diethylene glycol can be satisfactorily used instead of ethanolamine (Elix and Sargent[58]).

PART II

THE PREPARATION OF SOME LONG CHAIN HYDROPEROXIDES AND t - BUTYL PEROXIDES

INTRODUCTION

1. INTRODUCTION

Organic peroxides are derivatives of hydrogen peroxide in which one or both hydrogen atoms are replaced by alkyl or acyl groups :

ROOH	alkyl peroxide	hydroperoxide
$ROOR^1$	dialkyl peroxide	
$R\overset{O}{\overset{\|}{C}}-OOH$	acyl peroxide	peroxy acid
$R\overset{O}{\overset{\|}{C}}OOCOR^1$	diacyl peroxide	

Peroxides are of considerable interest to lipid chemists since rancidity of fatty foods and oxidative polymerisation of oil - based paints result from initial formation of hydroperoxides. There is some evidence that lipid peroxides may participate in radiobiological damage[64], in cancer[65], and in ageing processes[66]. Peroxides are known to be intermediates in the biological conversion of polyene acids to prostaglandins[1].

We have examined a number of procedures for preparing hydroperoxides and peroxides to see if they could be usefully applied to the synthesis of long-chain compounds and we report here our limited success in this field. The more important synthetic procedures are first reviewed.

2. Synthetic Procedures :

A (i) Autoxidation :

Lipid chemists are mainly interested in the autoxidation (ie. the spontaneous reaction between atmospheric oxygen and organic compound) of unsaturated fatty acids and their derivatives which is believed to occur by a radical chain mechanism thus : (RH is an alkene with H in an allylic position).

Initiation : production of $R\cdot$ or $RO_2\cdot$ radicals.

Propagation

$$R\cdot + O_2 \longrightarrow RO_2\cdot$$

$$RO_2\cdot + RH \longrightarrow RO_2H + R\cdot$$

Termination

$$R\cdot + R\cdot \longrightarrow \text{non - initiating}$$

$$RO_2\cdot + R\cdot \longrightarrow \text{and non - propagating}$$

$$RO_2\cdot + RO_2\cdot \longrightarrow \text{products.}$$

With an ester such as methyl oleate there are two allylic groups which are subject to attack and since the radicals are resonance stabilised the product is a complex mixture of isomeric hydroperoxides in which the hydroperoxy group may be attached to C(8), C(9), C(10), or C(11) and the double bond may have cis or trans configuration (see overleaf).

Methyl linoleate follows a similar course in which the major products are methyl 9-hydroperoxyoctadeca -10, 12 - dienoate and 13 - hydroperoxy-octadeca 9, 11 - dienoate in various stereoisomeric forms.

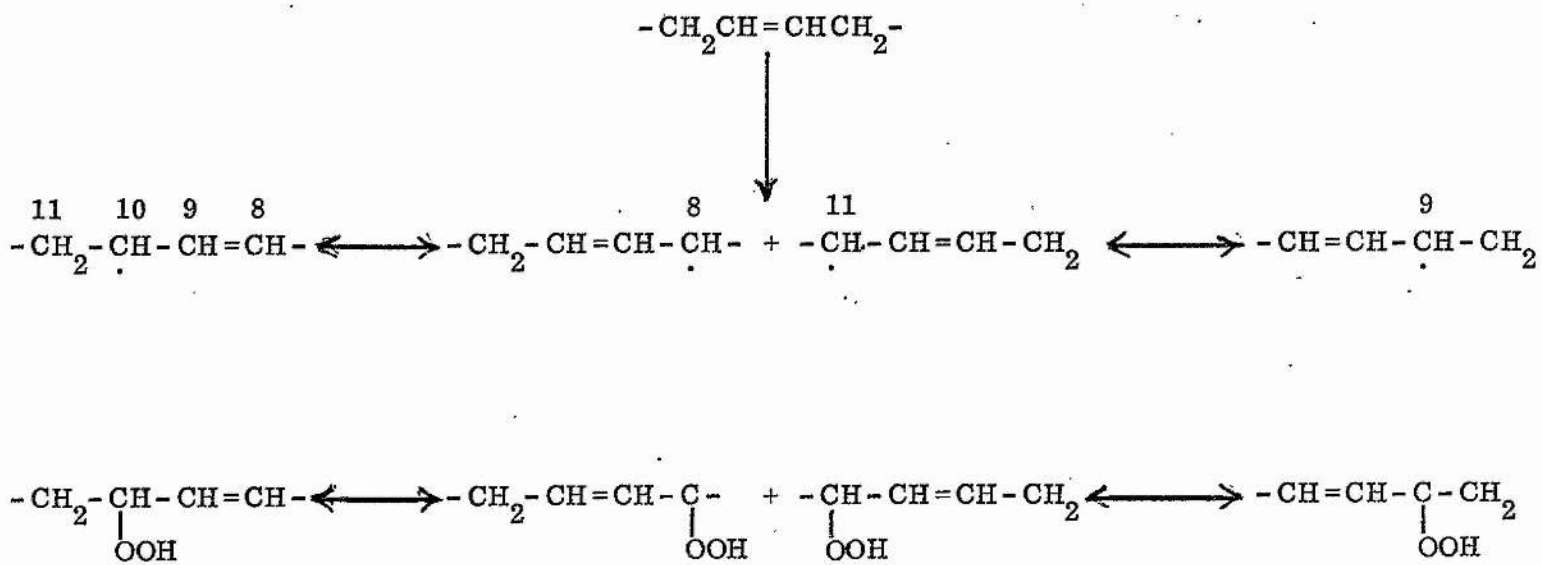
Clearly this is not a satisfactory procedure for the preparation of individual hydroperoxides.

ii) Photosensitized oxidation of olefins.

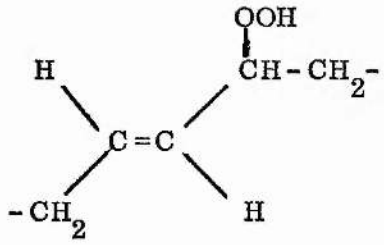
A useful synthesis of allylic hydroperoxides is the reaction of alkenes with oxygen in the presence of light and photosensitizers such as rose bengal, chlorophyll or hematoporphyrin[67].

Unlike free - radical autoxidation, the reaction invariably proceeds with migration of the double bond and is a nonchain process ;

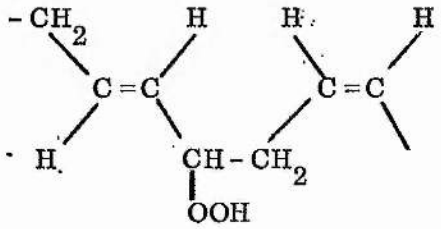
$$MeCH{=}CHMe \xrightarrow[h\nu \text{ sens}]{O_2} Me{-}\overset{O_2H}{C}HCH{=}CH_2$$


-CH2CH=CHCH2-
11 10 9 8
-CH2-CH-CH=CH-
8 11
-CH2-CH=CH-CH- + -CH-CH=CH-CH2
9
-CH=CH-CH-CH2
-CH2-CH-CH=CH-
OOH
-CH2-CH=CH-C-
OOH
-CH-CH=CH-CH2
OOH
-CH=CH-C-CH2
OOH

In a study of the monohydroperoxides of oleate and linoleate Hall and Roberts[68] report that the monohydroperoxides obtained by chlorophyll - catalysed oxidation of methyl oleate (1) have the hydroperoxide group in an α position to a trans double bond. Whilst atmospheric oxidation of methyl linoleate gives only conjugated diene hydroperoxides chlorophyll-catalysed oxidation gives conjugated dienes (2) and (3) along with products having isolated double bonds. There is no evidence for any product with a single carbon atom between two double bonds.



(1)



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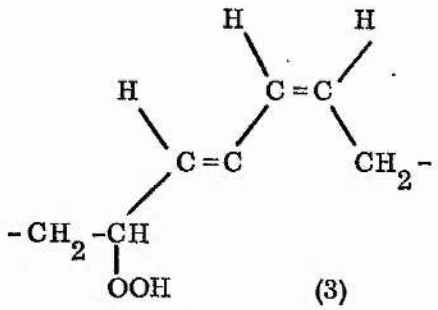


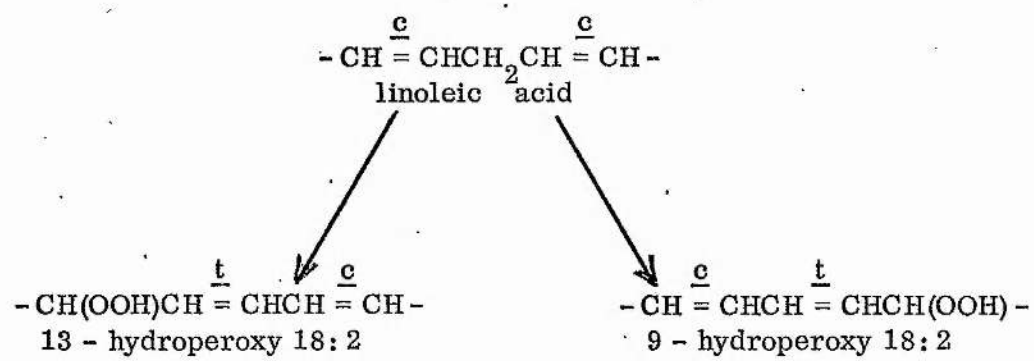
(3)

Rawls and Santen[69] have proposed a mechanism for the initiation of autoxidation of fatty acids involving singlet state oxygen, formed through a photosensitization reaction, as the reactive intermediate. They state that nonconjugated hydroperoxides could not be detected among the free radical

autoxidation products but were found in photoxidation products, as reported by Hall and Roberts[68].

B. Enzymic oxidation

In natural systems oxidation is catalysed by lipoxygenases which appear to react specifically with polyenoic acids. Depending on the source of the enzyme and on its preparation Linoleic acid may give mainly the 13- hydroperoxy (9c 11t) or the 9- hydroperoxy (10t 12c) diene acid or mixtures of these. The specificity of this process is further shown in the observation that the products are optically active. Other polyene acids may also be oxidised. There is a considerable interest in the secondary reaction of these enzymic oxidations[70] but these do not concern us here.



Although these hydroperoxides can be purified by chromatography[71] only small amounts of material can be usefully prepared in this way.

C. Oxidation of organometallic compounds

Organometallic compounds autoxidise to peroxide intermediates. Walling and Buckler[72] prepared hydroperoxides by oxidation of Grignard derivatives at -70°C in ether solutions.

$$RMgBr + O_2 \longrightarrow ROOMgBr \xrightarrow{Hcl} ROOH + MgClBr$$

At higher temperatures the Grignard reagent reduces the intermediate organometallic peroxide to an alcoholate. Since cadmium and zinc alkyls undergo this latter reaction less readily and are less reactive to carbon dioxide and water they appear to be more suitable for oxidation to hydroperoxides. Autoxidation of the cadmium alkyls has since been used to prepare hydroperoxides up to octyl hydroperoxide in 90% yields[73].

$$RMgX \xrightarrow[\text{low temp.}]{O_2} ROOMgX \xrightarrow[HX]{H_2O} ROOH + MgX_2$$

$$R_2Cd \xrightarrow{O_2} RCdOOR \xrightarrow{O_2} Cd(OOR)_2 \xrightarrow{H_2O} 2ROOH + CdO$$

Brown and Midland[74] have described a method of preparing hydroperoxides from trialkylboranes which is summarised by the sequence :

$$\text{alkene} \longrightarrow R_3B \xrightarrow{O_2} (ROO)_2BR \xrightarrow{H_2O_2} 2ROOH + ROH$$

It is apparent that at most two thirds of the alkene furnishes hydroperoxide and one third yields alcohol. With this proviso good yields are possible.

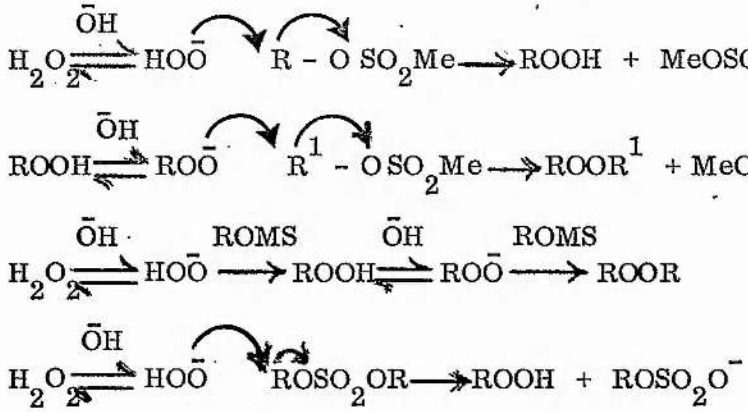
H. R. Schuler[75] in his study of alkylboranes from methyl oleate employed this reaction to prepare a mixture of methyl 9 and 10 hydroperoxystearate. This saturated hydroperoxide had not previously been reported.

D. Alkylation of hydrogen peroxide and of hydroperoxides

Hydrogen peroxide (and alkyl hydroperoxides) can be alkylated by a range of alkylating agents in alkaline or acidic solution. Under the former condition the reactivity of the peroxide is enhanced by ionisation whilst in

the latter ionisation of the alkylating agent is promoted.[76] Typical reactions are illustrated in the following equations :

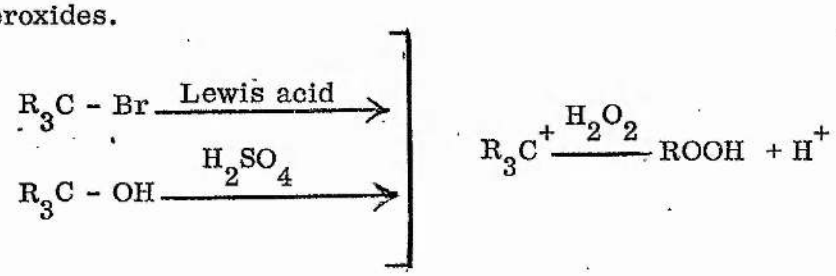
(i) Use of alkyl methanesulphonates (mesylates).



Reactions with methanesulphonates and with sulphates are restricted by the low solubility of the organic reactants in aqueous methanol and by the protracted reaction time during which the hydroperoxide (peroxide) decomposes. The method has been used to prepare primary hydroperoxides up to C_{18} and secondary hydroperoxides up to C_8 though in many cases the yields are disapprovingly low.

(ii) Alkyl halides are not sufficiently reactive for interaction with peroxide unless allylic or benzylic :

(iii) Reaction in acidic media proceeds via carbonium ions and is therefore more suitable for tertiary than for primary or secondary hydroperoxides.



DISCUSSION

3. Discussion

The most widely used route to hydroperoxides of long-chain acids is by reaction of the unsaturated acids with oxygen, alone, in the presence of catalyst, or under the influrence of a lipoxygenase. Since many of these procedures give mixtures of products it would be useful to have a general chemical method of preparing hydroperoxides specifically and in high yield. A number of procedures have been described (see Introduction) but these have seldom been applied to long-chain compounds. We report here our attempt to prepare a number of hydroperoxides and t - butyl peroxides by alkylation of hydrogen peroxide and of hydroperoxides.

Wawonek, Klimstra and Kallio[77], developing the earlier studies of Mosher et al[78], prepared a series of primary hydroperoxides by interaction of hydrogen peroxide (30%) with the appropriate mesylate in alkaline solution. The reaction was conducted in methanol at room temperature for 60-100 hr and typical yields for the conversion of a primary mesylate (RCH_2OMs)

$$ROH \longrightarrow ROSO_2CH_3 \xrightarrow{\bar{O}OH} ROOH$$

to the hydroperoxide (RCH_2OOH) were do decyl 56%, tetradecyl 42%, hexadecyl 31% and octadecyl 9%. Less satisfactory yields were reported with secondary alcohol derivatives eg. 2- butyl 20%, 2- hexyl 26% and 2- octyl 11%. After we had finished our experiments Radomsky and Gibian[79] emphasised the importance of controlling the pH of the reaction. They examined the reaction between a typical sulphonate ester, n - butyl methanesulphonate, and hydrogen peroxide in neutral and basic aqueous

solutions. Hydrogen peroxide itself (0.64M) had no effect on the ester ; n - butyl alcohol, the sole product below pH 10, was formed at the same rate as in the absence of peroxide. Above pH 11 n - butyl hydroperoxide is formed quite rapidly as the sole product, arising from attack by HO_2^-. The reaction proceeds solely by alkyl - oxygen, and not sulphur - oxygen scission. An attempt to observe S - O scission was made by examining neopentyl methanesulphonate in 40% t - butyl alcohol at a nominal pH of 12.5 with about 0.3M hydrogen peroxide. Neither loss of ester nor formation of product was observed in 21 days.

We tried to change the reaction solvent recommended by Wawzonek, Klimstra and Kallio[77] without success. Methanol and ethanol gave satisfactory results : acetonitrile, dimethylformamide, dimethylsulphoxide, hexamethylphosphoramide, propan-2-ol and ethane-1,2-diol did not. As a preliminary to conducting the reaction at a higher temperature we examined the stability of hydrogen peroxide (50%) in hot methanol and ethanol. We found that a mixture of hydrogen peroxide (50% 0.6ml), potassium hydroxide (112mg) and ethanol 10ml had a half-life of 5 hr at $\sim 35^{\circ}C$. A similar mixture in methanol had a half-life of several days at $\sim 35^{\circ}$ and of 100 min at reflux temperature. In an attempt to get a better yield in shorter time we carried out the reaction in boiling methanol for 3 hr with additional hydrogen peroxide being added after 1 hr and after 2 hr. Under these conditions dodecanol, stearyl alcohol, oleyl alcohol and linoleyl alcohol were converted into their corresponding hydroperoxides in 40 - 83% yields. The two unsaturated hydroperoxides have not been prepared before.

Stearyl, oleyl and linoleyl t - butyl peroxides were also prepared for the first time, in 25 - 40% yield, in a similar manner replacing the hydrogen peroxide by t - butyl hydroperoxide. The reaction was continued for 6 hr without adding more hydroperoxide.

We made an attempt to prepare methyl octadec-12-hydroperoxy-10t-enoate via the mesylate, but did not succeed. We believe the product was almost entirely methyl octadec-12-methoxy-10t-enoate.

Although alkaline solutions of hydrogen peroxide do not react in any useful way with alkyl halides they do react with the more reactive allyl halides which can be prepared from alkenes by allylic bromination with N-bromo-succinimide. We have exploited this reaction in the conversion of cyclohexene to 3-hydroperoxy-cyclohexene (46%), 3-t-butylperoxy-cyclohexene (51%) and tridec-1-ene to 1-t-butylperoxytridec-2-ene (57%). We believe that the reaction occurred with double bond migration on the basis of the NMR spectrum of the hydroperoxide.

$$RCH_2CH = CH_2 \xrightarrow[Bu^tOOH]{NBS} RCH = CHCH_2OOBu^t.$$

In particular we observed signals at 2.0 - 2.06 δ [2H, app. d, $-CH_2\underline{C}H = CH-$] and 4.23 δ [2H, app. d, $-\underline{C}H_2OOBu^t$] and none related to [$R\underline{C}H(OOBu^t)\underline{C}H = CH_2$]

We failed to produce any hydroperoxytridec-2-ene in a similar reaction with hydrogen peroxide.

The bromide ion eliminated in this reaction can be oxidised, by hydrogen peroxide or t - butyl hydroperoxide, to bromine which may then add

to the olefinic reactants and products. This difficulty is reduced by carrying out the reaction in the presence of excess alkene to take up the bromine or, better, in the presence of a base when the oxidation step is considerably reduced or eliminated.

Our results summarised in Table 1 show the yields of hydroperoxides and peroxides. Many of these compounds are new. For those that have been prepared before our yields compare favourably with earlier preparations (eg. dodecyl hydroperoxide 56%, octadecyl hydroperoxide 9%). The yield of diene hydroperoxide is somewhat lower than the others and the yield of C_{18} t-butyl peroxides lower than those of the corresponding hydroperoxides. The major impurities are the corresponding alcohol and methyl ether resulting, no doubt, from competitive interaction of the mesylate with $\bar{O}H$ and $\bar{O}Me$.

Although a great deal of work has been carried out on autoxidation studies, hydroperoxides and peroxides[76], there is little or no mention of gas liquid chromatographic analysis of long-chain hydroperoxides and peroxides. We found that the hydroperoxides and peroxides were generally unstable under our conditions of gas liquid chromatography (20% DEGS, 170 °C, with a N_2 flow rate of 60 ml per min) and gave two peaks corresponding to the appropriate alcohol and aldehyde (or ketone) which are however not formed in equimolar amounts. Cyclohex-2-enyl hydroperoxide, for

$$RCH_2OOH \longrightarrow RCH_2OH \text{ and } RCHO$$

example gave two peaks corresponding to cyclohexenol (~23%) and cyclohexenone (~77%).

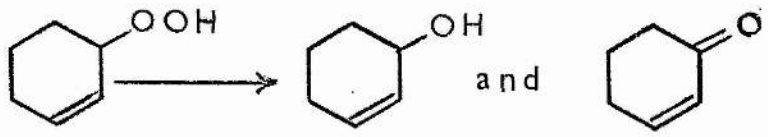


TABLE 1

Per cent yields of alkyl hydroperoxides and t-butyl peroxides with by products

	HYDROPEROXIDES			t-BUTYL PEROXIDES		
	ROOH	ROMe	ROH	$ROOBu^t$	ROMe	ROH
PRIMARY						
Dodecyl	61	4	9			
Octadecyl	64	3	5	40	45	8
Octadecenyl	83	7	10	26	28	26
Octadecadienyl	40	4	28	27	21	16
SECONDARY						
Cyclohexenyl	46			51		
Tridecenyl				57		

Nuclear magnetic resonance spectrometry was useful in confirming the structure of the peroxides. In addition to the expected signals for CH_3 (0.88 δ, t), $\left[-(CH_2)-_2\right]$ (1.26 δ), $\left[-CH=CHCH_2-\right]$ (1.95 - 2.0 app. d.), $\left[-CH=CHCH_2CH=CH-\right]$ (2.7 δ, t) and $\left[-CH=CH-\right]$ (5.26 δ, m) diagnostically useful signals were observed for the following :

		δ Values
hydroperoxide	$-\underline{CH_2}OOH$	3.92(t) $OO\underline{H}$ 8.54, 8.14 8.04 (s)
alcohol	$-\underline{CH_2}OH$	3.50(t) OH 2.55 (s)
methyl ether	$-\underline{CH_2}OCH_3$	3.26(t) OCH_3 3.22 (s)

EXPERIMENTAL

4. Experimental. (See also pages 58 and 64)

A. General procedures.

Thin layer chromatographic identification of hydroperoxides and peroxides.

Hydroperoxides and peroxides were identified on thin layer plates as red-brown spots after spraying with a reagent prepared in the following manner : ferrous sulphate (4g) and ammonium thiocyanate (4g) were dissolved in hydrochloric acid (1M, 70 ml). The spray reagent was decolourised prior to use by washing with pentan-1-ol. The hydroperoxide and peroxide spots must be marked quickly as they tend to fade.

Reduction of esters to alcohols.

The ester (5g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1g) in dry ether (75 ml) contained in a three-necked flask (1 l). After stirring for a further 30 min the excess of hydride was carefully destroyed with wet ether (50 ml) followed by water (50 ml). After addition of sulphuric acid (2M, 100 ml) the product was extracted with ether (3 x 50).

Purdie methylation.

Hydroxy compounds were converted to methyl ethers by refluxing for 6 hr with methyl iodide and freshly prepared silver oxide (equimolar amount based on hydroxy compound). The reaction mixture was filtered after dilution with ether and purified by preparative TLC.

Allylic bromination with

N-Bromosuccinimide

N-bromosuccinimide (18.0g, 0.1 mol), carbon tetrachloride (75 ml), cyclohexene (12.6g, 0.15 mol), benzoyl peroxide (as catalyst 0.25g) were added in that order to the reaction flask (fitted with a nitrogen inlet). The mixture was refluxed for 2 hr, cooled in an ice-bath and the succinimide filtered and washed with carbon tetrachloride (15 ml). Carbon tetrachloride was removed from the filtrate and washings under reduced pressure (water pump) and the residue distilled through a modified claisen head with a 4" Vigreux column to give 3-bromocyclohexene [9.7g, 65%, b.p. 58-60°/13 mm. (lit. 61.9°C/11 mm [80]) and 3,6-dibromocyclohexene (1.0g).

B. Primary alkyl hydroperoxides

(i) Dodecyl hydroperoxide.

A solution of dodecanol (1.0g, 5.4 mmoles; prepared by reduction of pure (99%) methyl dodecanoate) in dry pyridine (8 ml) contained in a three-necked flask equipped with mechanical stirrer and dropping funnel was chilled in an ice-bath during the slow addition of methanesulphonylchloride (1.5g, 13 mmoles) over 15 min. After stirring for a further 2 hr at room temperature, ice and hydrochloric acid (2M, 50 ml) were added slowly and the mesylate (1.2g, 90%) was recovered from an ether extract (3 x 50 ml) which had been washed with sulphuric acid (1M, until acidic), water (50 ml), potassium carbonate (1% aqueous, until neutral or basic) and water (50 ml).

An IR spectrum showed bands at 1125, 1290 and 1315 cm^{-1} associated with S=O stretching and the NMR spectrum showed signals at 0.88

$\left[3H, t, \underline{CH_3}CH_2-\right]$, 1.26 $\left[-(\underline{CH_2})_n-\right]$, 2.88 $\left[3H, s, -SO_2\underline{CH_3}\right]$ and 4.12 δ $\left[2H, t, -\underline{CH_2}OSO_2CH_3\right]$.

Dodecyl mesylate (266 mg, 1.0 mmole), hydrogen peroxide (50% aqueous solution, 0.6 ml, 10 mmoles), potassium hydroxide (112 mg, 2 mmoles) and methanol (10 ml) were refluxed for 3 hr with additions of further peroxide (0.6 ml) after the first hour and again after the second hour. The product was extracted with benzene (4 x 10 ml) after addition of water and hydrochloric acid (1M, until acidic) and purified by prep TLC (PE 5 or PE 10) to give some methyl ether (8 mg, 4%, ECL 8.9), the hydroperoxide (124 mg, 61%) and dodecanol (16 mg, 9%, ECL 13.5). The alcohol and its methyl ether were identified by comparison (TLC and GLC) with authentic samples.

Dodecyl hydroperoxide gave two peaks on GLC (170^o) of ECL 11.4 and 13.5 identical with the ECL of dodecanal and dodecanol respectively.

The hydroperoxide gave NMR signals at 0.88 $\left[3H, t, \underline{CH_3}CH_2-\right]$, 1.26 $\left[-(\underline{CH_2})_n-\right]$, 3.92, J=6Hz $\left[2H, t, -\underline{CH_2}OOH\right]$, and 8.54 δ $\left[1H, s, -OO\underline{H}\right]$.

(ii) Octadecyl hydroperoxide.

Octadecanol (1.03g) was converted via its mesylate into hydroperoxide as described for the C_{12} compound. The reaction product was separated by TLC (PE 10) to give the methyl ether (6 mg, 3%, ECL 14.8), the hydroperoxide (144 mg, 64%, m.p. 49^o, lit $49-50^o$ [77], ECL 17.3 and 19.5) and the alcohol (11 mg, 5%, ECL 19.5).

The mesylate gave NMR signals at 0.88 $\left[3H, t, \underline{CH_3}CH_2-\right]$, 1.26 $\left[-(\underline{CH_2})_n-\right]$, 2.88 $\left[3H, s, -OSO_2\underline{CH_3}\right]$ and 4.12 δ, J=6Hz $\left[2H, t, -\underline{CH_2}\right.$

OSO_2CH_3] and the hydroperoxide gave signals at 0.88 [3H, t, CH_3CH_2-], 1.26 [-$(CH_2)_n$-], 3.92, J = 6Hz [2H, t, -CH_2OOH] and 8.14 δ [1H, b.s, -OOH].

(iii) Octadec - cis - 9- enyl hydroperoxide

Octadec - cis - 9 - enyl hydroperoxide was prepared similarly from oleyl alcohol (3.13g). The reaction product was separated by TLC into the methyl ether (14 mg, 7%, ECL 15.3), hydroperoxide (78 mg, 83%, ECL 17.8 and 20.0) and alcohol (22 mg, 10%, ECL20.0).

The hydroperoxide gave NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.26 [-$(CH_2)_n$-], 1.96 to 2.02 [4H, app. d, -CH_2CH=CH-], 3.92, J=6Hz [2H, t, -CH_2OOH], 5.28, J=6Hz [2H, m, -CH=CH-] and 8.05 δ [1H, s, -OOH].

(iv) Octadec - cis - 9, cis - 12 - dienyl hydroperoxide

Octadec - cis - 9, cis - 12 - dienyl hydroperoxide was prepared similarly from linoleyl alcohol (1.0 g). The products were again the methyl ether (9 mg, 4%, ECL 16.1), the hydroperoxide (85 mg, 40%, ECL 17.4 and 20.9) and the alcohol (57 mg, 28%, ECL20.8).

The mesylate showed NMR signals at 0.89 [3H, t, CH_3CH_2-], 1.33 [-$(CH_2)_n$-], 2.00 to 2.06 [4H, app. d, -CH_2CH=CH-], 2.73 [2H, t, -CH=CH CH_2CH=CH-], 2.89 [3H, s, -OSO_2CH_3], 4.13 [2H, t, -$CH_2OSO_2CH_3$] and 5.29 δ [4H, m, -CH=CH-] and the hydroperoxide at 0.88 [3H, t, CH_3CH_2-], 1.30 [-$(CH_2)_n$-], 1.98 to 2.04 [4H, app. d, -CH_2CH=CH-], 2.70 [2H, t, -CH=CHCH_2CH=CH-], 3.89 [2H, t, -CH_2OOH], 5.26 [4H, m, -CH=CH-] and 7.98 δ [1H, s, -OOH].

C. Alkyl t-butyl peroxides

(i) Octadecyl t-butyl peroxide

Octadecyl methansulphonate (186 mg, 0.53 mmoles) was refluxed with potassium hydroxide (2 mmoles), t-butyl hydroperoxide (1.0 ml, 10 mmoles) and methanol (10 ml) for 6 hr. The reaction product purified by prep TLC (PE 10) gave octadecyl t-butyl peroxide (44 mg, 40%, ECL 17.1 and 19.2), the corresponding methyl ether (42 mg, 45%. ECL 14.9 (and the alcohol (7 mg, 8%, ECL 19.6).

The peroxide showed NMR signals at 0.88 δ [3H, t, CH_3CH_2-], 1.16 [9H, s, $-C(CH_3)_3$], 1.26 [$-(CH_2)_n-$] and 3.80 δ [2H, t, $-CH_2OOBu^t$].

(ii) Octadec-cis-9-enyl t-butyl peroxide.

Octadec-cis-9-enyl t-butyl peroxide was prepared similarly from oleyl mesylate (332 mg, 1 mmole). The products formed were the peroxide (42 mg, 26%, ECL 16.7 (unidentified), 17.8 and 19.9) accompanied by the methyl ether (38 mg, 28%, ECL15.7) and alcohol (33 mg, 26%, ECL 20.6).

The peroxide showed NMR signals at 0.88 δ [3H, t, CH_3CH_2-], 1.16 [9H, s, $-C(CH_3)_3$], 1.26 [$-(CH_2)_n-$], 1.95 to 2.0 [4H, app. d, $-CH_2CH=CH-$], 3.80, J=6Hz [2H, t, $-CH_2OOH$] and 5.26 δ, J=6Hz [2H, m, $-CH=CH-$].

(iii) Octadec-cis-9, cis-12-dienyl t-butyl peroxide.

Octadec-cis-9, cis-12-dienyl t-butyl peroxide was prepared from linoleyl mesylate (152 mg). The products formed were the peroxide (39 mg, 27%, ECL 18.6, 20.8), the methyl ether (24 mg, 21%, ECL 16.0) and the alcohol (18 mg, 16%, ECL 20.6).

The peroxide showed NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.16 [9H, s, $-C(CH_3)_3$], 1.30 [$-(CH_2)_n-$], 2.0 - 2.02 [4H, app. d, $-CH_2CH=CH-$], 3.8 [2H, t, $-CH_2OOBu^t$] and 5.26 δ [4H, m, -CH=CH-].

(iv) Tridec-2-enyl t-butyl peroxide

Tridec-1-ene (4.0g, 22 mmoles) treated with N-bromosuccinimide (4.0 g, 0.02 mol) and benzoyl peroxide (0.05 mg) gave a product (4.7 g) which was 90% monobromide by GLC. A mixture of this monobromide (1.3 g, 5 mmoles) cyclohexene (0.8 g, 10 mmoles), tetramethylammonium hydroxide (450 mg, 5mmoles), acetonitrile (150 ml, 80%aqueous) and t-butyl hydroperoxide (3.25 g, 3 mmoles) was allowed to stand at room temperature for two days. This mixture was then diluted with water (3 volumes), acidified (1M hydrochloric acid) and extracted with PE 20. The peroxide (698 mg, 57%) was purified by column chromatography being eluted from silica with PE 5.

The peroxide gave NMR signals at 0.88 [3H, t, CH_3CH_2-], 1.18 [9H, s, $-C(CH_3)_3$], 1.26 [$-(CH_2)_n-$] 2.0 - 2.06 [2H, app. d, $-CH_2CH=CH-$], 4.23 [2H, app. d, $-CH_2OOBu^t$] and 5.52 δ [2H, m, -CH=CH-].

D. Cyclohexenyl peroxides

(i) Cyclohexenyl hydroperoxide

Cyclohexene (12.6 g, 0.15 mol), benzoyl peroxide (0.25 g), N-bromosuccinimide (18.0 g, 0.1 mol) and carbon tetrachloride (75 ml) were reacted to give 3-bromocyclohex-2-ene (9.7 g, 65%). A mixture of 3-bromocyclohex-2-ene (345 mg), hydrogen peroxide (1.2 ml, 20 mmoles), pyridine (0.35 ml, 4 mmoles) and sufficient acetonitrile (~3 ml) to make

the mixture homogeneous was kept at room temperature for 3 hr and then acidified (1M hydrochloric acid) to pH 4 and extracted with ether (4 x 5 ml). The extract containing acetonitrile, cyclohex-2-enyl hydroperoxide, a less polar impurity and cyclohex-2-enol was purified by prep TLC (PE 20). The hydroperoxide (36 mg, 46%) gave two peaks on GLC corresponding to cyclohexenone and cyclohexenol and showed NMR signals at 1.68 [2H, m, $-CH_2\underline{CH_2}CH_2-$], 1.96 [4H, m, $=CHC\underline{H_2}$ and $-C\underline{H_2}OOH$], 4.36 [1H, m, $>C\underline{H}OOH$], 5.60 [1H, m, $=C\underline{H}CH_2-$], 5.96 [1H, m, $=C\underline{H}CHOOH-$] and 9.06δ [1H, b.s, $-O\underline{O}H$]. Cyclohexenol (20 mg, 29%) gave NMR signals at 1.24 [2H, m, $-CH_2\underline{CH_2}CH_2-$], 1.96 [4H, m, $=CHC\underline{H_2}$ and $-C\underline{H_2}OH$], 3.33 [1H, s, $-O\underline{H}$], 4.04 [1H, m, $-C\underline{H}OH$], 5.54 [1H, m, $=C\underline{H}CH_2-$] and 5.76 δ [1H, m, $=C\underline{H}OH$].

(ii) Cyclohex-2-enyl t-butyl peroxide.

Cyclohex-2-enyl t-butyl peroxide was prepared in the same way as the hydroperoxide but t-butyl hydroperoxide was substituted for hydrogen peroxide.

Bromocyclohexene (466 mg), t-butyl hydroperoxide (2 ml, 20 mmoles) and pyridine (0.5 ml, 6 mmoles) were reacted at room temperature overnight. Cyclohex-2-enyl t-butyl peroxide (96 mg, 51%) was extracted with hexane and isolated by prep TLC (PE 10). The by product was again cyclohexenol.

The peroxide gave NMR signals at 1.2 [9H, s, $C(C\underline{H_3})_3$], 1.34 [2H, m, $-CH_2\underline{CH_2}CH_2-$], 1.98 [4H, m, $=CHC\underline{H_2}$ and $C\underline{H_2}CHOOBu^t$], 4.26 [1H, app. d, $-C\underline{H}OOBu^t$], 5.58 [1H, m, $=C\underline{H}CH_2$] and 5.90 δ [1H, m, $=C\underline{H}CHOOBu^t$].

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