SYNTHETIC OCTADECENOIC ACIDS

being a thesis

presented by

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to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

AUGUST 1966

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.

CERTIFICATE

I hereby certify that Mr. Ifthikarudeen Ahamed Ismail has spent eleven terms at research work under my supervision, has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and is qualified to submit the accompanying Thesis in application for the Degree of Doctor of Philosophy.

Research Supervisor.

CAREER

I entered the University of Ceylon in October 1956 and was awarded an "Exhibition" on the results of the General Science Qualifying Examination and graduated in 1960 with Second Class (Upper Division) Honours in Chemistry.

I joined Lever Brothers (Cey)Limited in February 1961 as a Chemist and served in that capacity until I was awarded a Commonwealth Scholarship to read for the degree of Ph.D. at St. Andrews University under the supervision of Dr. F.D. Gunstone, D.Sc.

ACKNOWLEDGEMENTS

I am deeply grateful to Dr. F.D. Gunstone for the help, guidance and encouragement he so readily gave me throughout this work.

I also wish to thank Mr. D. McGhee for making some of the necessary glass apparatus and Mrs. M. Smith for typing the thesis.

In addition I would like to thank Messrs. R. Morris, J. Sherriff, T. Norris and J. Rennie for their help in many matters and Mr. A. Watson for "running" the n.m.r. spectra of the different compounds.

I wish to thank Miss G. Harris, who occasionally assisted in the preparation of a few intermediates and to those in "Prof.'s Laboratory" for bearing with such patience the commandeering of the F11 Gas Chromatograph and the spinning band distillation column.

I must also say that it was a pleasure to work amongst my colleagues in Research III and will miss the discussions and arguments - serious or frivolous.

Finally, may I thank the Commonwealth Scholarship Commission for enabling me to pursue this course and Lever Brothers (Cey)Limited for granting me leave of absence for three yaars.

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PREFACE

Mounting interest in lipid chemistry emphasises the need for the systematic survey of the physical, chemical, and biological properties of unsaturated acids. In the past such studies have been concentrated on a few common natural acids such as oleic.

Studies of this kind are now proceeding in this department and the present work is concerned with the octadecenoic acids. Most of these have been reported before but must have been impure and in order to make careful comparative studies, it is necessary to have all the isomers available at the same time.

We have now prepared all the possible isomers of octadecenoic acid (thirty one) along with ten octadecynoic acids, five dodecenoic acids, five dodecynoic acids, all the ω-acetylenic acids from C_5 - C_{12} and many other long-chain compounds. In view of the extensive work planned we have obtained 12-17 grammes of most of the cis-octadecenoic acids.

Using these, a study has been made of some of their chromatographic and spectroscopic properties and of the interconversion of cis and trans isomers. The full value of this synthetic programme however remains to be exploited, and plans are in hand to study (here or elsewhere) the following properties:

(i) The conversion of these olefinic acids to closely related compounds including the alcohols and their acetates, the aldehydes and their acetals, the C_{19} cyclopropane acids and, possibly, the dideutero- and ditritiostearic acids.

(ii) Mass spectral studies of olefinic esters.

(iii) Crystal structure studies of the olefinic acids. So far only oleic acid[1] has been examined in this way and our melting point studies suggest that the double bond position has an interesting effect on molecular packing in the crystal state.

(iv) Important enzymic reactions occurring with oleic acid include

(a) two-carbon elongation.

(b) introduction of additional double bonds between the existing double bond and the CH_3 group (plant systems) and between the existing double bond and the carbonyl group (animal systems).

(c) conversion to cyclopropane acids.

In all cases it will be interesting to examine the specificity of the necessary enzymes with respect to the double bond position in the C_{18} chain.

(v) The recent realization[2] that unsaturated long chain compounds such as octadec-11-enyl acetate behave as insect pheromones suggests that these acids and their derivatives should be screened for activity.

INTRODUCTION

THE SYNTHESIS OF LONG CHAIN MONO-OLEFINIC ACIDS.

Although oleic acid was isolated in the early part of the 19th century[3] and its structure determined correctly by Meyer in 1893[4] it was only in the period 1925-1935 that synthetic preparations of oleic acid[5] were recorded. Little further progress was made till about 1940, after which more workers attempted to synthesise long chain unsaturated fatty acids.[6,7,8] The more important routes now available are briefly reviewed.

1. Synthesis proceeding through acetylenic intermediates.

The general procedure based on the ease with which ethynyl compounds readily form organo-metallic derivatives is the most important general method of synthesising unsaturated fatty acids. The present use of this method stems from the work of Ahmad and Strong[9] though useful pointers had been provided before this by Moureu and Delange[10] who showed that metallic derivatives of acetylenes react with carbon dioxide or ethyl carbonate to give $\Delta 2$ - ethynoid acids .

$$\left.\begin{array}{l} CH_3(CH_2)_n\,C\vdots CNa \\ \\ CH_3(CH_2)_n\,C\vdots CMgBr \end{array}\right) + CO_2 \rightarrow CH_3(Cl_2)_nC{:}C\ COOH.$$

Sometime later Simonsen[11] synthesised behenolic (docos-13-ynoic) acid by condensing the sodium derivative of dec-1-yne with methyl 12-bromododecenoate. Interaction of the sodium or Grignard derivative of dec-1-yne with p-toluenesulphonate of 5-chloropentanol gave tetradec-5-ynoic acid.[12]

It was left to Ahmad and Strong to fully realize the potentialities of alkyl acetylenes. This method made possible the synthesis of many unsaturated long-chain acids, and with certain modifications, has been used more than all other methods together in the synthesis of unsaturated fatty acids. Applications of the original Strong procedure include the synthesis of all the octynoic acids[13] and all the nonynoic acids except the Δ^3 isomer.[14] Similarly the cis and trans Δ^7, Δ^8, Δ^9 Δ^{10}, Δ^{11}, and Δ^{12} acids have been prepared via the octadecynoic acids.[15] With minor modifications octadec-6-ynoic acid has also been obtained and converted to the cis and trans olefinic acids.[16]

Although Simonsen et al. used a bromo-ester as one of the intermediates in the synthesis of behenolic acid,[11] the ω-bromo and ω-acetylenic acids, though accessible, have rarely been employed. Ames[17] took advantage of the resistance shown by N,N-dimethylamides to many organo-metallic reagents and used this group to protect the carboxylic radical during the reaction. He showed that the

N,N-dimethylamide of an acetylenic acid gave a sodium derivative with $NaNH_2/NH_3$ and that this reacts with alkyl bromides to give a long chain unsaturated amide which could be hydrolysed to the ethynoid acid. Mono-acetylenic acids have been prepared most often by one of three routes.

(i) An alkyne is condensed with an $\alpha\,\omega$-chloro-iodide and the less reactive chloride group later converted to the carboxylic group.[9]

e.g. $RC\equiv CH \xrightarrow{1,} RC\vdots C(CH_2)_nCl \xrightarrow{2,} RC\vdots C(CH_2)_nCOOH$

1, $NaNH_2$, liq. NH_3; $I(CH_2)_nCl$ 2, NaI, NaCN; KOH; HCl

(ii) Condensation of an alkyne with an ω-bromo-ester as first proposed by Battacharya, Saletore and Simonsen.[11]

(iii) Condensation of N,N-dimethylamides of ω-acetylenic acids with alkyl bromides or alternatively the N,N-dimethylamides of ω-bromo-acids with alkynes as described by Ames.[17]

(a) $RC\equiv CH + Br(CH_2)_nCONMe_2 \xrightarrow{1,} RC\equiv C(CH_2)_nCONMe_2 \xrightarrow{2,}$
$RC\equiv C(CH_2)_nCOOH$

(b) $R'Br + HC\equiv C(CH_2)_nCONMe_2 \xrightarrow{1} R'C\equiv C(CH_2)_nCONMe_2 \xrightarrow{2}$
$R'C\equiv C(CH_2)_nCOOH$

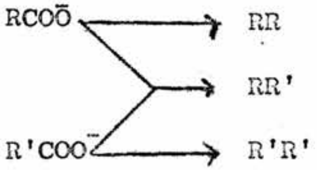
1, $NaNH_2$, liq. NH_3. 2, Hydrolysis.

2. Anodic Synthesis.[18]

Faraday[19] (1834) reported the formation of hydrocarbons when solutions of acetates were electrolysed and Kolbe[20] obtained symmetrical hydrocarbons by electrolysing salts of carboxylic acids.

$$2RCO_2^- \rightarrow RR + 2CO_2$$

When Wurtz[21] (1885) used a mixture of two acids, he produced two symmetrical hydrocarbons along with an unsymmetrical hydrocarbon.



A significant advance was made by Brown and Walker[22] when they showed how it was possible to prepare acids rather than hydrocarbons by using half esters of dibasic acids.

$$RO_2C(CH_2)_nCO_2^- \rightarrow RO_2C(CH_2)_{2n}CO_2R$$

This procedure was extended by Linstead and Weedon[23] who used it to synthesise higher saturated acids. They electrolysed methanolic solutions of appropriate mixtures of a monocarboxylic acid and an excess of the methyl hydrogen ester of a dibasic acid.

$$R'CO_2^- + RO_2C(CH_2)_nCO_2^- \rightarrow R'(CH_2)_nCO_2R$$

This method was then modified to cover the synthesis of long chain unsaturated fatty acids.[24] Mono-olefinic acids result from the electrolysis of starting materials which contain a double bond, a triple bond, or an α-diol system. With the last two, olefinic compounds are obtained by further reaction of the coupled products. Erucic acid was prepared by each of these methods as follows.[24,25]

$$\begin{tikzcd}
CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH \arrow[r, "I"] & CH_3(CH_2)_7C{\equiv}C(CH_2)_7(CH_2)_4COOMe \arrow[d] \\
CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH \arrow[r, "I"] & CH_3(CH_2)_7CH{=}CH(CH_2)_7(CH_2)_4COOMe \\
CH_3(CH_2)_7CH(OH)CH(OH)(CH_2)_7COOH \arrow[r, "I"] & CH_3(CH_2)_7CH(OH)CH(OH)(CH_2)_{11}COOMe \arrow[u]
\end{tikzcd}$$

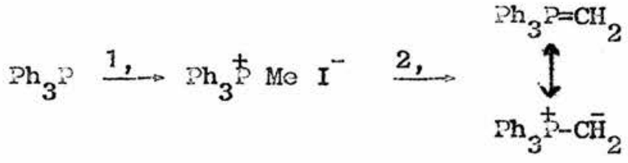
$$I \quad = \quad HO_2C(CH_2)_4COOMe$$

Other mono-unsaturated acids synthesised by anodic coupling are stearolic,[25] tariric,[26] vaccenic,[27] cis-tetracos-15-enoic,[28] and eicos-14-enoic acids.[29]

A drawback of this method is that only relatively small amounts of material can be prepared at a time. On the other hand chain extension using anodic coupling does not involve any stereomutation of the ethenoid bonds or any change in the configuration of the hydroxyl groups. Asymmetric centres in the molecule are preserved thereby making it an ideal method of preparing optically active acids.[30]

3. Wittig Synthesis.

Wittig and Geissler[31] observed that benzophenone condensed with the phosphorane produced from methyl triphenyl phosphonium iodide and phenyl lithium to give 1,1-diphenyl ethylene



$$\mathrm{Ph_3P} \xrightarrow{1,} \mathrm{Ph_3\overset{+}{P}\ Me\ I^-} \xrightarrow{2,} \begin{array}{c} \mathrm{Ph_3P{=}CH_2} \\ \updownarrow \\ \mathrm{Ph_3\overset{+}{P}{-}\overset{-}{C}H_2} \end{array}$$

$$\xrightarrow{3,} \mathrm{Ph_2P{=}O} + \mathrm{Ph_2C{=}CH_2}$$

1, MeI. 2, PhLi. 3, Ph_2CO.

This reaction generally yields both the cis and trans isomers and is therefore not very useful for the synthesis of fatty acids, the cis isomers of which are generally desired. The method has been used extensively in other fields.[32,33,34,35,36] In a systematic investigation of the reaction of aldehydes with alkylidene triphenyl phosphoranes, Bergelson and co-workers[37] showed that the stereochemistry can be controlled with suitable reaction conditions and structural features. In the presence of a sufficiently nucleophilic Lewis base such as bromides, iodides, or certain amines and polar aprotic solvents such as dimethyl formamide, the cis isomer predominates. Two different approaches described by these workers are as follows.

Method A

$$\mathrm{X\ CH_2(CH_2)_nCOOR} \xrightarrow{1,} \mathrm{[Ph_3P{-}CH_2(CH_2)_nCOOR]X}$$

$$\xrightarrow{2,} \mathrm{Ph_3P{=}CH(CH_2)_nCOOR} \xrightarrow{3,} \mathrm{CH_3(CH_2)_mCH{=}CH(CH_2)_nCOOR}$$

X = I or Br

1, Ph_3P 2, CH_3ONa 3, $CH_3(CH_2)_mCHO$, D.M.F., I^-

Method B

$$X\ CH_2(CH_2)_nCOOR \xrightarrow{1,} OHC(CH_2)_nCOOR$$

$$\xrightarrow{2,} CH_3(CH_2)_m\overset{cis}{CH=CH}(CH_2)_nCOOR$$

X = I or Br

1, $(CH_3)_3NO$; $H_3\overset{+}{O}$ 2, $CH_3(CH_2)_mCH=PPh_3$, D.M.F., I^-

cis Vaccenic and oleic have been made by method A.[37] Petragnani and Schill[38] used this modified Wittig reaction to synthesise docosa-1:12-diynoic acid, cis hexadec-11-enoic acid, all trans-octadeca-8,10,12-trienoic acid and heneicosa-11c,13t,15t-trienoic acid. Even with this improvement, the reaction is limited in value by the requirement for a very large excess (150X) of the phosphorane, $Ph_3P=CH(CH_2)_nCOOMe$ over the aldehyde. This makes the reaction uneconomic in terms of the ω-bromo-esters which are not always easy to obtain.

Method using Malonic Ester.

The method described by Bowman and his colleagues[39] using malonic esters as the coupling unit was used by them to prepare tetradec-9-enoic, hexadec-9-enoic, heptadec-8-enoic, octadec-4-enoic, octadec-9-enoic, eicos-9-enoic and docos-13-enoic acids. This method, though useful in the past, is seldom used now.

The general methods available for the synthesis of fatty acids have been reviewed by Gensler,[40] Gunstone,[41,42] and more recently by Markley.[43]

THE OCTADECENOIC AND OCTADECYNOIC ACIDS.

Previous attempts to synthesise these acids are reported in subsequent pages. They include a number of preparations reported whilst our work was in progress.

1. Octadec-2-enoic Acid.

An early claim by Saytzeff and Saytzeff in 1888[44] to have prepared the Δ^2 isomer by treating oleic acid with hydrogen iodide followed by alcoholic potassium hydroxide must be based on the view then held that oleic acid was the Δ^2 or Δ^3 isomer.

The octadec-2-enoic acid obtained by Ponzio[45] (1904) by reaction of 2-iodo-stearic acid with caustic potash must have been, wholly or predominantly, the trans-isomer and the cis-isomer was probably not prepared until 1951 by Myers[46] who obtained it from the trans-isomer by a series of stereospecific reactions - hydroxylation, bromination and dehydrobromination. The trans-isomer was removed by repeated crystallization and the mother liquors were subsequently chromatographed.

Whilst our work was in progress Grimmer and Hildebrandt[47] reported a preparation of the cis and trans- olefinic acids from octadec-2-ynoic acid thus -

$$\begin{tikzcd}
RC\equiv CH \arrow[r, "1{,}2{,}"] & RC\equiv CCOOH \arrow[r, "3{,}"] & \overset{cis}{RCH=CHCOOH} \arrow[d, "4{,}"] \\
RC\equiv CH \arrow[r, "5{,}"] & RC\equiv CCH_2OH \arrow[r, "6{,}"] & \overset{trans}{RCH=CHCOOH}
\end{tikzcd}$$

$R = CH_3(CH_2)_{14}$

1, EtMgBr. 2, CO_2. 3, H_2/Lindlar

4, $Hg(OAc)_2$. 5, EtMgBr/CH_2O. 6, CrO_3/Bu^tOH.

2. Octadec-3-enoic Acid

This acid was first prepared in 1913 by the action of alcoholic potassium hydroxides on 3-iodostearic acid.[48] The reaction yielded a mixture of the Δ^3 isomer together with small amounts of Δ^2 and 3-hydroxy stearic acid. Pure octadec-3-enoic acid was claimed to have been obtained by repeated crystallization. This acid must have been in the trans-form. No other synthesis of this acid has been reported to date, though Δ^3 acids of other chain lengths have been described. Newman and Wotiz[13] claimed to have synthesised oct-3-ynoic acid as follows

$$CH_3(CH_2)_3C\equiv CH \xrightarrow{1,} CH_3(CH_2)_3C\equiv CCH_2OH \xrightarrow{2,3,}$$

$$CH_3(CH_2)_3C\equiv CCH_2CN \xrightarrow{4} CH_3(CH_2)_3C\equiv CCH_2COOCH_3$$

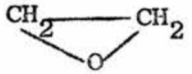
1, $NaNH_2/CH_2O$. 2, PBr_3. 3, $Cu_2(CN)_2$ 4, CH_3OH/HCl.

When this method was used for non-3-ynoic acid, the product was contaminated with allenic and chlorine substituted olefinic esters.[14]

Knight and Diamond,[49] and Wood and Reiser[50] synthesised the C_8 and C_{12} acids respectively by treating the Grignard derivative of the required alkyne with ethylene oxide and oxidising the acetylenic alcohol to the acid with chromium trioxide.

$$RC{\equiv}CH \xrightarrow{1} RC{\equiv}CCH_2CH_2OH \longrightarrow RC{\equiv}CCH_2COOH$$

$R = CH_3(CH_2)_3$ or $CH_3(CH_3)_7$

1, = $NaNH_2$;  2, CrO_3, H_2SO_4

Ames et al.[51] prepared the C_{15} acid by the oxidation of pentadec-3-yn-1ol obtained by condensing the dilithium salt of but-3-yn-1-ol with 1-bromoundecane.

$$RBr + LiC{\equiv}CCH_2CH_2OLi \xrightarrow{1} RC{\equiv}CCH_2CH_2CH \xrightarrow{2} RC{\equiv}CCH_2COOH$$

$R = CH_3(CH_2)_{10}$

1, liq. NH_3; H_2O. 2, CrO_3, H_2SO_4.

They also prepared this acid from 1-bromo-tetradec-2-yne by the procedure set out below though as mentioned by Wotiz and Hudak this method gave an impure product.[14]

$$RC\equiv CCH_2Br \xrightarrow{1} RC\equiv CCH_2CN \longrightarrow RC\equiv CCH_2COOCH_3$$

$R = CH_3(CH_2)_{10}$

1, $Cu_2(CN)_2$, xylene 2, MeOH, HCl

Recently Knipprath and Stein[52] published the following II stage synthesis of trans hexadec-3-enoic acid.

$$RC{=}CH_2 \xrightarrow{1,2} RCH{=}CHBr \xrightarrow{3} RC\equiv CH \xrightarrow{4,5}$$

$$RC\equiv CCOOH \xrightarrow{6,7,8} RCH{=}CHCH_2Br \xrightarrow{9,10,11} \overset{\text{trans}}{RCH{=}CHCH_2COOH}$$

$R = CH_3(CH_2)_{11}$

1, Br_2 2, KOH 3, $NaNH_2$ 4, EtMgBr

5, CO_2 6, Na, liquid NH_3 7, $LiAlH_4$ 8, PBr_3

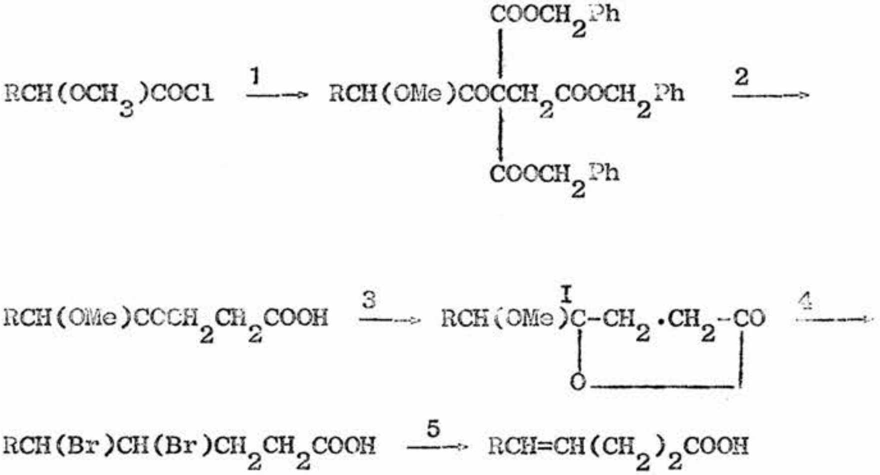
9, KCN or $K^{14}CN$ 10, MeOH, HCl 11, KOH

They claim their acid to be at least 99.5% pure as shown by g.l.c. using an Apiezon L column.

3. Octadec-4-enoic Acid

Octadec-4-enoic acid probably in the trans form was obtained together with the Δ^3 isomer and hydroxy stearic acid by the action of alcoholic potash on 4-iodostearic acid.[48] The latter was prepared pure from octadec-3-enoic acid. These workers (Eckert and Halla) claimed to have separated the Δ^4 isomer from the reaction mixture.

In 1952 Bowman and Ames,[53] prepared both the cis and trans acidsin low yields by their "methoxy ketone" route. Reaction of 2-methoxypentadecanoic acid and oxalyl chloride gave 2-methoxypentadecanoyl chloride which when treated with the sodium derivative of tribenzyl ethane-1,1,2-tricarboxylate gave 4-keto-5-methoxyoctadecanoic acid. Catalytic reduction of the corresponding ester followed by hydrolysis and distillation, furnished the methoxylactone I, which on treatment with hydrogen bromide in the presence of sulphuric and acetic acid gave a mixture of solid and liquid dibromo-octadecanoic acids. Debromination of the solid dibromo-acid (threo) gave the 4t acid and the liquid dibromo-acid which was enriched with the erythio isomer gave a mixture of 4c and 4t isomers .



$$RCH(OCH_3)COCl \xrightarrow{1} RCH(OMe)CO\overset{COOCH_2Ph}{\underset{COOCH_2Ph}{C}}CH_2COOCH_2Ph \xrightarrow{2}$$

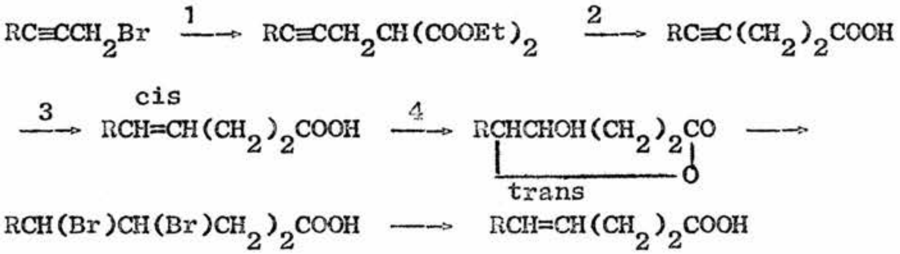
$$RCH(OMe)CCCH_2CH_2COOH \xrightarrow{3} RCH(OMe)\overset{I}{C}\text{-}CH_2\cdot CH_2\text{-}CO \xrightarrow{4}$$

$$RCH(Br)CH(Br)CH_2CH_2COOH \xrightarrow{5} RCH{=}CH(CH_2)_2COOH$$

$R = CH_3(CH_2)_{12}$

1, Na; $PhCH_2OCOCH_2CH(COOCH_2Ph)_2$ 2, debenzylation, decarboxylation, and hydrolysis 3, H_2,Raney nickel 4, $HBr/Acetic/H_2SO_4$ 5, Zn.

More recently Ames and his colleagues [54] prepared these two ethylenic acids from the corresponding acetylenic acid, obtained by the condensation of 1-bromohexadec-2-yne with diethyl malonate. Semihydrogenation gave the 4c acid and this was converted to the trans isomer via the erythro dibromide.



$$RC\equiv CCH_2Br \xrightarrow{1} RC\equiv CCH_2CH(COOEt)_2 \xrightarrow{2} RC\equiv C(CH_2)_2COOH$$

$$\xrightarrow{3} \overset{\text{cis}}{RCH=CH(CH_2)_2COOH} \xrightarrow{4} \underset{\text{trans}}{\underbrace{RCHCHOH(CH_2)_2CO}_{O}} \longrightarrow$$

$$RCH(Br)CH(Br)CH_2)_2COOH \longrightarrow RCH=CH(CH_2)_2COOH$$

$R = CH_3(CH_2)_{12}$

1, Na; diethyl malonate 2, NaOH; HCl; $\Delta 160^{\circ}$

3, H_2, Pd, $BaSO_4$ 4, H_2O_2, formic; H_2O

5, HBr/Acetic/H_2SO_4 5, Zn.

4. Octadec-5-enoic Acid

Trans octadec-5-enoic acid was found to occur in the fatty acids of thalictrum polycarpum seed oil.[55] Recently, growing and resting cells of Bacillus megaterium were found to convert stearic acid to the cis octadec-5-enoic acid.[56]

Posternak[57] prepared the trans-isomers of this acid from tariric acid which gave a mixture of the Δ^5, Δ^6 and Δ^7 octadecynoic acids when treated with alkali. The Δ^5 acid was isolated and treated first with hydrogen iodide and then with zinc and acetic acid. The purity of the 5 trans acid will depend on the purity of the 5-ynoic acid.

Ames et al.[17] synthesised the acetylenic acid and thence the cis mono-enoic acid by reacting dodecyl bromide with N,N-dimethyl-hex-1-ynamide. Hydrolysis of the resulting amide furnished octadec-5-ynoic acid.

$$CH{\equiv}C(CH_2)_3CONMe_2 \xrightarrow{1} RC{\equiv}C(CH_2)_3CONMe_2 \xrightarrow{2}$$

$$RC{\equiv}C(CH_2)_3COOH \xrightarrow{3} RCH{=}CH(CH_2)_3COOH$$

$R = CH_3(CH_2)_{11}$

1, $NaNH_2$; dodecyl bromide 2, NaOH aq,

3, H_2, Pd, $BaSO_4$

They also obtained this acid by oxidising octadec-5-yn-1-ol with chromium trioxide.[51] The alcohol was prepared by condensing hex-5-yn-1-ol as its dilithium salt with dodecyl bromide.

5. Octadec-6-enoic Acid.

Though much less common than unsaturation in the Δ^9 position, natural acids with unsaturation between the $C_{(6)}$ and $C_{(7)}$ are well known, for both the cis-olefinic (petroselenic) and the acetylenic (tariric) acid occur naturally.

Petroselenic acid occurs commonly in seed fats of the Umbelliferae as for example in parsley (82%) carrot (73%)

parsnip (60%), caraway (47%) and chervil (53%).[58]

Tariric acid, until recently the only mono-ynoic C_{18} acid to occur naturally, has been known since 1892.[59] It occurs throughout the Picramnia genus. P. sow for example contains 95% of this acid.[60]

Taylor and Strong[61] failed to synthesise octadec-6-ynoic acid by condensing the sodium salt of tridecyne with 1,4-chloro-iodobutane in liquid ammonia due to the insolubility of the sodium alkyne in the reaction mixture. Lumb and Smith,[16] however, successfully condensed the appropriate lithium alkyne with chloro-iodopropane in dioxan, and converted the resulting 1-chlorohexadec-4-yne to the octadec-6-ynoic acid by the malonic ester synthesis. Partial reduction of the acetylenic acid with Lindlar's catalyst afforded the cis mono-enoic acid.

$$RC{\equiv}CH \xrightarrow{1} RC{\equiv}C(CH_2)_3Cl \xrightarrow{2} RC{\equiv}C(CH_2)_4COOH \xrightarrow{3} \overset{cis}{RCH{=}CH}(CH_2)_4COOH$$

$R = CH_3(CH_2)_{10}$

1, $NaNH_2$; $I(CH_2)_3Cl$ 2, NaI, malonic ester etc.

3, H_2, Lindlar.

An elegant synthesis of octadec-6-ynoic acid was achieved by Linstead and Baker[23] by the "anodic cross coupling" of methyl hydrogen dodec-6-yndioate with an excess of n-octanoic acid. The former component was obtained by condensing 6-chlorohex-1-yne with 1,4-bromochlorobutane and hydrolysing the dichlorodec-6-yne to the dibasic acid.

6. Octadec-7-enoic Acid.

Posternak prepared this acid in the trans form by reducing the product, obtained by the addition of hydrogen iodide to octadec-7-ynoic acid, with zinc and acetic acid[57] (cf. Δ^5).

Using the general procedure of Ahmad and Strong, Huber[15] prepared the Δ^7 to Δ^{12} octadecynoic acids and the corresponding octadecenoic acids in the cis and trans forms. He prepared the Δ^7 ethynoid acid by condensing 1,5-chloro-iodopentane with the sodium salt to dodec-1-yne and converting the chloro-alkyne obtained to the acid via the nitrile. Semi-hydrogenation in the presence of W-6 Raney nickel yielded the cis acid which on selenium isomerization gave the trans form.

$$\mathrm{RC{\equiv}CH} \xrightarrow{\quad 1 \quad} \mathrm{RC{\equiv}C(CH_2)_5Cl} \xrightarrow{2}$$

$$\mathrm{RC{\equiv}C(CH_2)_5COOH} \xrightarrow{3} \overset{\text{cis}}{\mathrm{RCH{=}CH(CH_2)_5COOH}}$$

$$\xrightarrow{4} \overset{\text{trans}}{\mathrm{RCH{=}CH(CH_2)_5\ COOH}}$$

$\mathrm{R = CH_3(CH_2)_9}$

1, $\mathrm{NaNH_2;I(CH_2)_5Cl}$ 2, NaCN;KOH ; HCl 3, $\mathrm{H_2}$,Ni

4, Se

The cis acid was also prepared using the same reaction sequence by Fusari et al.,[62] the only difference being in the preparation of the chloro-iodopentane.

7. Octadec-8-enoic Acid.

This acid, probably in the trans configuration, is formed together with the 10t isomer during partial catalytic hydrogenation of oleic and elaidic acids.[63] Arnaud and Posternak claimed to have obtained the olefinic acid by the action of potassium hydroxide on 9-iodo-stearic acid[64] and surprisingly by dehydration of 10-hydroxystearic acid.[65] These preparations would certainly have given rise to a mixture of Δ^8 and Δ^9 isomers present in the trans form.

Huber[15] and Fusari[62] independently synthesised both the cis and trans isomers via the corresponding acetylenic acid using the alkyl acetylene route.

$$\mathrm{RC{\equiv}CH} \xrightarrow{1,2} \mathrm{RC{\equiv}C(CH_2)_6Cl} \xrightarrow{3} \mathrm{RC{\equiv}C(CH_2)_6COOH}$$

$$\xrightarrow{4} \mathrm{RCH\overset{cis}{=}CH(CH_2)_6COOH} \xrightarrow{5} \mathrm{RCH\overset{trans}{=}CH(CH_2)_6COOH}$$

$R = CH_3(CH_2)_8$

1 , $NaNH_2$, liq. NH_3 2 , $I(CH_2)_6Cl$ 3 , NaCN, KOH, HCl

4 , H_2, Ni 5 , Se.

8. Octadec-9-enoic Acid.

The first recognition (1815) of oleic acid as a constituent of several common fats was described by Chevreul in his Recherches sur les corp gras.[3] Since then, it has been found that oleic acid comprises 50% or more of the total acids of many fats and that few fats contain less than 10% of this acid.

When Varrentrapp[66](1840) obtained palmitic acid in large quantities on fusing oleic acid with caustic potash, this acid was believed to be the Δ^2 isomer. It was not until 1893 that Meyer and Jacobsen[4] proposed that oleic acid was octadec-9-enoic acid, a result which was confirmed by Baruch[67] by a complicated but dubious[68] sequence of changes. Specific oxidation processes have provided a simple, but unequivocal, proof of the structure of oleic acid.

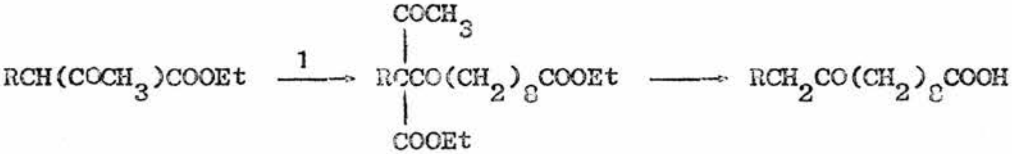
Many claims have been made over the years that pure oleic acid was obtained from natural sources.[69,70]

Octadec-9-ynoic acid (stearolic) has recently been recognised as a minor component of some seed fats.[71,72,73]

Saytzeff, as early as 1887,[44] and Arnaud(1910) observed, that oleic acid was formed as one of the products on heating 10-iodostearic acid with alcoholic potash. This procedure would have resulted in the trans Δ^9 and Δ^{10} octadecenoic acids.

Robinson and Robinson[5] claimed to have achieved a complete synthesis of oleic acid by synthesising the 10-iodostearic acid required by the method of Saytzeff or of Arnaud. However, this method gave a mixture of oleic and elaidic acids.

Robinson and Robinson first obtained 10-ketostearic acid by treating the sodium derivative of 2-acetylnonanoate with ethyl 9-chlorocarbonylnonanoate. This was reduced to the hydroxy compound and then treated with hydrogen iodide to yield 10-iodostearic acid.



$$RCH(COCH_3)COOEt \xrightarrow{1} R\overset{COCH_3}{\underset{COOEt}{C}}CO(CH_2)_8COOEt \longrightarrow RCH_2CO(CH_2)_8COOH$$

R = $CH_3(CH_2)_6$

1, Na, toluene, $ClCO(CH_2)_8COOEt$ 2 , $NaOH, H_2SO_4$

A partial synthesis of an equilibrium mixture of cis and trans octadec-9-enoic acids was described by Noller and Bannerot[74] using the Boord olefinic synthesis. The desired 1-methoxy-1,2-dibromo-alkane was produced by treating ω-chlorononanol with bromine followed by methanolic hydrogen bromide. This intermediate was coupled with octylmagnesium bromide to give a product which on heating with zinc yielded 1-chloro-heptadec-8-ene. Conversion of the chloro compound to the required acid was affected by hydrolysis via the nitrile. The ω-chlorononanol was obtained by ozonolysis of octadec-9-enyl chloride itself derived from oleic acid.

$$\mathrm{Cl(CH_2)_7CH_2CHO \xrightarrow{1} Cl(CH_2)_7CH(Br)CHO \xrightarrow{2} Cl(CH_2)_7CH(Br)CH(OCH_3)Br}$$

$$\mathrm{\xrightarrow{3} Cl(CH_2)_7CH(Br)CH(OCH_3)(CH_2)_7CH_3 \xrightarrow{4} Cl(CH_2)_7CH{=}CH(CH_2)_7CH_3}$$

$$\mathrm{\xrightarrow{5} CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH}$$

1, Br_2 2, CH_3OH, HBr 3, $CH_3(CH_2)_7MgBr$

4, Zn 5, NaCN; KOH, HCl

A later synthesis (Baudart[8]) from decanal also gave the mixed 9c and 9t acids.

$$\mathrm{RCH_2CHO \xrightarrow{1} RCH(Br)CH(Br)OEt \xrightarrow{2} RCH(Br)CH(OEt)(CH_2)_5CH_2OMe}$$

$$\mathrm{\xrightarrow{3} RCH{=}CH(CH_2)_5CH_2OMe \xrightarrow{4} RCH{=}CH(CH_2)_5CH_2Br}$$

$$\mathrm{\xrightarrow{5} RCH{=}CH(CH_2)_5CH_2I \xrightarrow{6} RCH{=}CH(CH_2)_7COOH}$$

$R = CH_3(CH_2)_7$

1, Br_2, EtOH 2, $BrMg(CH_2)_5CH_2OMe$ 3, Zn, BuOH

4, Br_2, HBr; Zn, EtOH 5, NaI, Acetone 6, malonic ester synthesis.

Yet another preparation of this type has been reported by Baudart.[75]

Linstead and co-workers[25] electrolytically coupled pentadec-6-ynoic acid and methyl hydrogen glutarate to obtain stearolic acid. Better yields were obtained with benzyl hydrogen glutarate.

Huber[15] accomplished the synthesis of octadec-9-ynoic acid and the corresponding cis and trans isomers by the alkyl acetylene route.

The Δ^9 acid has also been synthesised by the methoxy ketone variant of the malonic ester synthesis by Ames and Bowman[76] and by methods enploying magnesium alkyl halides by Gensler and Thomas.[7]

9. Octadec-10-enoic Acid.

The presence of trans octadec-10-enoic acid has been reported in the body fats of the ox and sheep[77] and in pork lipids by Channon et al.[78]

Saytzeff et al.[44] prepared the 10 isomer along with the Δ^9 isomer by the action of alcoholic potash on 10 iodostearic acid, and also by the distillation of 10 hydroxystearic acid.

Bauer and Panagoulias[79] claimed that the Δ^{10} acid resulted when oleic acid was treated with zinc chloride.

Huber[15] achieved an unequivocal synthesis of octadec-10-ynoic acid by condensing the sodium derivative of non-1-yne with 1,8-chloro-iodo-octane, and subsequent conversion of the chloro-alkyne to the acid. Both cis and trans forms of the ethylenic acid have been reported by him.

10. Octadec-11-enoic Acid.

Although the 11 trans acid, commonly referred to as vaccenic acid, is only a minor constituent of fats, it has attracted considerable attention because it is unusual among natural mono-ethenoid acids in having the trans configuration and because of a claim that it shows growth promoting properties.[80]

Bertram[81] gave the name vaccenic to an acid present in small proportions (0.1 -1.0%) in ox and sheep body fats and in butter fat, and considered it to be trans octadec-11-enoic acid. After much controversy it is now clear that ruminants produce a mixture of isomeric cis and trans octadecenoates by bio-hydrogenation of dietary linoleic and linolenic acid and that vaccenic acid is a constituent and perhaps the major component of this mixture.[82]

The claim of Boer and co-workers[80] that this acid showed growth-promoting properties was challenged by Deuel and Greenberg[83] and by Hilditch et al[77] and now seems unlikely. Of greater importance is the discovery that the 11 cis acid may be of wider occurrence than hitherto recognised. It was first discovered in horse brain by Morton and Todd[84] and subsequently in fats produced by many micro-organisms. Recently it has been claimed that the 11c isomer is a normal constituent of animal tissue and accompanies the more common 9c isomer.[85]

Strong[86] synthesised trans octadec-11-enoic acid and compared it with a pure sample of natural acid. They were similar in melting point and infra red spectra but different in crystal spacings determined by x-ray diffraction.[87] Since the elaidinized sample prepared by Strong did not show appreciable double bond migration it was concluded that the difference in the x-ray diffraction pattern was due to the presence of isomeric acids in the natural variety.

Hilditch[77] confirmed this explanation by showing that specific oxidative fission of natural vaccenic acid gave several mono and dicarboxylic acids and concluded that it was "a mixture of more than one trans-ethenoid acid, and certainly contains trans octadec-10-enoic as well as trans octadec-11-enoic acids".

The acid has now been synthesised via acetylenic precursors, by anodic syntheses and by the Wittig reaction but the preparation by partial reduction of eleostearic acid (9c, 11t, 13t) is unlikely to be satisfactory.

Ahmad and Strong[86] in 1948 prepared the 11c and 11t isomers from the appropriate octadecynoic acid. Reaction of the sodium derivative of octyne with 1,9-chloro-iodononane in liquid ammonia gave 10-chloroheptadec-1-yne, which was then converted to the acetylenic acid. Cis vaccenic was obtained by partial reduction in the presence of Raney nickel and the trans acid was prepared by elaidinizing the cis isomer with selenium.

Huber[15] and Fusari[62] independently prepared these isomers by substantially the same procedure.

By reaction of pentylmagnesium bromide with methyl ω-bromotridec-11-enoate, Gensler[7] prepared methyl trans octadec-11-enoate. Hydrolysis of the ester gave, in low yield, a mixture of cis and trans acids.

$$\begin{tikzcd}
CH_2{=}CH(CH_2)_8COOH \arrow[r, "1,2,3"] & CH_2{=}CH(CH_2)_{10}COOMe \\
\arrow[r, "4"] & CH_2{=}CHCH(Br)(CH_2)_9COOMe \arrow[d, shift right] \\
 & BrCH_2CH{=}CH(CH_2)_9COOMe \arrow[u, shift right] \arrow[r, "5,6"] & CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH
\end{tikzcd}$$

1, $LiAlH_4$ 2, $SOCl_2$ 3, malonic ester

4, NBS 5, pentyl Grignard 6, saponification

Gensler[88] attributed the low yields to the competing reaction of pentyl magnesium bromide with the ester linkage and solved the problem by condensing allylically brominated 11-chloro-undec-1-ene, rather than the ester, and then extending the chloro-alkene to the acid of correct chain lengths by malonation.

Van Loon and Van der Linden,[89] considering Ahmad and Strong's method too complicated, devised a partial synthesis of cis and trans acids involving chain extension of hexadec-9-enoic acid obtained from whale oil. The C_{16} acid was converted first to the bromo derivative via the alcohol and then extended by malonation to a mixture of cis and trans acid in a ratio of (1:2).

Linstead[27] achieved the same chain-elongation by anodic synthesis with a large excess of ethyl hydrogen succinate and obtained the cis isomer in 12% yield. Triaconta-7,23-diene and methyl adipate were obtained as by products from the reaction. Since no specific method for the preparation of trans acid was then available these workers prepared erythro dibromo-octadecanoate from the cis ethylenic acid and then debrominated it with zinc to give the trans octadec-11-enoate.

Cis vaccenic has also been prepared by Bergelson[37] using the modified Wittig synthesis.

$$ICH_2(CH_2)_9COOMe \xrightarrow{1} Ph_3\overset{+}{P}-CH_2(CH_2)_9COOMe\ \bar{X}$$

$$\xrightarrow{2} Ph_3P{=}CH(CH_2)_9COOMe \xrightarrow{3} CH_3(CH_2)_5\overset{cis}{CH{=}CH}(CH_2)_9COOMe$$

1, Ph_3P 2, CH_3ONa 3, $CH_3(CH_2)_5CHO$

11. <u>Octadec-12-enoic Acid.</u>

The 12t isomer is said to be one of the products of partial reduction of eleostearic acid[90] but this is unlikely to provide a pure sample of this acid. (See Δ^{13} octadecenoic acid).

The 12c and 12t acids will also be present among the partial reduction products of linoleic and linolenic acids but with the possible exception of the reduction with hydrazine,[91] this is unlikely to be of preparative value.

$$18{:}2(9c,\ 12c)\ \xrightarrow{N_2H_4}\ \underset{18:1(9c\text{ and }12c)}{\text{monoenes}}\ \longrightarrow\ \text{saturated}$$

$$18{:}3\ (9c,\ 12c,\ 15c)\ \xrightarrow{N_2H_4}\ \text{dienes}\ \xrightarrow{N_2H_4}\ \underset{18:1(9c,\ 12c\text{ and }15c)}{\text{monoenes}}\ \longrightarrow\ \text{saturated}$$

Fokin[92] claimed to have prepared octadec-12-enoic acid together with the 11-isomer by the action of alcoholic potash on 12-bromostearic acid and by the dehydration of 12-hydroxystearic acid with phosphorus pentoxide.

Huber,[15] with heptyne and 1,10-chloro-iododecane as starting material, used the alkyl acetylene route to prepare the 11-ynoic and the two forms of 11-enoic acids.

$$CH_3(CH_2)_4C{\equiv}CH\ \xrightarrow{1}\ CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}Cl\ \xrightarrow{2}$$

$$CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}COOH\ \xrightarrow{3}\ CH_3(CH_2)_4\overset{cis}{CH{=}CH}(CH_2)_{10}COOH$$

$$\xrightarrow{4}\ CH_3(CH_2)_4\overset{trans}{CH{=}CH}(CH_2)_{10}COOH$$

1, NanH$_2$; I(CH$_2$)$_{10}$Cl 2, NaCN; KOH 3, H$_2$; Ni

4, Se.

Bharucha and Gunstone[93] prepared the trans acid by debrominating 12,13-dibromostearic acid with zinc. The dibromo compound was obtained from naturally occurring 12-13-epoxyoleic acid. Baker and Gunstone[29] obtained octadec-12-ynoic acid by electrolysing a solution of tetradec-9-ynoic acid and excess methylhydrogen adipate in methanol. The tetradecynoic acid was synthesised by the use of acetylenic intermediates. The C_{18} acetylenic acid was later partially reduced to the cis isomer.

12. Octadec-13-enoic Acid.

Allen and Keiss[90] found that the Δ^{13} acid was formed together with the Δ^{9}, Δ^{10}, Δ^{11} and Δ^{12} isomers when methyl eleostearate was partially hydrogenated.

A synthesis of this acid has not been recorded.

13. Octadec-14-enoic Acid.

No synthesis of this acid has been published.

14. Octadec-15-enoic Acid.

Bauer and Ermann[94] reported that this acid, together with other isomers, was formed during partial hydrogenation of linoleic acid. This discovery was confirmed by Dutton and co-workers[95] who found that the double bond in both cis and trans monoenes was found in all carbon positions 7 through 16. The major cis bonds however remained at carbons 9,12 and 15. By far the best method of partial reduction to give the 15c isomer involves the use of hydrazine.[91]

A protracted Boord-type synthesis for the Δ^{15} isomer starting from ethyl erucate was described by Yamamoto.[6] This involves the condensation of 1-chloro-12,13-dibromo-13-methoxytridecane with ethyl magnesium bromide to give 12-bromo-1-chloro-13-methoxypentadecane and proceeds as follows.

$$CH_3(CH_2)_7CH{=}CH(CH_2)_{11}COOEt \xrightarrow{1,2} CH_3(CH_2)_7CH{=}CH(CH_2)_{11}CH_2Cl \xrightarrow{3}$$

$$CH_3(CH_2)_7CH(OH)CH(OH)(CH_2)_{12}Cl \xrightarrow{4} Cl(CH_2)_{12}CHO \xrightarrow{5}$$

$$Cl(CH_2)_{11}CH(Br)CH(OMe)Br \xrightarrow{6} Cl(CH_2)_{11}CH(Br)CH(OMe)CH_2CH_3 \xrightarrow{7}$$

$$Cl(CH_2)_{11}CH{=}CHCH_2CH_3 \xrightarrow{8,9} CH_3CH_2CH{=}CH(CH_2)_{11}COOEt$$

$$\xrightarrow{10} CH_3CH_2CH{=}CH(CH_2)_{11}CH_2OH \xrightarrow{11,12} CH_3CH_2CH{=}CH(CH_2)_{13}COOH$$

1, Na, BuOH   2, $SOCl_2$ 3, H_2O_2, acetic   4, $Pb(OAc)_4$

5, Br_2; HBr, MeOH   6, EtMgBr   7, Zn, BuOH

8, KCN, Alcohol; KOH   9, EtOH   10, Na, BuOH

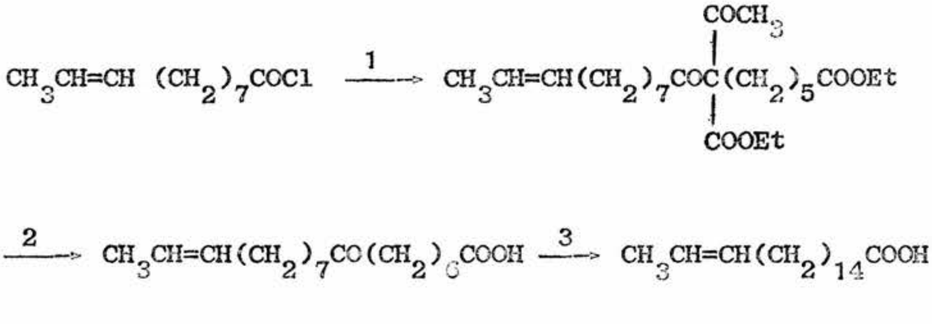
11, HBr   12, malonation etc.

The Boord synthesis is non-stereospecific and the final product was a mixture of cis and trans acids.

15. <u>Octadec-16-enoic Acid.</u>

By a process which included fractional distillation in vacuo, low-temperature crystallisations and column chromatography with activated silica, an acid (0.2%) was isolated from summer butterfat and was shown to be trans octadec-16-enoic acid.[96] It is also present in sheep and ox fats and is one of the many products formed during the partial reduction of linolenic acid.[95]

Trans octadec-16-enoic acid was synthesised by Kapp and Knoll[97] in 1943. Ethyl 7-acetyl-7-carbethoxy-8-keto octadec-16-enoate prepared by the acetoacetate ester synthesis with 9,10-undecenoyl chloride, was hydrolysed and decarboxylated to give ethyl 8-keto-octadec-16-enoate. The keto-acid when subjected to the Wolff Kishner reduction yielded octadec-16-enoic acid of unknown configuration, though the melting point would suggest it was in the trans form.



$$CH_3CH{=}CH\ (CH_2)_7COCl \xrightarrow{1} CH_3CH{=}CH(CH_2)_7CO\overset{\displaystyle COCH_3}{\underset{\displaystyle COOEt}{C}}(CH_2)_5COOEt$$

$$\xrightarrow{2} CH_3CH{=}CH(CH_2)_7CO(CH_2)_6COOH \xrightarrow{3} CH_3CH{=}CH(CH_2)_{14}COOH$$

1, Na; $CH_3COCH(COOEt)(CH_2)_5COOEt$

2, KOH; aq. H_2SO_4; aq. NaOH 3, N_2H_4; KOH

The purity of the undec-9-enoic acid used in the reaction is doubtful since it was prepared from undec-10-enoic acid by bromination, debromination, and partial reduction of undec-9-ynoic acid. (see p. 37 for further discussion).

$$CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} BrCH_2CH(Br)(CH_2)_8COOH \xrightarrow{2}$$

$$CH_3C{\equiv}C(CH_2)_8COOH \xrightarrow{3} CH_3CH{=}CH(CH_2)_8COOH$$

1, Br_2 2, KOH; Aq. acid 3, HI, acetic; Zn.

16. <u>Octadec-17-enoic Acid.</u>

Huber[15] and Kapp and Knoll[97] have described two methods of synthesising this isomer both requiring the Wolff Kishner reduction in the final stage of the reaction sequence. Huber's method involved the condensation of di-undec-10-enyl cadmium with ethyl 6-chlorocarbonylhexanoate to yield ethyl 7-keto-octadec-17-enoate which gave octadec-17-enoic acid by Wolff Kishner reduction.

$$CH_2{=}CH(CH_2)_8COOEt \xrightarrow{1} CH_2{=}CH(CH_2)_8CH_2MgBr \xrightarrow{2}$$

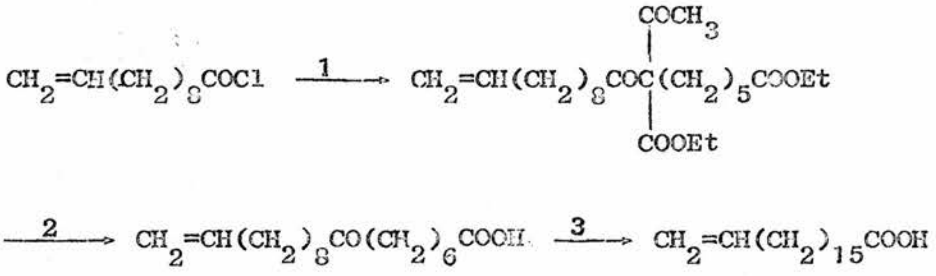
$$(CH_2{=}CH(CH_2)_9)_2Cd \xrightarrow{3} CH_2{=}CH(CH_2)_9CO(CH_2)_5COOEt$$

$$\xrightarrow{4,5} CH_2{=}CH(CH_2)_{15}COOH$$

1, $LiAlH_4$; PBr_3; Mg. 2, $CdCl_2$ 3, $EtO_2C(CH_2)_5COCl$

4, aq. NaOH 5, N_2H_4; KOH ; HCl

Kapp and Knoll on the other hand, reacted undec-10-enoyl chloride with the sodium derivative of ethyl acetyl suberate to give ethyl 7-acetyl-7-carbethoxy-8-keto-octadec-17-enoate. The latter on hydrolysis and decarboxylation gave 8-keto-octadec-17-enoic acid.



$$\mathrm{CH_2{=}CH(CH_2)_8COCl \xrightarrow{1} CH_2{=}CH(CH_2)_8CO\overset{COCH_3}{\underset{COOEt}{C}}(CH_2)_5COOEt}$$

$$\mathrm{\xrightarrow{2} CH_2{=}CH(CH_2)_8CO(CH_2)_6COOH \xrightarrow{3} CH_2{=}CH(CH_2)_{15}COOH}$$

1, Na; $\mathrm{EtO_2CCH(COCH_3)(CH_2)_5COOEt}$ 2, NaOH; $\mathrm{H_2SO_4}$

3, $\mathrm{N_2H_4}$; KOH; HCl.

REACTION FLOW SHEETS

The sequence of reactions leading to the methyl octadecenoates is shown in the following sixteen pages.

Methyl Octadec-2-enoate

$$CH_3(CH_2)_{14}COOH \xrightarrow{1} CH_3(CH_2)_{14}Br \xrightarrow{2} CH_3(CH_2)_{14}C{\equiv}CH$$

$$\xrightarrow{3} CH_3(CH_2)_{14}C{\equiv}C.COOH \xrightarrow{4} CH_3(CH_2)_{14}C{\equiv}CCOOMe \xrightarrow{5}$$

$$CH_3(CH_2)_{14}CH\overset{cis}{=}CHCOOMe$$

1, $AgNO_3$; Br_2 2 , $NaC{\equiv}CH$, liquid ammonia

3 , EtMgBr; CO_2 4 , MeOH, HCl 5 , H_2, Lindlar

Octadec-3-enoic Acid

$$CH_3(CH_2)_{13}OH \xrightarrow{1} CH_3(CH_2)_{13}Br \xrightarrow{2} CH_3(CH_2)_{13}C{\equiv}CH$$

$$\xrightarrow{3} CH_3(CH_2)_{13}C{\equiv}CCH_2CH_2OH \xrightarrow{4} CH_3(CH_2)_{13}\overset{cis}{CH{=}CH}CH_2CH_2OH$$

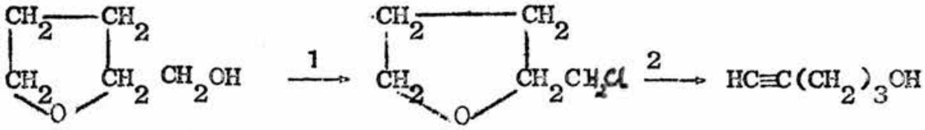
$$\xrightarrow{5} CH_3(CH_2)_{13}\overset{cis}{CH{=}CH}CH_2COOH$$

1, Br_2, red phosphorus 2, NaC≡CH, liquid ammonia

3, PhLi, ethylene oxide, liq. NH_3 4, H_2, Lindlar

5, CrO_3, H_2SO_4, acetone.

Methyl Octadec-4-enoate



$$\xrightarrow{3} \mathrm{HC{\equiv}C(CH_2)_2COOH} \xrightarrow{4} \mathrm{HC{\equiv}C(CH_2)_2CONMe_2} \xrightarrow{5}$$

$$\mathrm{CH_3(CH_2)_{12}C{\equiv}C(CH_2)_2CONMe_2} \xrightarrow{6} \mathrm{CH_3(CH_2)_{12}C{\equiv}C(CH_2)_2COOH}$$

$$\xrightarrow{7} \mathrm{CH_3(CH_2)_{12}C{\equiv}C(CH_2)_2COOMe} \xrightarrow{8} \mathrm{CH_3(CH_2)_{12}CH\overset{cis}{=}CH(CH_2)_2COOMe}$$

1, $SOCl_2$, pyridine   2, $NaNH_2$, liquid ammonia

3, CrO_3, H_2SO_4, acetone   4, $SOCl_2$; $HNMe_2$

5, $NaNH_2$, liquid ammonia; 1-Bromotridecane

6, NaOH, EtOH; HCl   7, MeOH, HCl   8, H_2, Lindlar

Methyl Octadec-5-enoate

$\mathrm{Br(CH_2)_3Cl} \xrightarrow{1} \mathrm{HC{\equiv}C(CH_2)_3Cl} \xrightarrow{2} \mathrm{HC{\equiv}C(CH_2)_3COOH} \xrightarrow{3}$

$\mathrm{HC{\equiv}C(CH_2)_3CONMe_2} \xrightarrow{4} \mathrm{CH_3(CH_2)_{11}\ C{\equiv}C\ (CH_2)_3CONMe_2} \xrightarrow{5}$

$\mathrm{CH_3(CH_2)_{11}C{\equiv}C(CH_2)_3COOH} \xrightarrow{6} \mathrm{CH_3(CH_2)_{11}C{\equiv}C(CH_2)_3COOMe}$

$\xrightarrow{7} \mathrm{CH_3(CH_2)_{11}CH\overset{cis}{=}CH(CH_2)_3COOMe}$

1, NaC≡CH, liquid ammonia 2, NaI, NaCN; KOH; HCl

3 , $\mathrm{SOCl_2}$; $\mathrm{HNMe_2}$ 4, $\mathrm{NaNH_2}$, liquid ammonia; 1-bromododecane

5, NaOH, EtOH 6 , MeOH, HCl 7, $\mathrm{H_2}$, Lindlar

Methyl Octadec-6-enoate

$$HO(CH_2)_4OH \xrightarrow{1} Cl(CH_2)_4Cl \xrightarrow{2} I(CH_2)_4Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_4Cl \xrightarrow{4} HC{\equiv}C(CH_2)_4COOH \xrightarrow{5} HC{\equiv}C(CH_2)_4CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4CONMe_2 \xrightarrow{7} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOH$$

$$\xrightarrow{8} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOMe \xrightarrow{9} CH_3(CH_2)_{10}CH\overset{cis}{=}CH(CH_2)_4COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4 , NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$
6, $NaNH_2$, liquid ammonia; 1 bromo-undecane 7, NaOH, EtOH
8, MeOH, HCl 9, H_2, Lindlar.

Methyl Octadec-7-enoate

$$HO(CH_2)_5OH \xrightarrow{1} Cl(CH_2)_5Cl \xrightarrow{2} I(CH_2)_5Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_5Cl \xrightarrow{4} HC{\equiv}C(CH_2)_5COOH \xrightarrow{5} HC{\equiv}C(CH_2)_5CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_9C{\equiv}C(CH_2)_5CONMe_2 \xrightarrow{7} CH_3(CH_2)_9C{\equiv}C(CH_2)_5COOH$$

$$\xrightarrow{8} CH_3(CH_2)_9C{\equiv}C(CH_2)_5COOMe \xrightarrow{9} CH_3(CH_2)_9\overset{cis}{CH{=}CH}(CH_2)_5COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4, NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$ 6, $NaNH_2$, liquid ammonia; 1-bromodecane 7, NaOH, EtOH 8, MeOH, HCl 9, H_2, Lindlar

Methyl Octadec-8-enoate

$$HO(CH_2)_6OH \xrightarrow{1} Cl(CH_2)_6Cl \xrightarrow{2} I(CH_2)_6Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_6Cl \xrightarrow{4} HC{\equiv}C(CH_2)_6COOH \xrightarrow{5} HC{\equiv}C(CH_2)_6CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_8C{\equiv}C(CH_2)_6CONMe_2 \xrightarrow{7} CH_3(CH_2)_8C{\equiv}C(CH_2)_6COOH$$

$$\xrightarrow{8} CH_3(CH_2)_8C{\equiv}C(CH_2)_6COOMe \xrightarrow{9} CH_3(CH_2)_8CH\overset{cis}{=}CH(CH_2)_6COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, $NaC{\equiv}CH$, liquid ammonia 4, NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$ 6, $NaNH_2$, liquid ammonia; 1-bromononane 7, NaOH, EtOH 8, MeOH, HCl 9, H_2, Lindlar.

Methyl Octadec-9-enoate

$HO(CH_2)_6OH \xrightarrow{1} Cl(CH_2)_6Cl \xrightarrow{2} I(CH_2)_6Cl \xrightarrow{3}$

$HC{\equiv}C(CH_2)_6Cl \xrightarrow{4} HC{\equiv}C(CH_2)_6CH(COOEt)_2 \xrightarrow{5}$

$HC{\equiv}C(CH_2)_6CH_2COOH \xrightarrow{6} HC{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{7}$

$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{8} CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH$

$\xrightarrow{9} CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOMe \xrightarrow{10} CH_3(CH_2)_7CH\overset{cis}{=}CH(CH_2)_7COOMe$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid
ammonia 4, NaI, $HC(Na)(COOEt)_2$, EtOH 5, NaOH; HCl;
160°, 6, $SOCl_2$; $HNMe_2$ 7, $NaNH_2$, liquid ammonia;
1-bromo-octane 8, NaOH, EtOH- HCl 9, MeOH, HCl
10, H_2, Lindlar.

Methyl Octadec-10-enoate

$$\mathrm{HOOC(CH_2)_8COOH} \xrightarrow{1} \mathrm{HOOC(CH_2)_8COOMe} \xrightarrow{2} \mathrm{Br(CH_2)_8COOMe}$$

$$\xrightarrow{3} \mathrm{Br(CH_2)_8COOH} \xrightarrow{4} \mathrm{Br(CH_2)_8CONMe_2} \xrightarrow{5} \mathrm{I(CH_2)_8CONMe_2}$$

$$\xrightarrow{\quad 6 \quad} \mathrm{CH_3(CH_2)\ C{\equiv}C\cdot(CH_2)_8CONMe_2} \xrightarrow{7} \mathrm{CH_3(CH_2)_6C{\equiv}C(CH_2)_8COOH}$$

$$\xrightarrow{8} \mathrm{CH_3(CH_2)_6C{\equiv}C(CH_2)_8COOMe} \xrightarrow{9} \mathrm{CH_3(CH_2)_6CH\overset{cis}{=}CH(CH_2)_8COOMe}$$

1, diethyl sebacate, EtOH 2 , KOH; $AgNO_3$; Br_2,CCl_4

3, 0.5N NaOH 4, $SOCl_2$; $HNMe_2$ 5, NaI, acetone

6, $NaNH_2$, liquid ammonia; nonyne 7, NaOH,EtOH; HCl

8, MeOH, HCl 9, H_2, Lindlar

Methyl Octadec-11-enoate

$CH_2=CH(CH_2)_8COOH \xrightarrow{1} Br(CH_2)_{10}COOH \xrightarrow{2} Br(CH_2)_9COOH$

$\xrightarrow{3} Br(CH_2)_9CONMe_2 \xrightarrow{4} CH_3(CH_2)_5C\equiv C(CH_2)_9CONMe_2 \xrightarrow{5}$

$CH_3(CH_2)_5C\equiv C(CH_2)_9COOH \xrightarrow{6} CH_3(CH_2)_5C\equiv C(CH_2)_9COOMe$

$\xrightarrow{7} CH_3(CH_2)_5\overset{cis}{CH=CH}(CH_2)_9COOMe$

1, HBr, petroleum ether, O_2 2 , Barbier-Wieland R^n
3 , $SOCl_2$; $HNMe_2$ 4 , $NaNH_2$, liquid ammonia; octyne
5, NaOH, EtOH; HCl   6, MeOH,HCl   7 , H_2, Lindlar

Methyl Octadec-12-enoate

$$\mathrm{CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} Br(CH_2)_{10}COOH \xrightarrow{2} Br(CH_2)_{10}CONMe_2}$$

$$\mathrm{\xrightarrow{3} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}CONMe_2 \quad \xrightarrow{4} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}COOH}$$

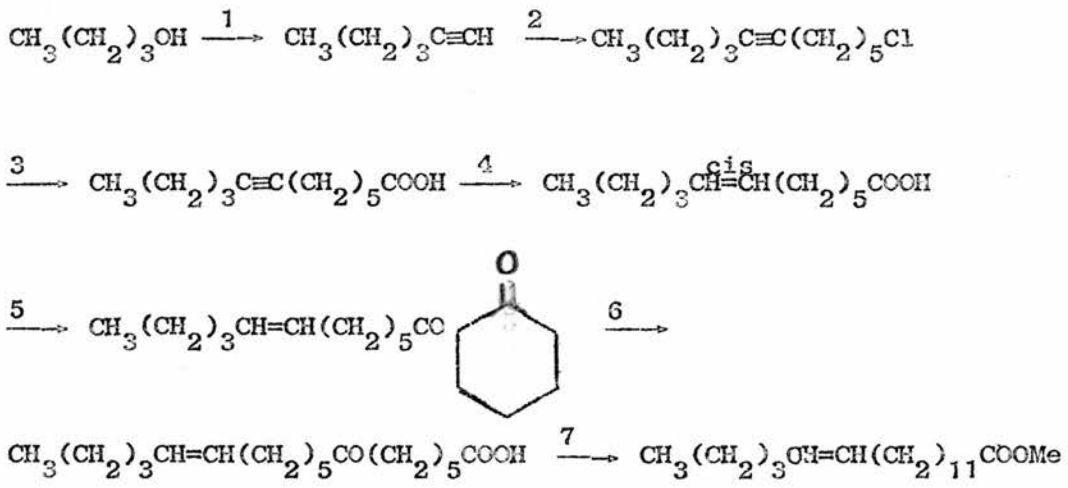
$$\mathrm{\xrightarrow{5} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}COOMe \xrightarrow{6} CH_3(CH_2)_4CH\overset{cis}{=}CH(CH_2)_{10}COOMe}$$

1, HBr, petroleum ether, O_2 2, $SOCl_2$; $HNMe_2$

3, $NaNH_2$, liquid ammonia; Heptyne 4, NaOH, EtOH; HCl

5, MeCH, HCl 6, H_2, Lindlar

Methyl Octadec-13-enoate



$$CH_3(CH_2)_3OH \xrightarrow{1} CH_3(CH_2)_3C{\equiv}CH \xrightarrow{2} CH_3(CH_2)_3C{\equiv}C(CH_2)_5Cl$$

$$\xrightarrow{3} CH_3(CH_2)_3C{\equiv}C(CH_2)_5COOH \xrightarrow{4} CH_3(CH_2)_3\overset{cis}{CH{=}CH}(CH_2)_5COOH$$

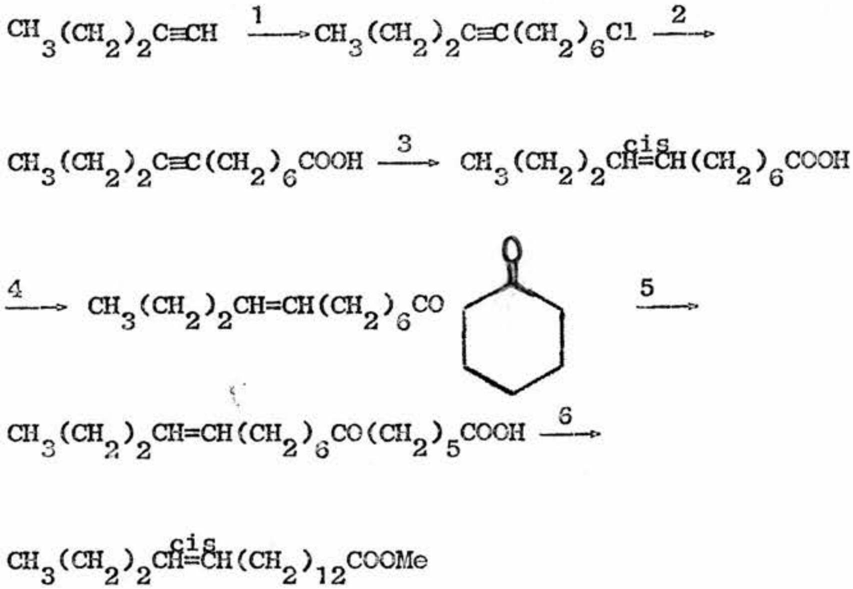
$$\xrightarrow{5} CH_3(CH_2)_3CH{=}CH(CH_2)_5CO \xrightarrow{6}$$

$$CH_3(CH_2)_3CH{=}CH(CH_2)_5CO(CH_2)_5COOH \xrightarrow{7} CH_3(CH_2)_3CH{=}CH(CH_2)_{11}COOMe$$

1, Br_2, red phosphorus; $NaC{\equiv}CH$, liquid ammonia

2, $NaNH_2$, liquid ammonia; $I(CH_2)_5Cl$ 3, NaI, NaCN; KOH 4, H_2, Lindlar 5, $SOCl_2$; morpholino-cyclohex-1-ene; HCl 6, KOH, HCl 7, N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl.

Methyl Octadec-14-enoate



$CH_3(CH_2)_2C{\equiv}CH \xrightarrow{1} CH_3(CH_2)_2C{\equiv}C(CH_2)_6Cl \xrightarrow{2}$

$CH_3(CH_2)_2C{\equiv}C(CH_2)_6COOH \xrightarrow{3} CH_3(CH_2)_2\overset{cis}{CH{=}CH}(CH_2)_6COOH$

$\xrightarrow{4} CH_3(CH_2)_2CH{=}CH(CH_2)_6CO$ $\xrightarrow{5}$

$CH_3(CH_2)_2CH{=}CH(CH_2)_6CO(CH_2)_5COOH \xrightarrow{6}$

$CH_3(CH_2)_2\overset{cis}{CH{=}CH}(CH_2)_{12}COOMe$

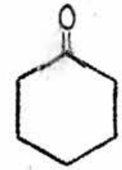
1, $NaNH_2$, liquid ammonia; $I(CH_2)_6Cl$ 2 , NaI, NaCN; KOH; HCl 3 , H_2, Lindlar 4 , $SOCl_2$; morpholino-cyclohex-1-ene; HCl 5, KOH, H_2O; HCl 6 , N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl.

Methyl Octadec-15-enoate

$$\mathrm{CH_2{=}CH(CH_2)_8COOH} \xrightarrow{1} \mathrm{HC{\equiv}C(CH_2)_8COOH} \xrightarrow{2} \mathrm{HC{\equiv}C(CH_2)_7COOH}$$

$$\xrightarrow{3} \mathrm{HC{\equiv}C(CH_2)_7CONMe_2} \xrightarrow{4} \mathrm{C_2H_5C{\equiv}C(CH_2)_7CONMe_2} \xrightarrow{5}$$

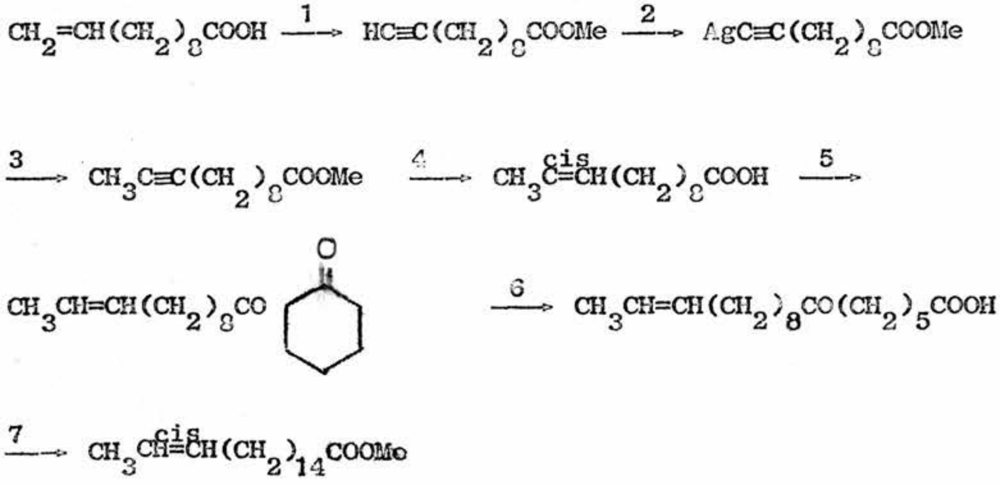
$$\mathrm{C_2H_5CH\overset{cis}{=}CH(CH_2)_7COOH} \xrightarrow{6} \mathrm{C_2H_5CH{=}CH(CH_2)_7CO}$$



$$\xrightarrow{7} \mathrm{C_2H_5CH{=}CH(CH_2)_7CO(CH_2)_5COOH} \xrightarrow{8} \mathrm{C_2H_5CH\overset{cis}{=}CH(CH_2)_{13}COOMe}$$

1, Br_2, petroleum ether; KOH   2, Barbier-Wieland R^n
3, $SOCl_2$; $HNMe_2$ 4 , $NaNH_2$, liquid ammonia; ethyl iodide
5 , NaOH,EtOH; HCl; H_2, Lindlar   6, $SOCl_2$, morpholino-cyclohex-1-ene; HCl   7, NaOH; HCl   8, N_2H_4, ethanolamine; KOH; HCl; MeOH,HCl

Methyl Octadec-16-enoate



$$CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} HC{\equiv}C(CH_2)_8COOMe \xrightarrow{2} AgC{\equiv}C(CH_2)_8COOMe$$

$$\xrightarrow{3} CH_3C{\equiv}C(CH_2)_8COOMe \xrightarrow{4} CH_3\overset{cis}{C{=}C}H(CH_2)_8COOH \xrightarrow{5}$$

$$CH_3CH{=}CH(CH_2)_8CO \xrightarrow{6} CH_3CH{=}CH(CH_2)_8CO(CH_2)_5COOH$$

$$\xrightarrow{7} CH_3\overset{cis}{CH{=}CH}(CH_2)_{14}COOMe$$

1, Br_2, petroleum ether; KOH 2, $AgNO_3/NH_4OH$

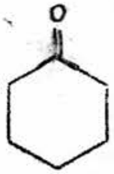
3, CH_3I 4, H_2, Lindlar; NaOH; HCl 5, $SOCl_2$;

morpholinocyclohex-1-ene; HCl 6, NaOH; HCl

7, N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl.

Methyl Octadec-17-enoate

$$\mathrm{HO(CH_2)_9OH \xrightarrow{1} Cl(CH_2)_9Cl \xrightarrow{2} I(CH_2)_9Cl \xrightarrow{3} HC{\equiv}C(CH_2)_9Cl}$$

$$\mathrm{\xrightarrow{4} HC{\equiv}C(CH_2)_9COOH \xrightarrow{5} CH_2{=}CH(CH_2)_9COOH \xrightarrow{6} CH_2{=}CH(CH_2)_9CO}$$ 

$$\mathrm{\xrightarrow{7} CH_2{=}CH(CH_2)_9CO(CH_2)_5COOH \xrightarrow{8} CH_2{=}CH(CH_2)_{15}COOMe}$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4, NaI,NaCN; KOH; HCl 5, H_2, Lindlar 6, $SOCl_2$; morpholino cyclohex-1-ene; HCl 7, NaOH, H_2O 8, N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl

DISCUSSION

PART I SYNTHESES

The preparation of the isomeric octadecenoic acids is discussed and compared with those of other workers.

It is convenient to group the esters: (a) the Δ^{2} isomer (b) the Δ^{3} isomer (c) the Δ^{4} - Δ^{12} isomers and (d) the Δ^{13} - Δ^{17} isomers but these groups will be discussed in the order in which the syntheses were effected.

The purity of the cis esters was carefully checked by

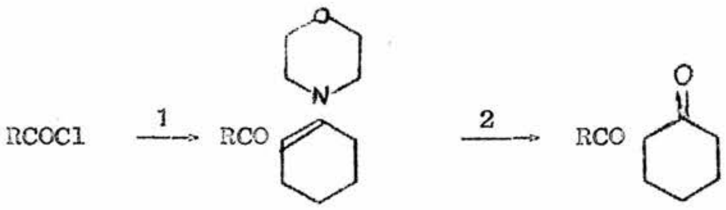
1. Gas liquid chromatography using packed columns with both polar and non-polar phases.
2. Thin layer chromatography using silica impregnated with silver nitrate.
3. Von Rudloff oxidation and examination of the products by gas liquid chromatography.
4. Determination of saturated acid content by gas liquid chromatography.
5. Determination of trans acid content by infra-red spectroscopy and gas liquid chromatography.

Methyl Δ^{13} - Δ^{17} Octadecenoates.

The general alkyl acetylene method devised by Ahmad and Strong[9] cannot be applied directly for the preparation of these esters because of the low solubility of long chain α, ω -chloro-iodo-alkanes. The C_{10} dihalide is the longest so far used for the synthesis of an octadecenoic acid.[15]

Anodic synthesis is unattractive because of the need for half esters of very long dibasic acids, and the necessity to repeat the coupling sequence several times to obtain the C_{18} acids in 15 gram quantities.

Not long before this work was undertaken Hunig[98] successfully extended undec-10-enoic acid to heptadec-16-enoic acid by the enamine synthesis and it was decided to obtain the C_{18} acids from the corresponding C_{12} acids by this method. This has the added advantage that useful information about C_{12} acids can be obtained at the same time. The sequence of reactions involved is as follows.



$\xrightarrow{3}$ $RCO(CH_2)_5COOH$ $\xrightarrow{4}$ $R(CH_2)_6COOH$

1, morpholino-cyclohex-1-ene, NEt_3; 2, HCl; 3, NaOH; HCl
4, Huang Minlon etc.

The Dodecynoic and Dodecenoic Acids.

The five dodec-ynoic acids were prepared by using acetylenic intermediates.

Dodec-7-enoic acid.

The acetylenic acid was prepared by condensing hexyne with 1,5-chloro-iodopentane and converting the C_{11} chloro-alkyne to the acid. Reduction of this acid in the presence of Lindlar's catalyst gave the desired ethylenic acid. These two acids have been prepared before in a similar manner.[61]

Dodec-8-enoic acid.

Pentyne, condensed with 1,6-chloro-iodohexane gave a C_{11} chloride which was converted first to a C_{12} acetylenic acid and then by semihydrogenation, to a C_{12} ethylenic acid. The C_{11} chloride and the two unsaturated acids have not been described before. In order to obtain pentyne in good yield certain precautions had to be taken: (i) a dry ice condenser was used throughout the reaction (ii) prefractionated petroleum ether (100-120°) was added to the reaction mixture after propyl bromide had reacted with sodium acetylide for 2 hr. (iii) during the addition of ammonium hydroxide, escaping gases were passed through Drechsel bottles containing more petroleum ether. (iv) the solvent from these traps was used to extract the aqueous layer. By these means, yields were increased to about 60%. Some

Some pentyne was lost in the distillation because in the later stages it co-distilled with the solvent.

Dodec-9-enoic acid.

The most obvious way to prepare this acid would have involved the condensation of propyne and chloro-iodo-octane neither of which is readily available and an alternate synthesis was devised based on one of Ames' method.[17] This involves the condensation of an alkyl halide with the N,N-dimethylamide of an ω -acetylenic acid.

Undec-10-enoic acid was converted to its acetylenic analogue and then degraded to dec-9-ynoic acid.[99] Its N,N-dimethylamide was only about 70% pure and contained impurities similar to those in the corresponding C_{11} amide (see page 37).

The condensation of this crude C_{10}-ynamide with ethyl bromide was effected in several ways, as summarised in the table below, but the best results followed when the C_{10} amide (1 mole) in tetrahydrofuran was added to sodium acetylide and followed, after stirring for 4 hours, by ethyl iodide (1.15 mole) in tetrahydrofuran. Stirring was continued for a further 12 hours and during the evaporation of ammonia (6 hrs.).

Ethyl Halide *	Solvent	Stirring of sodium acetylide	Stirring after addition of ethyl halide	Stirring during evaporation of ammonia	Ratio of C_{12} and C_{10} amides
Bromide	Ether	3 hr.	7 hr.	-	35 - 65
Iodide	Ether	3 hr.	7 hr,	-	40 - 60
Bromide	T.H.F.	4 hr.	10 hr.	-	50 - 50
Iodide	T.H.F.	4 hr.	10 hr.	-	70 - 30
Iodide	T.H.F.	4 hr.	12 hr.	6 hr.	90 - 10

* Sodium (1.1 mole) and C_{10} amide (1.0 mole)were used along with the halide (1.15 mole) in all preparations.

The C_{12} amide in 95% purity was obtained in good yields by careful fractionation of the reaction product through a ½ metre Fenske column. The olefinic acid, obtained after hydrolysis and semihydrogenation, was purified further by a wasteful distillation to give a product containing dodecanoic acid (1 - 1.5%) as the only impurity.

Dodec-10-enoic acid.

Attempts were first made to prepare this acid by condensation of methyl iodide and N,N-dimethylundec-10-ynamide. Undec-10-ynoic acid was prepared from undec-10-enoic acid by the method used by Black and Weedon.[99]

$$CH_2{=}CH.(CH_2)_8COOH \xrightarrow{1} BrCH_2\text{-}CH(Br)(CH_2)_8COOH$$

$$\xrightarrow{2} CH{\equiv}C(CH_2)_8COOH$$

$1 = Br_2$; $2 = KOH$

Dehydrohalogenation requires drastic alkaline conditions (10N, KOH, at 170°) and this may be the source of impurities found to be present. The Δ^9 isomer is one of the major impurities resulting from migration of the unsaturated centre. Despite a claim[100] to the contrary we found that the reaction with sodamide to be less satisfactory. The undec-10-ynoic acid gave sebacic acid in 89-93% when oxidised by the Von Rudloff procedure whilst gas liquid chromatography showed the ester to be only about 85% pure. The dimethylamide prepared from this acid was about 71% pure (G.L.C.). Condensation with methyl iodide converted the C_{11} amide to its C_{12} homologue in about 80% yield so that the product contained approximately 55% of the desired material. Purification proved to be difficult and could not be achieved by distillation through a Fenske column.

In an attempt to convert unreacted C_{11} amide to an acidic compound, the product was treated first with sodamide and then with carbon dioxide but the recovered neutral product was not improved.

Pure products can be obtained by preparative gas liquid chromatography of the amides or of the methyl esters derived from them, but because of the fairly long retention times and certain difficulties in trapping all the eluate, only 3.4 grams. of pure methyl dodec-10-ynoate was collected in 30 hours.

This approach was therefore scrapped in favour of that of Isabelle and Leitch.[101] Crude methyl undec-10-ynoate containing the Δ^9 isomer was converted to its silver derivative from which the unreacted esters were removed by prolonged extraction with petroleum ether or by crystallisation from 1:1 mixtures of benzene and petroleum ether. Further quantities of the silver derivative were obtained by treating the non-metallic fraction with further portions of silver nitrate and the final yield of silver compound was about 60%. The unreacted material contained 26% of the Δ^9 ester.

Dodec-11-enoic acid.

This acid was prepared from 1,9-chloro-iodononane via the hitherto unknown 11-chloro-undec-1-yne and also by chain extension of undec-10-en-1-ol via the bromide and the corresponding Grignard derivative. The commercial C_{11} alcohol contained about 4% of the Δ^9 isomer which was carried through the reaction but the first preparatiion gave a very pure product.

Enamine Chain Extension

The Δ^8 and Δ^9 acetylenic acids and the five dodecenoic have been converted to their C_{18} homologues by chain extension with the enamine from cyclohexanone and morpholine.

Dodec-8-ynoic acid was treated with thionyl chloride, then with morpholino-cyclohex-1-ene in the presence of triethylamine in chloroform. The product was hydrolysed directly with dilute hydrochloric acid to a diketone, alkaline hydrolysis of which provided 7-keto-octadec-14-ynoic acid. Von Rudloff oxidation showed this acid to be wholly the Δ^{14} acid. The keto acid, reduced by Hünig's[98] adaptation of the Huang-Minlon method gave a C_{18} octadecynoic ester along with a little (~ 5%) unchanged keto compound. Oxidation of the acetylenic acid however showed about 8% each of the Δ^{13} and Δ^{15} isomer along with the desired Δ^{14} compound.

Similar results were obtained with dodec-9-ynoic acid and with the olefinic acids derived from these two acetylenic acids.

The possibility of migration of unsaturated centres during the prolonged treatment with alkali though not recognised by the early investigators[15,97,102] has been reported more recently.[103] Reaction occurs, presumably through the isomerization of carbanion thus:

$$-CH_2-CH=CH\cdot \underset{\longleftarrow}{\xrightarrow{OH^-}} -\bar{C}H.CH=CH- \underset{\longleftarrow}{\longrightarrow} CH=CH\bar{C}H \underset{\longleftarrow}{\longrightarrow} -CH=CH.CH_2-$$

Other methods for reducing ketones include (1) Clemmensen reduction[104] and the Clemmensen-Martin-Shermann modification.[105] (2) Reduction of the hydrazone using potassium tertiary butoxide in refluxing toluene[106] or in dimethyl sulphoxide at room temperature.[107] (3) Reduction of the tosylhydrazone derivatives with sodium borohydride,[108] but we found it preferable to modify the Huang-Minlon reaction by moderating the reaction conditions. We found it possible to effect the reaction in boiling ethanolamine (176°) instead of triethanolamine (at 195-200°) and showed that the decomposition of the hydrazone was almost complete in 30 min. at 176°. Very satisfactory results were obtained when the hydrazone was decomposed for 90 min. at this temperature. This contrasts with the procedure of Hünig, which requires the decomposition to be carried out over 3 hr. at 200°.

The keto acids obtained from the five dodecenoic acids were reduced under these conditions and the products (as their methyl esters) were freed from the C_{12} compounds and from unreacted keto-acids by distillation through a spinning band column.

None of these keto-octadecenoic acids except the Δ^{17} isomer have been reported before.

Ester	total migration on either side %	saturated ccid %	trans g.l.c. %	trans i.r. %
$\Delta 13$	0.5	2.5	7.6	8.4
$\Delta 14$	0.5	2	2	2.5
$\Delta 15$	0.5	2	2	3.2
$\Delta 16$	0.5	2	2	2.5
$\Delta 17$	13.5% of 16	5.8	-	-

The high trans content of the Δ^{13} ester was due to an unsatisfactory semihydrogenation of the dodec-7-ynoic acid which required 12 hours rather than the usual 3 hours because of a poor batch of catalyst. Later preparations using equal quantities of acetylenic compound and catalyst gave olefins with less than 1% each of the saturated and trans acids (see preparations of Δ^{4} - Δ^{12} ethylenic esters).

This reduction procedure which proved satisfactory for the Δ^{13} - Δ^{16} keto acids was still too drastic for the Δ^{17} isomer. Attempts to purify this last product by thin layer chromatography on silica impregnated with silver nitrate or by preferential hydroxylation were unsuccessful.

A new approach was therefore tried. The keto-acid was converted to its tosylhydrazone which was reduced by sodium borohydride. This gave the Δ^{17} acid (45%) along with a large proportion (55%) of saturated acid and several attempts to improve this method made little difference. Reduction probably arose by interaction of the olefin with di-imide (N_2H_2) produced from the tosyl hydrazone under the alkaline conditions of the reaction.[109] This crude product could however be purified by thin layer chromatography. The Δ^{17} acid contained only 1% more of Δ^{16} isomer than the keto-acid from which it was derived.

The most satisfactory method of preparation of the Δ^{17} isomer would probably be to subject 6 keto-octadec-17-ynoic acid instead of the ethylenic analogue to the Huang-Minlon reduction. The terminal acetylenic acid could then be freed from the non-terminal isomers via its silver salt. Partial reduction of the C_{18} acetylenic acid would then give the desired octadec-17-enoic acid.

The properties of these acids and their esters to be reported later were determined on material which had been purified by distillation (Δ^{14}, Δ^{15}, and Δ^{16} isomers) and also by thin layer chromatography (Δ^{13} and Δ^{17} isomers). For melting point determinations, all the esters were purified by thin layer argentation (to remove saturated and trans olefinic compounds) and then hydrolysed.

Melting Points of Δ^{13}- Δ^{17} Ethylenic Acids

Position of double bond	Present Work		Other Work	
	Cis	Trans	Cis	Trans
$\Delta 13$	26.5-27.0	43.5-44.5		
$\Delta 14$	41.5-42.5	53-53.5		
$\Delta 15$	40.5-41.5	58.0-59.0	-	61.0-61.5[6]
$\Delta 16$	53.5-54.5	65.5-66.5	62.8-63.5[97]	
$\Delta 17$	55.5-56.5		55.0-55.5[97]	55.5-56.1[15]

Octadec-13-enoic acid.

No melting points have been given hitherto for the cis and trans acids and the previous preparation of this acid by the partial reduction of methyl eleostearate[90] is obviously unsatisfactory.

TABLE I. Melting Points* (Δ^{6} - Δ^{12} Octadecenoic acids)

	Present Work			Huber[15]			Other Workers		
Acid	≡	cis	trans	≡	cis	trans	≡	cis	trans
Δ^{6}	50.5°	28.5°	53.5°	-	-	-	50.5° [16] 50.5° [60]	29.0° [16] 29.5° [119] 30.0° [118]	52.5° [16] 52.5° [120]
Δ^{7}	48.5°	12.5°	45.0°	49.0°	12.0°	44.0°	49.0° [62]	13.0° [62]	45.0° [62]
Δ^{8}	47.5°	23.5°	52.0°	47.0°	23.5°	52.0°	46.5° [62]	24.0° [62]	50.5° [62]
Δ^{9}	46.0°	10.5°	45.0°	47.0°	11.0°	45.0°	46.5° [123] 45.5° [25]	13.0° [121] 13.5° [62] 16.0° [121]	44.0° [62] 45.5° [7] 44.5° [76]
Δ^{10}	46.0°	23.0°	53.0°	46.0°	22.5°	52.5°			
Δ^{11}	47.0°	13.0°	44.0°	46.5°	13.5°	44.0°	46.0° [86]	14.0° [27] 14.0° [122] 15.0° [62]	43.5° [27] 39.0° [81] 44.0° [62]
Δ^{12}	46.5°	27.5°	52.5°	46.5°	27.0°	52.5°	46.5° [29] 46.5° [123]	27.0° [29]	

* Melting points given in this table represent the average of the range over which these acids were found to melt.

Octadec-14-enoic acid.

No synthesis for this acid has been reported.

Octadec-15-enoic acid.

The value given for the melting point of the trans[15] ethylenic acid[6] is comparable with our value.

Octadec-16-enoic acid.

Our melting points indicate that the acid prepared by Kapp and Knoll[97] was predominantly in the trans form.

Octadec-17-enoic acid.

The melting point obtained in the present work agrees quite closely to those reported by Kapp and Knoll[97] and by Huber.[15]

Previous preparation of all these ethylenic acids were not so rigorously checked for purity as ours. This is particularly true of the position of unsaturation.

Methyl Δ^{4} - Δ^{12} Octadecenoates.

When this work was undertaken, unequivocal syntheses of the acetylenic, cis and trans ethylenic acids of the Δ^{6} through to the Δ^{12} isomers had been reported. A long synthesis by Ames and Bowman[53] was available for the cis and trans Δ^{4} ethylenic acids and a less satisfactory preparation had been described for the Δ^{5} ethylenic acid, probably as the trans isomer.[57] During the course of this work Ames and co-workers[51,54] have published unequivocal syntheses for the

Δ^4 and Δ^5 acetylenic, the two cis ethylenic acids and the trans Δ^4 isomer.

In the present work, we have prepared all these esters either by condensing ω- halo, N,N -dimethylamides with appropriate 1-alkynes (Δ^{10}, Δ^{11}, and Δ^{12} isomers) or by the reaction of the ω-acetylenic amides with alkyl bromides (Δ^4 - Δ^9 isomers). The different components used for these reactions are given below.

C_{18} Ester Position of Double Bond	N,N-Dimethylamides of the Following Acids	Bromides or Acetylenes
Δ^4	pent-4-ynoic	1-bromotridecane
Δ^5	hex-5-ynoic	1-bromododecane
Δ^6	hept-6-ynoic	1-bromo-undecane
Δ^7	oct-7-ynoic	1-bromodecane
Δ^8	non-8-ynoic	1-bromononane
Δ^9	dec-9-ynoic	1-bromo-octane
Δ^{10}	9-iodononanoic	non-1-yne
Δ^{11}	10-bromodecanoic	oct-1-yne
Δ^{12}	11-bromo-undecanoic	hept-1-yne

Pentynoic acid was prepared by the oxidation of pent-

4-yn-1-ol,[110] itself obtained from tetrahydrofurfuryl alcohol.[111]

The C_6-C_9 acetylenic acids were synthesised by condensing the α,ω-chloro-iodo-alkanes (except bromo-chloro-propane) with sodium acetylide and then converting the chloro-alkyne to the acids via the nitrile. The dihalides were conveniently prepared by the method described for 1,6-chloro-iodohexane by Raphael and Sondheimer.[112]

Decynoic acid was prepared several times by the Barbier-Wieland degradation of undec-10-ynoic acid[99] and on one occasion by the malonation of 8-chloro-octyne. The latter method gave a much superior product.

11-Bromo-undecanoic acid, required for the preparation of the Δ^{12} octadecenoic acid, was synthesised by the anti-Markownikoff addition of hydrogen bromide to undec-10-enoic acid.[113] The reaction was slow if the hydrogen bromide contained any free bromine. The crystallised product was shown by gas liquid chromatography and nuclear magnetic resonance spectroscopy to be free of 10-bromo-undecanoic acid.

Barbier-Wieland degradation of the 11-bromo-acid gave 10-bromodecanoic acid[114] required for the synthesis of the Δ^{11} C_{18} acid.

The condensation of heptyl bromide and undec-10-ynamide would have led to methyl octadec-10-enoate but we chose to react nonyne with 9-iodo-nonanamide. A Hunsdiecker reaction on methyl silver sebacate gave methyl 9-bromononanoate. The latter had been hydrolysed before with hydrogen bromide in glacial acetic acid to furnish the bromo-acid.[115] We hydrolysed the ester with 0.5N sodium hydroxide to give a mixture of hydroxy and bromo-acids which was easily converted to 9-iodo-N,N-dimethyl nonanamide.

The alkyl bromides, except the C_9 and C_{13}, were prepared by the action of bromine on a mixture of red phosphorus and the corresponding alcohol.[116] 1-Bromononane was purchased (Koch Light). The C_{13} bromide was prepared by a Hunsdiecker reaction on silver myristate. Although the preparations of these bromides were easy, their purification required careful distillation through a ½ metre Fenske column.

Unlike Ames and his colleagues,[17] we did not purify the crude C_{18} amides, but hydrolysed them directly to the acetylenic acids. In order to keep the reaction temperature at a minimum, the hydrolyses were carried out with 5N sodium hydroxide in ethanol rather than with methoxy ethanol.

Octadec-4-ynamide was prepared by condensing N,N-dimethyl pentynamide with 1-bromotridecane. The product, when examined by thin layer chromatography, showed a similar range of compounds obtained on reacting other alkyl bromides with acetylenic amides but found to contain relatively less of the C_{18} amide. The amide was hydrolysed to the acid and its ester was shown, by gas liquid chromatography, to contain 45% of the Δ^4 isomer together with more polar material on impurities. Distillation,of the semi-hydrogenated crude ester,increased the content of the C_{18} ester to about 65%.

The acetylenic acids were partially hydrogenated as their esters and then distilled through a spinning band column to give the methyl octadecenoates. The resulting esters except the Δ^4 isomer were shown to be isomerically pure by Von Rudloff oxidation. Gas liquid chromatography showed these esters to contain less than 1% of the trans acid and about the same amount of saturated acid. These esters were prepared in about 15 gram quantities except for methyl octadec-4-enoate which could be purified only in small amounts by thin layer chromatography.

About 25 mg. of each ester was freed from traces of trans and saturated esters by thin layer chromatography on silica impregnated with silver nitrate and then hydrolysed to give samples of the pure cis acid for melting point determination.

Octadec-4-enoic acid.

Eckert and Halla[48] reported a melting point of 52° and an iodine value of 27 (Hübi) for this acid. Ames and Bowman[53] found that the cis and trans ethylenic acids melt at 40-41° and 59.5 - 60.5° respectively, and has an I.V. (84.9-89.0°) in good agreement with the theoretical value. These workers, on the basis of Linstead's[117] observation that Δ^2 unsaturated acids gave low iodine values, concluded that the acid, prepared by Eckert and Halla, was a mixture of the Δ^2 and Δ^4 isomers.

The melting points, obtained in the present work, are in good agreement with those recorded by Ames and co-workers[54] for a more recent preparation of the Δ^4 acetylenic, cis and trans ethylenic acids.

Acid	Ames	Present Work
Acetylenic	75-76°	74-75°
Cis	44.5-45.5°	45.5-46.5°
Trans	58-59°	58.5-59.5°

Octadec-5-enoic acid.

This acid, first obtained by the partial reduction of octadec-5-ynoic acid, had a melting point of 47.5°.[57] Ames and co-workers[51] have recently reported that the acetylenic and cis ethylenic acids melt at 51-52° and 13° (f.p.) respectively. The following results were obtained in the present work: acetylenic acid - 51.5 - 52.5°; cis isomer - 12.5-13.5°; trans isomer - 46.5 - 47.5°. These values indicate that the acid obtained by the early reduction of the Δ^5 acetylenic acid was possibly the trans isomer as would be expected by the method of preparation.

Δ^6 - Δ^{12} Octadecenoic acids.

Several syntheses of these acids were reported even before the application of the more modern methods using acetylenic compounds, anodic coupling and the Wittig reaction. The trans isomers have usually been prepared by stereomutation of the cis acids with selenium at 200°; a method which we now find to cause considerable double bond migration (see page 60)

Our melting points are compared with some of those previously reported in Table I.

Methyl Octadec-2-enoate.

The acetylenic acid obtained by the carbonation of the Grignard derivative of heptadec-1-yne was partially reduced to the cis acid which was in turn converted to the trans acid by the U.V. irradiation. Hydrolysis of the cis ester also gave the trans ethylenic acid.

In the course of our work, Grimmer and Hilderbrandt[47] reported an identical synthesis for the acetylenic and cis ethylenic acids and obtained the trans acid either via a mercury adduct of the cis acid or by oxidising octadec-2-en-1-ol with chromium trioxide.

Von Rudloff oxidation of methyl octadec-2-enoate showed the presence of the Δ^3 isomer to an extent of 3.2% and this isomerisation could have taken place only when the Grignard complex was treated with carbon dioxide since drastic alkaline or acidic conditions were avoided during this preparation.

Since the double bond in the Δ^2 position is in conjugation with the carboxylic group, it is less prone to migration in alkaline or acidic media and therefore it is not surprising that the melting points recorded on ethylenic acids from different preparations agree closely.

Acid	Present Work	Grimmer and Hildebrandt[47]	Myers[46]	Ponzio[45]
Acetylenic	56-57°	56.7-57.5°	-	-
Cis	49-50°	48.4-49.2°	50.5-51°	-
Trans	57.5-58.5°	57.2-59°	57-57.5°	58.5°

Methyl Octadec-3-enoate

Wood and Reiser[50] failed to synthesise methyl dodec-3-ynoate by reaction of methyl bromo-acetate with sodium decynide in liquid ammonia. We failed to condense methyl bromo-acetate with lithium hexadecyne in refluxing dioxan or with the Grignard derivative of hexadecyne. Examination of the products from the reaction by g.l.c. showed only some early running peaks.

An alternative route to obtain the Δ^3 acid involved the oxidation of octadec-3-yn-1-ol which could be prepared by reaction of hexadecyne with ethylene oxide. Although sodium and Grignard derivatives of alkynes of short chain lengths have been made to react with ethylene oxide, no reference to the use of long chain alkynes was found in the literature.

Long-chain alkynes have limited solubility in liquid ammonia at -35°. The lithium derivative, made by reaction of hexadecyne and preformed phenyl lithium, was condensed with ethylene oxide in liquid ammonia at room temperature in an autoclave ($\sim$ 10 atm.), yielding octadec-3-yn-1-ol (87% after purification). This technique developed late in our experimental programme, overcomes the difficulties caused by low solubility of the higher alkynes and should be useful in the synthesis of many long-chain compounds.

Oxidation of the Δ^3 alcohol appeared to give substantial quantities of the Δ^4 acetylenic acid. Ozonolysis and von Rudloff oxidation of the unsaturated acid gave variable results but indicated up to 34% of the Δ^4 isomer. It had been thought that the conversion of Δ^3 to Δ^2 isomer was more likely but the content of the 2-ynoic acid was never greater than 5%. Gas liquid chromatography also showed the presence of closely related impurities and allenic compounds may have been present but we did not pursue this point.

Oxidation of the olefinic alcohol with chromic acid in acetone proceeded more satisfactorily. The product was obtained in only moderate yields ($\sim$ 50%) but it was a 3-enoic acid (90-94%) with only traces (0.5%) of the Δ^4 isomer. Its methyl ester was easily freed from the Δ^2 isomer by thin layer chromatography on silica impregnated with silver nitrate. This was possible because the R_f value for the Δ^2 isomer was considerably greater than that for the Δ^3 isomer.

The pure cis ethylenic acid for melting point determinations was obtained by repeated recyrstallisation (4 times) of the distilled acid from a mixture of hexane and acetone. A sample of recrystallised acid, as its methyl ester, was shown to be free of the Δ^2 isomer by g.l.c. using a capillary column coated with a polar phase and t.l.c on silica impregnated with silver nitrate.

The trans ethylenic acid was obtained by hydrolysing the corresponding ester, for fifteen minutes, with boiling one normal sodium hydroxide. The acidic product, obtained by repeated recrystallisation was found by gas liquid chromatography to contain only the Δ^3 isomer.

Octadec-3-enoic acid prepared by **Eckart** and **Halla** by the dehydro iodination of 3-iodo stearic acid with alcoholic potash would have been a very impure product because in our experience the double bond at the Δ^3 position migrates easily to the Δ^4 and Δ^2 positions under acidic or alkaline conditions.

The syntheses of the Δ^3 acids of chain lengths other than C_{18} described in the introduction required alkaline and acidic reaction conditions and the products probably contained isomeric impurities with one exception. The final products were not checked for purity with respect to the position of the double bond. Wood and Reiser however claimed that trans methyl dodec-3-enoate prepared by selenium isomerisation of the cis isomer contained over 90% of the Δ^3 isomer. This ethylenic ester was synthesised from dodec-3-yn-1-ol via the corresponding acetylenic acid.

PART II - Cis-Trans Isomerization of Mono-Enoic Esters.

Ever since Poutet[124] (1819) reported the solidification of olive oil by "oxides of nitrogen", many other reagents effecting a similar cis-trans isomerization of unsaturated fatty acids have been found. Some of the catalysts reported have been as follows: "oxides of nitrogen";[125,126,127] selenium,[128,129] tellurium;[130] sulphur dioxide;[131] various phosphorus compounds,[132] catalytic hydrogenation,[133,134] mercaptans,[135] silicates,[136] iodine,[137] U.V. light,[138] and electron radiation.[139] Of these reagents, selenium and the "oxides of nitrogen" have been most frequently used.

The phenomenon of cis-trans isomerisation has attracted much attention due to its possible commercial applications. The trans isomers have higher melting points than the corresponding cis ethylenic acids and hence cis-trans isomerization can be used to harden fats without any loss of unsaturation. The trans acids are also more resistant to oxidation than the cis acids and soaps made from trans acids have superior wetting and detergency properties.

Isomerization by oxides of nitrogen

Many workers have used the "oxides of nitrogen" produced in a number of ways[124,127] to catalyse the cis-trans isomerization and have reported the production of undesirable nitrogeneous by-products during this process. Little attention had been paid to the analysis and removal of these by-products until Litchfield and co-workers (1965)[140] found that these by-products can be easily removed on a column of silicic acid.

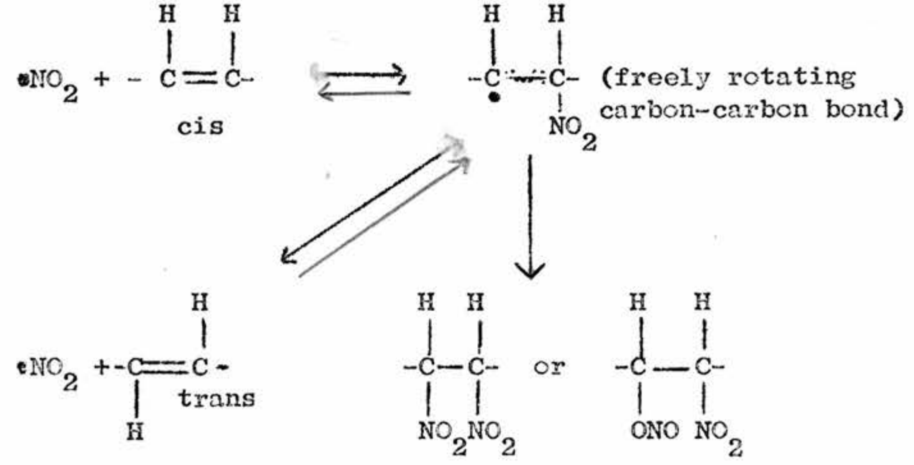
There has been much disagreement on the identity of the active catalytic species in the "oxides of nitrogen" but recent work by Litchfield et al. confirms Khan's [141] observation that the NO_2 radical is the active species causing the cis-trans isomerization to occur in the following manner:

$$2NaNO_2 + 2HNO_3 \longrightarrow 2HNO_2 + 2NaNO_3$$

$$2HNO_2 \xrightarrow{HNO_3} H_2O + N_2O_3$$

$$N_2O_3 \longrightarrow \bullet NO_2 + NO$$

$\bullet NO_2$ (in water phase) $\longrightarrow$ $\bullet NO_2$ (in fatty acid phase)



It is interesting to note that in the cis-trans isomerization of technical oleic acid using nitric acid and sodium nitrite Litchfield [140] found that the trans content began to drop after 30 min. This is due to the decrease in the total unsaturation of the system resulting from the formation of either 9,10-dinitrostearic acid or the related nitro-nitrite compounds.

Selenium Isomerization

Cis trans isomerization at elevated temperatures in the presence of selenium was first described by Bertram in 1936. [128] Fitzpatrick and Orchin (1957) [129] found that elaidic acid prepared in this way, when distilled, changed in part to oleic acid. This chance observation led them to suspect that a soluble form of selenium might be responsible for the original isomerization. They suggested the formation of a π complex between the oleic acid and selenium resulting in the solution of the latter. This complex undergoes partial isomerization to the trans isomer at a certain temperature. According to these workers a high reaction temperature (around 200°) was needed to dissociate the poly-atomic molecules of selenium. With olefinic compounds containing a hydrogen atom on the carbon adjacent to the double bond the catalytic activity of the selenium disappeared slowly, presumably by irreversible rearrangement of the π complex to a new species in which a carbon-selenium σ bond was formed. Kinetic studies of selenium-catalysed isomerization of cis-stilbeneand oleic acid established that the rate of conversion was independent of the initial concentration of selenium despite the slow disappearance of selenium in the solid phase during the reaction.

Double bond migration

Moussebois and Dale [142] showed that cis-trans isomerization of non-conjugated cyclic olefins by irradiation in the presence of iodine or by heating at 200° in the presence of selenium of benzenethiyl radical-producing compounds was accompanied by extensive migration of the double bond.

Migration of the double bond had been observed by Mehta and co-workers [143] when oleic acid was heated with selenium at 200° but seems to have been neglected in subsequent work.

Teeter et al.[144] reported that at 250°, selenium causes cyclization of conjugated octadecadienoic acid by a reaction involving the abstraction of hydrogen from the methylene groups adjacent to the double bonds. Litchfield [145] found three impurities when linoleic or linolenic acids were heated with selenium at 200° and explained these in terms of hydrogen abstraction and transfer reactions similar to that reported by Teeter et al. He did not, however, observo such impurities when oleic or elaidic acids were isomerized. This negative observation with mono-olefinic acids, does not necessarily exclude the possibility of double bond migration in their case. The apparent single peaks (g.l.c.) for the cis and trans isomers could result from incomplete separation of the undesired Δ^8 and Δ^{10} isomers from the Δ^9 isomers.

Double bond migration in mono-unsaturated acids can arise via a carbanion formed by the abstraction of hydrogen by the selenium from the methylene group adjacent to the isolated double bond.

Moussebois and Dale[142] found that benzenethiyl radicals, produced photochemically, effect rapid stereomutation of isolated double bonds, at room temperature, with little or no (∼ 1%) double bond migration.

Ratio of cis and trans isomers

Griffith and Hilditch[127] studied cis-trans isomerization of oleic, elaidic, petroselenic and erucic acids using nitrous acid or sulphur dioxide and concluded that the cis and trans isomers at equilibrium were in ratio 1:2 respectively. Bertram[128] reached the same conclusion using selenium as the catalyst.

Litchfield and co-workers[145] studied cis-trans isomerization using the modern techniques of gas liquid chromatography and infra-red spectroscopy, and showed that the equilibrium mixture of oleic, linoleic and linolenic acids contains 74–80% of the trans acids. They claimed confirmation of their results in the work of Berger et al.[146] who had obtained an equilibrium mixture of 75–80% trans and 20–25% cis, when a polymer of 1,3-butadiene, which contains a 1,4-diene system similar to linoleic and linolenic acids, was isomerized with ultra-violet light in the presence of phenyl disulphide. Litchfield explained the different results of Griffith and Hilditch on the basis that these workers precipitated the trans acid as its lead salt and the result of 66% represented a yield figure and not necessarily the equilibrium between oleic and elaidic acids. He claimed that after correction, Hilditch's results indicated that the content of trans acid was 75–87%.

The stereomutation of the octadecenoic acids (Δ^2- Δ^{16})

We carried out the cis-trans isomerization in order to obtain information about (a) the ratio of cis-trans isomers of all the octadecenoic acids (b) retention data on g.l.c. (c) the melting points of the trans ethylenic acids.

The ratio of cis-trans isomers at equilibrium was obtained by gas liquid chromatography by a combination of a polar (neopentylglycol succinate) and a non-polar (Apiezon L) capillary columns. By this means it is possible to determine the proportion of the cis and trans isomers on all except the Δ^3, Δ^4 and Δ^{12} esters.

The first comprehensive set of experiments were carried out on 100 mg. each of the cis ethylenic esters using catalytic amounts of selenium (2%) at 200° for 4 hr. The cis-trans ratio did not alter when such mixtures were heated for greater periods of time. Listed in Table II are the relative amounts of the two isomers for each of the methyl octadecenoates. The proportions of the trans isomer obtained at equilibrium in the present work for all but the Δ^2 isomer lie between 74-80% and are in excellent agreement with the equilibrium value for oleic acid given by Litchfield and co-workers.[145] In the Δ^2 isomer the trans content approached 84%.

We have confirmed the observation of Moussebois and Dale[142] and found extensive double bond migration. The extent of migration on either side of the original position of the double bond is also shown in Table II. The double bond remains in its original position to the extent of 73-90% and the major isomers are, in most cases, those with the double bond on either side of the original position, usually in similar amounts.

In order to obtain the trans acid with the double bond exclusively in the original position we used the procedure of Moussebois and Dale involving the U.V. irradiation of the cis-olefinic ester in the presence of diphenyl sulphide.

Initial experiments with the Δ^5, Δ^9 and Δ^{14} methyl octadecenoates over 7 hr. gave 75-80% of the trans isomer with less than 0.5% of double bond migration. The trans ester content rose to 83.1% after irradiation for 12 hr. (Time has not permitted the value at equilibrium to be established). Subsequent isomerizations to obtain pure trans acid for melting point determinations were carried out by irradiation of the cis ethylenic ester for 3 hr. when about 75% of the trans isomer was formed.

Our experiments show that the cis-trans isomerization by U.V. irradiation of methyl octadecenoates, in the presence of diphenyl sulphide, is preferred to the conventional procedure using selenium at 200°, particularly because stereomutation occurs without double bond migration.

TABLE II- Selenium Isomerization of Methyl Octadecenoates

Position of double bond	Equilibrium Mixture[a]		Lower	Von Rudloff Oxidation	
	Cis	Trans[b]	Isomers[c]	Isomer	Higher Isomer
Δ^{2}	16.3	83.7	-	84.0	16
Δ^{3}	-*	-*	14	84.0	12.0
Δ^{4}	-*	-*	1.6	91.8	6.6
Δ^{5}	22.7	77.3	9.0;3.0	85.0	6.0
Δ^{6}	21.4	78.6	6.0	90.0	4.0
Δ^{7}	24.9	75.1	5.9	73.0	19.0
Δ^{8}	22.5	77.5	8.7	77.7	13.6
Δ^{9}	23.9	76.1	0.7;10.7	75.8	12.8
Δ^{10}	24.3	75.7	1.0;10.0	74.5	14.5
Δ^{11}	22.8	77.2	10.5	78.2	11.3
Δ^{12}	-*	-*	1.2;10.3	79.3	9.2
Δ^{13}	20.4	79.6	10.0	79.4	10.6
Δ^{14}	20.8	79.2	1.0;8.1	80.3	10.6
Δ^{15}	25.9	74.1	10.0	81.8	8.2
Δ^{16}	26.0	74.0	7.3	89.2	3.5

[a] relative amounts of cis-trans isomers were determined on capillary columns coated with Apiezon L, except in the case of the Δ^{13} and Δ^{15}, which were estimated on columns coated with neopentyl glycol succinate.

[b] values based on total trans acids of all positional isomers caused by double bond migration.

[c] lower isomer refers to acid with double bond nearer the carboxylate group and vice versa

* The poor resolution of the cis-trans isomers does not permit the estimation of their relative amounts.

PART III - Melting Points

The melting points of cis and trans octadecenoic acids are listed in Table III and illustrated graphically in Figure I. The features of interest are:

(1) The change of melting point with double bond position follows a similar pattern for the cis and trans series of isomers (2) All melting points are lower than that for stearic acid (69.4°) and the cis isomers always melt lower than their trans isomers (3) The difference in melting point between the cis and trans isomers is greatest in the "central range", Δ^5 - Δ^{12}, and becomes less as the double bond moves towards either end of the molecule (4) Both series of compounds show an alternation of melting point.

Comment

(a) These interesting changes of melting point with double bond position reflect differences in stability of the crystals formed by these molecules and it is hoped, later, to make a detailed examination of the crystal structures which is presently restricted to oleic acid.[1]

(b) We are not able to explain the higher melting points observed in acids having a double bond close to either end of the molecule.

(c) An explanation for the phenomenon of alternation of melting points can be given by extending Malkin's[147] views on the difference of crystal structure of long chain compounds. According to Malkin, the zig-zag chains in these compounds allow two extreme poiitions "a" and "b" (see Figure II) for terminal methyl groups of adjacent molecules which may be regarded as closely or loosely packed. The plane "a" would be the favoured arrangement, for it offers lateral overlap between the methyl groups and the first methylene groups of adjoining chains. He considered that long-chain compounds formed "tilted" chains so that even membered chains can be arranged either as "a" or "b", with a great tendency to be "a". The odd members will possess alternate "a" and "b" planes.

This concept may be usefully extended to mono-unsaturated acids with the assumption that the double bond separates the chain into two parts. Thus, oleic acid, having two hepta-methylene chains would behave as an odd member whereas the Δ^8 acid would be similar to an even member.

The strong attraction between adjacent carboxylic groups would dominate over the end methyl groups and always possess the "a" plane. The methyl groups in the odd members would therefore be loosely packed ("b" plane). In the even members both the carboxylic and methyl groups can be closely packed resulting in higher melting points.

TABLE III Melting Points of n-Octadecenoic Acids.

Position of double bond	cis	trans
Δ^{2}	49.0-50.0	57.5-58.5
Δ^{3}	49.5-50.5	64.5-65.5
Δ^{4}	45.5-46.5	58.5-59.5
Δ^{5}	12.5-13.5	46.5-47.5
Δ^{6}	28.0-29.0	53.0-54.0
Δ^{7}	12.0-13.0	44.5-45.5
Δ^{8}	23.5-24.0	51.5-52.5
Δ^{9}	10.0-11.0	44.5-45.5
Δ^{10}	22.5-23.5	52.5-53.5
Δ^{11}	12.5-13.5	43.5-44.5
Δ^{12}	27.0-28.0	52.0-53.0
Δ^{13}	26.5-27.0	43.5-44.5
Δ^{14}	41.5-42.5	53.0-53.5
Δ^{15}	40.5-41.5	58.0-59.0
Δ^{16}	53.5-54.5	65.5-66.5
Δ^{17}	55.5-56.5	

FIGURE I

MELTING POINTS OF THE OCTADECENOIC ACIDS.

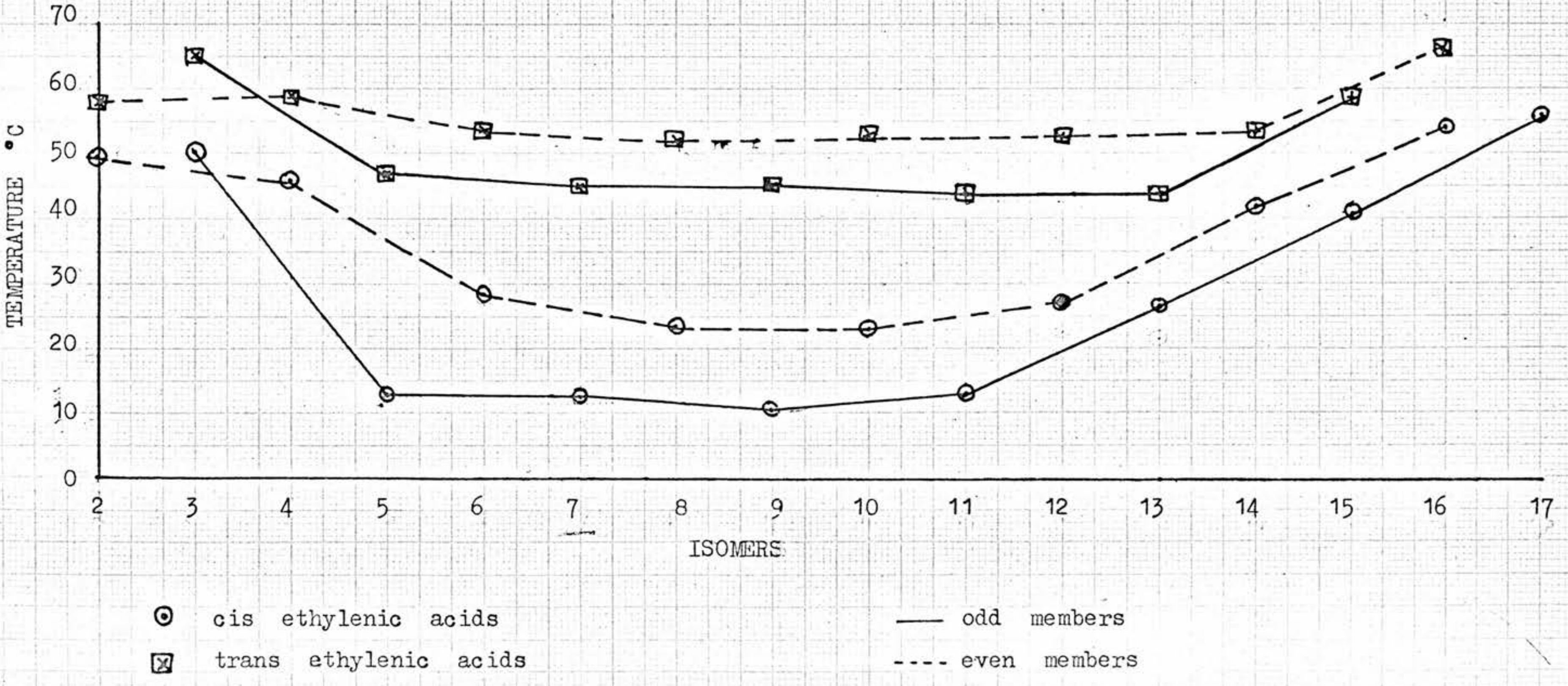
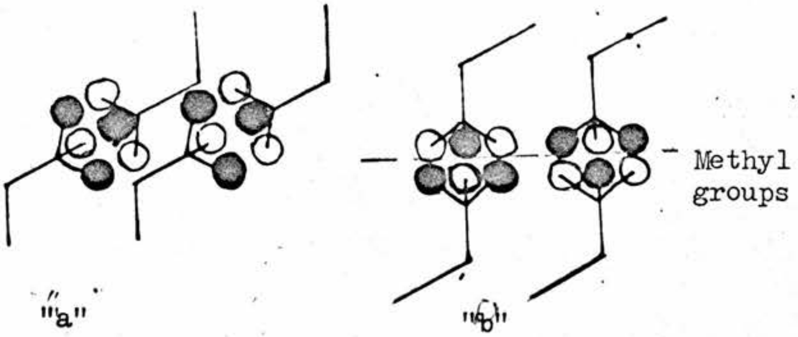
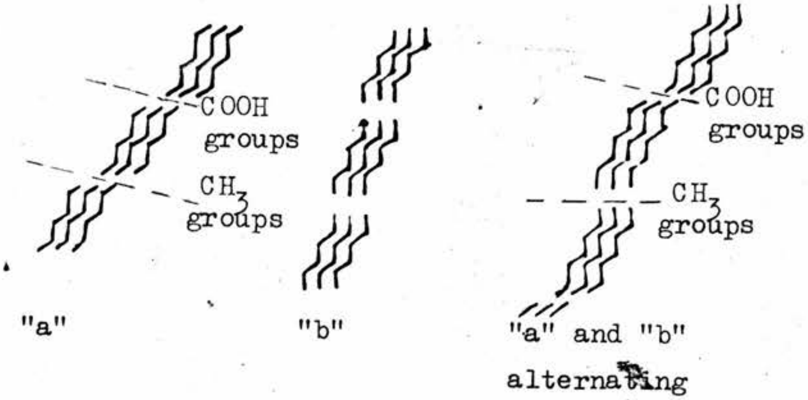


FIGURE II


Methyl groups
"a"
"b"


COOH groups
CH$_3$ groups
"a"
"b"
COOH groups
CH$_3$ groups
"a" and "b" alternating
Even members
Odd members

PART III- Spectroscopy

Infra-red Spectroscopy

We have extended the work of Susi[148] and found that the position of the double bond in the trans Δ^{4}- Δ^{16} octadecenoic acids in the solid state can be determined by studying the equally spaced absorption bands in the 1180-1350 cm^{-1} region.

Jones, McKay and Sinclair[149] observed a progression of absorption bands of uniform spacings and intensity between 1180 and 1380 cm^{-1} in the spectra of saturated fatty acids in the solid state, and studied the changes brought about in these bands by alteration of chain length and by the introduction of different substituents. They noticed that the regular appearance of these bands were either diminished or destroyed by the introduction of an unsaturated centre. Solid films of cis ethylenic acids such as oleic, linoleic and linolenic, where the carbon chain was bent gave several irregularly spaced, variable intensity bands which were nevertheless sharp and prominent. Trans octadec-9-enoic acid, however, behaved similarly to the shorter saturated acids, such as lauric, suggesting that in elaidic acid, the methylene chains on either side of the double bond behaved as independent groups. They explained the difference in the behaviour of the cis and trans ethylenic acids and the similarity of the latter to the saturated acids on the expectation that the hydrocarbon chain of the trans acids will line up in the crystal in a linear extended form similar to that in saturated fatty acids.

Meiklejohn and workers[150] (1957) found that in the saturated acids longer than C_{12}, the number of bands in the progression series is approximately equal to half the number of carbons in the chain, a phenomenon referred to as the "rule of two". There is no sound theoretical basis for this but it seems that this empirical rule is related to the symmetry and the length of the chain. In an infinite polymethylene chain, however, it is known that the number of infra-red bands in this region is restricted because of the presence of a centre of symmetry in the repeating unit making only certain vibrations of the methylene groups infra-red active while the others are Raman active.

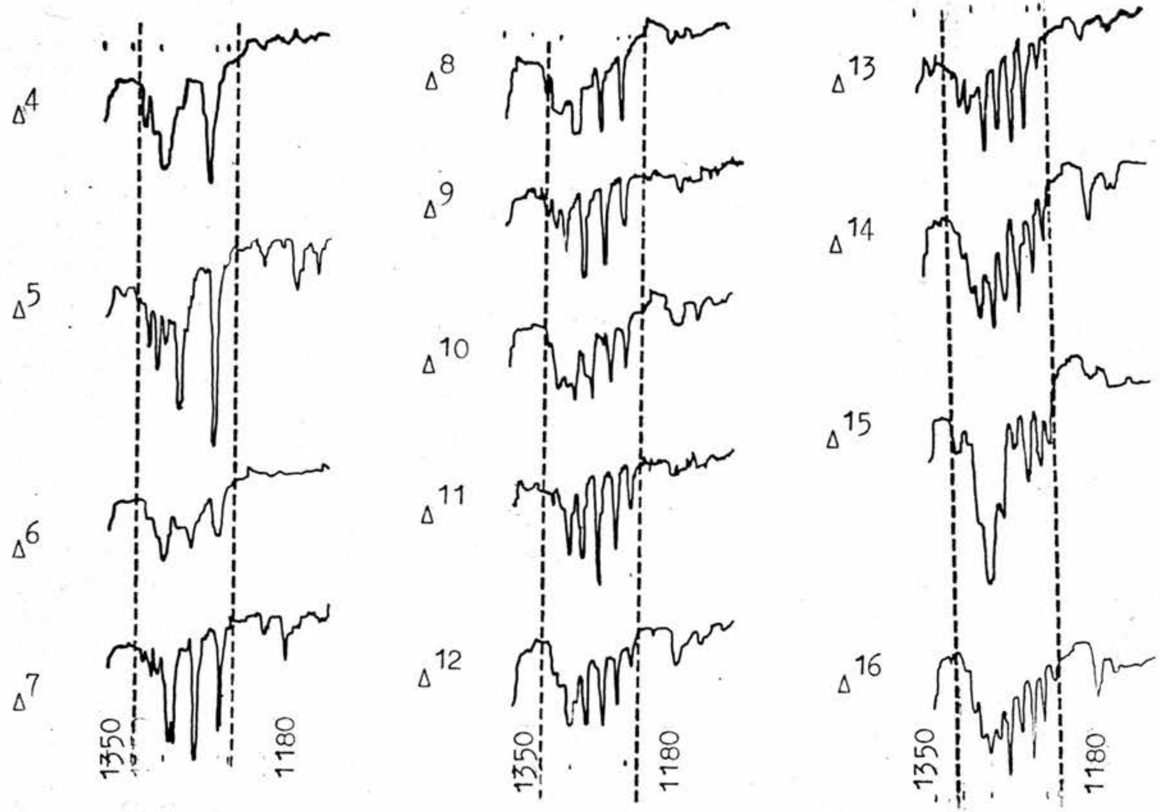
Jones et al.[149] suggested that the bands in the 1380-1180 cm^{-1} region arose from the rocking and/or twisting vibrations of the CH_2 groups but Ferguson (1956)[151] and Kirby an and co-workers (1965)[152] attribute them to the wagging vibrations, and it is now considered that bands caused by rocking-twisting vibrations are usually not observable due to their low intensity.

Susi[148] examined five positional isomers of trans octadecenoic acids (Δ^6 - Δ^9 and Δ^{11}) and found the number of bands in the progression series to be related to the number of methylene groups between the carboxyl group and the double bond. The number and arrangement of the bands was unique for each of the positional isomers and offered a method to determine the position of unsaturation in these trans isomers. They were able to apply Meiklejohn's "rule of two" to the number of carbons (n) in the chain segment between the carboxyl group and the double bond including the carbonyl and olefinic carbon atoms: thus for the trans octadec-10-enoic (an even member), the number of bands between 1350-1180 cm^{-1} region will be $\frac{10}{2} = 5$, and for the Δ^9 isomer which is an odd number the formula $\frac{n-1}{2}$ would apply and the number of bands will be $\frac{9-1}{2} = 4$. Although both the Δ^8 and Δ^9 C_{18} acids would give 4 bands, the intensities and arrangements of these bands make their identification possible.

The terminal chain segment (from double bond to the methyl group) does not seem to give rise to regularly spaced, medium intensity, bands. These methylene groups may give rise to irregular progression bands of much lower intensity superimposed on the main band or lie alongside them.

FIGURE III.

INFRA-RED SPECTRA OF THE trans OCTADECENOIC ACIDS.



The spectra of the Δ^2 and Δ^3 acids do not follow this trend and have spectra different from those of the other isomers.

Figure III illustrates the region between 1180 - 1350 cm^{-1} obtained in the present work on trans Δ^4 - Δ^{16} octadecenoic acids.

This method requiring only 1.2 - 2 mg. of the trans acid which can be recovered after the spectral information is obtained, is an excellent procedure for the unambiguous determination of the position of unsaturation in trans octadecenoic acids.

Infra-red Spectra of cis Ethylenic Esters in Solution

The infra-red spectra of the Δ^2 - Δ^{16} isomers of methyl octadecenoates in carbon tetrachloride were found to be independent of the position of unsaturation. They showed only the expected absorption bands for CH_2, CH and C=O.

Nuclear Magnetic Resonance Spectroscopy

Although some progress has been made in predicting chemical shifts and coupling constants on a theoretical basis, it is still not possible to calculate proton chemical shifts for the majority of structures. Identification of proton groups, is, therefore, accomplished by comparing the spectral values with those of similarly situated protons in related compounds of known structure.

Typical chemical shifts for protons in long chain fatty compounds have been compiled recently[153,154] and sterculic acid is an example where these spectral values have assisted to establish the structure of rather complicated fatty acids.[155]

We now report n.m.r. data on all the cis isomers of methyl octadecenoate and, by a combination of the spectra of some C_{12} and C_{18} acetylenic esters, we have also observed the spectral changes caused by all the different positions of the acetylenic function in long chain fatty acids.

Cis Ethylenic Esters

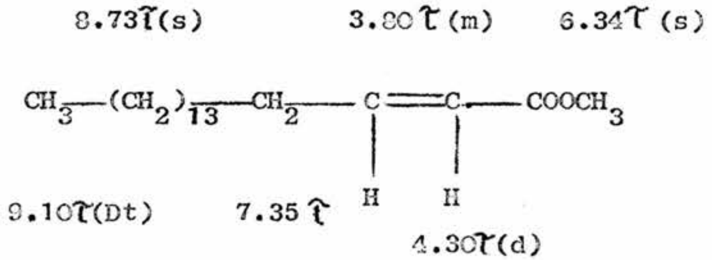
It is possible to distinguish the $\Delta^{2} - \Delta^{5}$ and $\Delta^{14} - \Delta^{17}$ from each other and from the $\Delta^{6} - \Delta^{13}$ isomers by their n.m.r. spectra. The spectrum of each ester except those of $\Delta^{6} - \Delta^{13}$, which will be considered as a single group, will now be considered.

Methyl octadec-2-enoate

Hopkins[156] found that the two olefinic protons of methyl-trans-octadec-2-enoate had separate signals. The C(2) proton band centred at 4.2 τ , was split by the C(3) proton into a doublet (J = 15.5 c/s) and the β proton, centred at 3.0 τ was split into two well-separated triplets (J = 15.5 c/s). Barker and co-workers (1962)[157] reported that the C(2) and C(3) protons in trans undec-2-enoic acid were at 4.2 τ and 3.1 τ respectively. These workers[158] also examined 10-hydroxy dec-2-enoic acid by n.m.r. and found the C(2) and C(3) protons were at 4.2 τ and 2.5 τ ; the coupling constant of 15.8 c/s proved that the double bond was trans.

The values obtained in the present work are given against the different proton sites

*



$$CH_3-(CH_2)_{13}-CH_2-\underset{H}{\underset{|}{C}}=\underset{H}{\underset{|}{C}}-COOCH_3$$

The signals for the olefinic protons and the methylene group (C(4)) adjacent to the double bond makes the Δ^2 isomer unique among the mono-ethylenic acids. The cis olefinic protons ($J_{\alpha\beta}$ = 12 c/s) can be differentiated from the trans olefinic protons (J = 15.5 c/s.).

Methyl Octadec-3-enoate

Hopkins and Chisholm[159] have reported the n.m.r. spectrum of a 3 trans ester (hexadecenoic) and found it to be easily distinguished from the Δ^2 ester and from other esters having double bonds further from the ester group.

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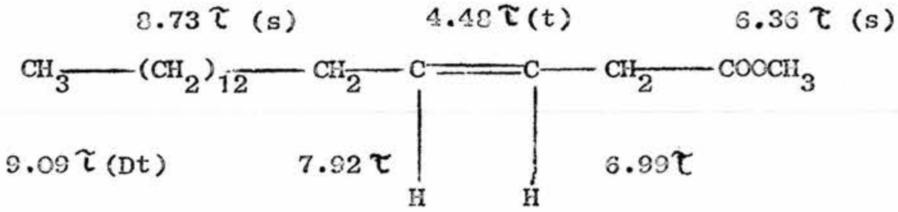
* The symbols s,d,m, and Dt indicate a singlet, doublet, multiplet and distorted triplet respectively.

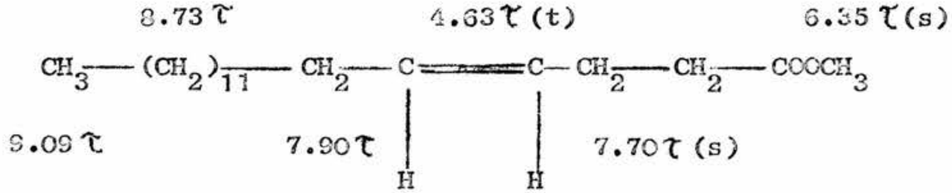
We found the absorption of the olefinic protons (4.48 τ, cf. Hopkins and Chisholm, 4.44 τ for a 3 trans ester) to differ from those of the Δ^2 cis ester and from those esters in which the double bond is further removed from the ester group (4.63 - 4.69). The CH_2 group lying between the double bond and the ester group also shows a distinctive signal at 6.99 τ (C and H, 6.93 τ) which is absent from all the other octadecenoates. The methylene group at C(5) give the usual band at 7.90 τ.



$CH_3-(CH_2)_{12}-CH_2-CH{=}CH-CH_2-COOCH_3$

Methyl Octadec-4-enoate

A combined signal for the C(2) and C(3) methylene protons (7.70 τ) between the ester and ethylenic groups distinguishes this isomer from the others.

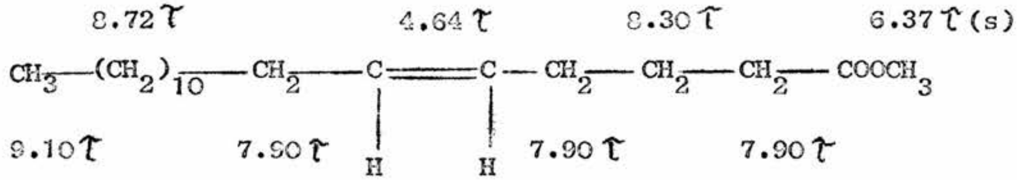


$CH_3-(CH_2)_{11}-CH_2-CH{=}CH-CH_2-CH_2-COOCH_3$

The olefinic protons are centred around 4.63 τ; a value very similar to that of an isolated double bond. Hopkins found that the olefin peaks of the trans C_{18} isomer appeared further downfield (at 4.54τ) than that observed by us on the cis isomer. Buttery and colleagues,[160] however, observed that the olefinic protons and the C(2) and C(3) methylene groups of methyl dec-4-enoate appeared at 4.69τ and 7.72 τ respectively and these chemical shifts are in close agreement with those obtained in the present work.

Methyl Octadec-5-enoate

The spectrum of this isomer can also be distinguished from that of any other isomer because in addition to the 6 protons associated with C(2), C(4) and C(7) (7.90 τ) the 2 protons of the C(3) methylene group give peaks centred at 8.3, not present in any of the other octadecenoates. The same peaks were also observed in the Δ^5 acetylenic esters of the C_{12} and C_{18} series



$$\underset{9.10\tau}{CH_3}-\overset{8.72\tau}{(CH_2)_{10}}-\underset{7.90\tau}{CH_2}-\underset{H}{C}\overset{4.64\tau}{=}\underset{H}{C}-\underset{7.90\tau}{CH_2}-\overset{8.30\tau}{CH_2}-\underset{7.90\tau}{CH_2}-\overset{6.37\tau(s)}{COOCH_3}$$

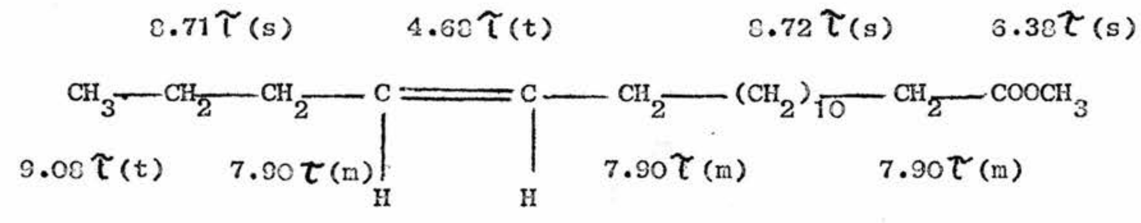
Methyl Δ^6 - Δ^{13} octadecenoates

The spectra of these esters are very similar and although they can be differentiated from the other isomers, they cannot be distinguished from each other. The chemical shifts of the various protons are given together with those of the other isomers in Table IV.

Methyl Octadec-14-enoate

Hopkins[156] found that the double bond protons (4.65τ) and the terminal methyl protons (9.11 τ) of cis hexadec-12-enoic acid had chemical shifts which were similar to those of unsaturated acids with isolated double bonds. He observed, however, that the greater splitting of the terminal methyl protons than in an isolated methyl band gave rise to a well-defined triplet (J = 6 c/s) and that this character may be sufficient to recognise a double bond commencing at the fourth carbon atom counting from the methyl end of the chain.

A comparison of the spectra of our C_{18} mono-ethylenic esters shows that the Δ^{14} isomer can be distinguished from the other isomers by the well separated triplet of the terminal methyl group (9.08 ; J = 6 c/s). Although the Δ^{15} isomer also gives a well separated triplet, for the methyl protons, the coupling constant is considerably higher, J = 7.8 c/s .

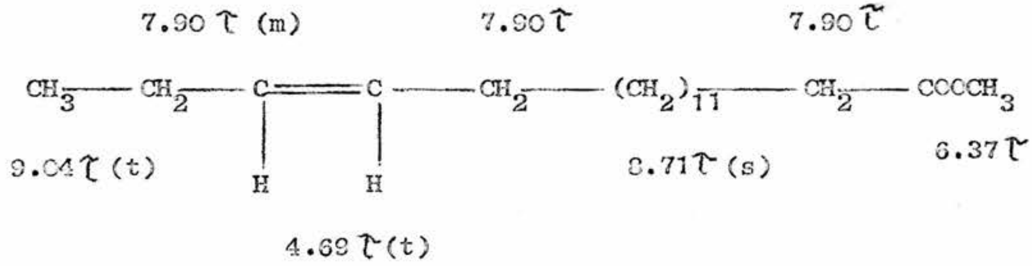


$$CH_3-CH_2-CH_2-\underset{H}{C}=\underset{H}{C}-CH_2-(CH_2)_{10}-CH_2-COOCH_3$$

Methyl Octadec-15-enoate

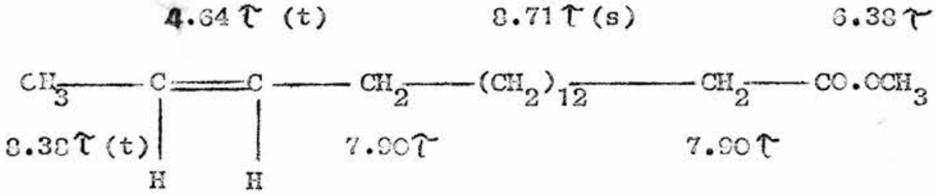
Shoolery and co-workers[161] found that the n.m.r. band for the methyl protons of linolenic acid (octadec-9,12,15-trienoic acid) had a distinctive pattern and appeared at a slightly lower field (9.02 τ ; J = 7.2 c/s) than the signal of an ordinary isolated terminal methyl group.

The spectra of methyl octadec-15-enoate is summarised below and the values agree closely with those given by Shoolery et. al., but for the coupling constant (J = 7.8 c/s as opposed to 7.2 c/s obtained by them).



$CH_3-CH_2-C(H)=C(H)-CH_2-(CH_2)_{11}-CH_2-COOCH_3$

Methyl Octadec-16-enoate

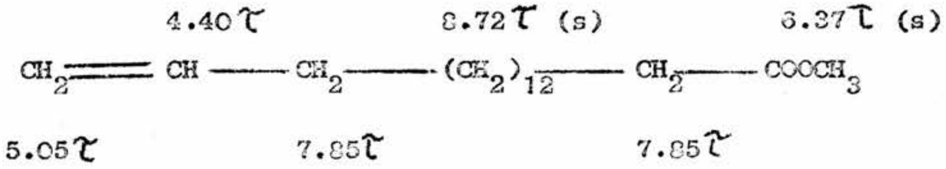


$CH_3-C(H)=C(H)-CH_2-(CH_2)_{12}-CH_2-CO.OCH_3$

The chemical shift of the terminal methyl protons of dec-4,8-dienoic acid was found by Buttery[160] to be 8.38 τ . The coupling constant of the methyl protons (8.38 τ) observed in this work was 5.2 c/s.

Methyl Octadec-17-enoic acid.

This isomer like the Δ^2 isomer gives two sets of signals for the olefinic protons.



$$\underset{5.05\tau}{CH_2}=\overset{4.40\tau}{CH}-\underset{7.85\tau}{CH_2}-\overset{8.72\tau\ (s)}{(CH_2)_{12}}-\underset{7.85\tau}{CH_2}-\overset{6.37\tau\ (s)}{COOCH_3}$$

The CH_2= peak centred at 5.05 τ is a doublet while the =CH peak at 4.4 τ is a multiplet caused by splitting of this proton by non-equivalent groups on either side. It differs also from the other isomers in that it has only 4 protons in the 7.90 band.

Isomeric acetylenic esters

The spectral data obtained on several C_{18} (Δ^2- Δ^5 and Δ^{10}) and C_{12} (Δ^5 - Δ^{11}) acetylenic esters are collected in Table V. The results resemble those obtained on the more complete series of cis olefinic esters and show again that those esters with unsaturation starting at the first, second, third and fourth carbon atoms from either end of the molecule can be readily identified but that other isomers are indistinguishable.

The end CH_3 group whichnormally gives a signal at 9.07-9.10 τ gives a different result for the four isomers with unsaturation close to the end group. Thus in the C_{12} series this becomes 9.02, 8.88, 8.27 and absent for the Δ^{8}, Δ^{9}, Δ^{10}, and Δ^{11} isomers respectively.

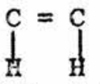
The Δ^{2} and Δ^{5} acids can be distinguished by a consideration of the behaviour and number of the methylene protons on carbon atoms adjacent to the carboxylate group and the triple bond. Thus the Δ^{2} and Δ^{3} acids give signals between 7 - 7.90τ equivalent to two and four protons respectively. The Δ^{4} acid shows six protons in this region but the four protons on C(2) and C(3) are combined as a single peak at 7.47τ. The protons associated with the other methylene group (C(6)) lie around 7.90τ. In the Δ^{5} acid the protons at C(3), which are slightly deshielded by the two functional groups (ester and olefin), give peaks centred at 8.2τ, not present in any other isomer and the protons at C(2), C(4) and C(7) behave normally and are centred at 7.69τ (C_{18} acid) and 7.76τ (C_{12} acid).

TABLE IV. Nuclear Magnetic Spectral Data of Methyl Octadecenoates.

Isomer	CH_3	$(CH_2)_n$	CH_2	$CH = CH$	CH_2	CH_2-COO	OCH_3
Δ^2	9.10	8.73	7.35	a	-	-	6.34
Δ^3	9.09	8.73	7.92	4.48	6.99	6.99	6.36
Δ^4	9.09	8.73	7.90	4.63	7.70	7.70	6.35
Δ^5	9.10	8,72	7.90	4.64	7.90	7.90	6.37
Δ^6	9.10	8.72	7.90	4.65	7.90	7.90	6.36
Δ^7	9.10	8.72	7.90	4.66	7.90	7.90	6.36
Δ^8	9.09	8.70	7.90	4.68	7.90	7.90	6.36
Δ^9	9.09	8.69	7.90	4.68	7.90	7.90	6.36
Δ^{10}	9.10	8.69	7.90	4.68	7.90	7.90	6.37
Δ^{11}	9.09	8.69	7.90	4.68	7.90	7.90	6.37

TABLE IV. contd.

Isomer=	CH_3	$(CH_2)_n$	CH_2	CH = CH	CH_2	CH_2-COO	OCH_3
Δ^{12}	9.09	8.69	7.90	4.68	7.90	7.90	6.37
Δ^{13}	9.09	8.71	7.90	4.69	7.90	7.90	6.38
Δ^{14}	9.08	8.72	7.90	4.68	7.90	7.90	6.38
Δ^{15}	9.04	8.71	7.90	4.69	7.90	7.90	6.37
Δ^{16}	8.38	8.71	7.90	4.64	7.90	7.90	6.38
Δ^{17}	–	–	–	c	7.85	7.85	6.37

a, 

$\underset{3.8\tau}{\underset{H}{C}} = \underset{4.3\tau}{\underset{H}{C}}$;

b, $C_{(3)}$ 8.30 τ;

c, $\underset{5.05\tau}{CH_2} = \underset{4.4\tau}{CH}$

TABLE V. Nuclear Magnetic Spectral Data of Positional Isomers of Acetylenic Esters

Isomer and chain leng.	CH_3	$(CH_2)_n$	CH_2	C≡C	CH_2	CH_2COO	OCH_3
$^2C_{18}$	9.09	8.70	7.67		-	-	6.29
$^3C_{18}$	9.10	8.73	7.91		7.91	7.91	*
$^4C_{18}$	9.09	8.73	7.90		7.47	7.47	*
$^5C_{18}$	9.09	8.70	7.69		7.69[a]	7.69	*
$^5C_{12}$	9.09	8.64	7.76		7.76[b]	7.76	6.36
$^6C_{12}$	9.07	8.58	7.87		7.87	7.87	6.36
$^7C_{12}$[c]	9.08	8.54	7.87		7.87	7.87	6.38
$^{10}C_{18}$[c]	9.10	8.65	7.90		7.90	7.90	*

TABLE V. contd.

Isomer and chain length	CH_3	$(CH_2)_n$	CH_2	$C\equiv C$	CH_2	CH_2COO	OCH_3
Δ^{8} C_{12}	9.02	8.58	7.88		7.88	7.88	6.38
Δ^{9} C_{12}	8.88	8.61	7.87		7.87	7.87	6.38
Δ^{10} C_{12}	8.27	8.66	7.87		7.87	7.87	6.36
Δ^{11} C_{12}	-	8.66	7.87		7.87	7.87	6.37

a, $C_{(3)}$ 8.1 τ b, C_3, 8.20 τ c, unsaturation at the central region of the chain

* N.m.r. recorded on acids.

FIGURE IV

N.M.R. SPECTRA– METHYL CIS OCTADECENOATES.

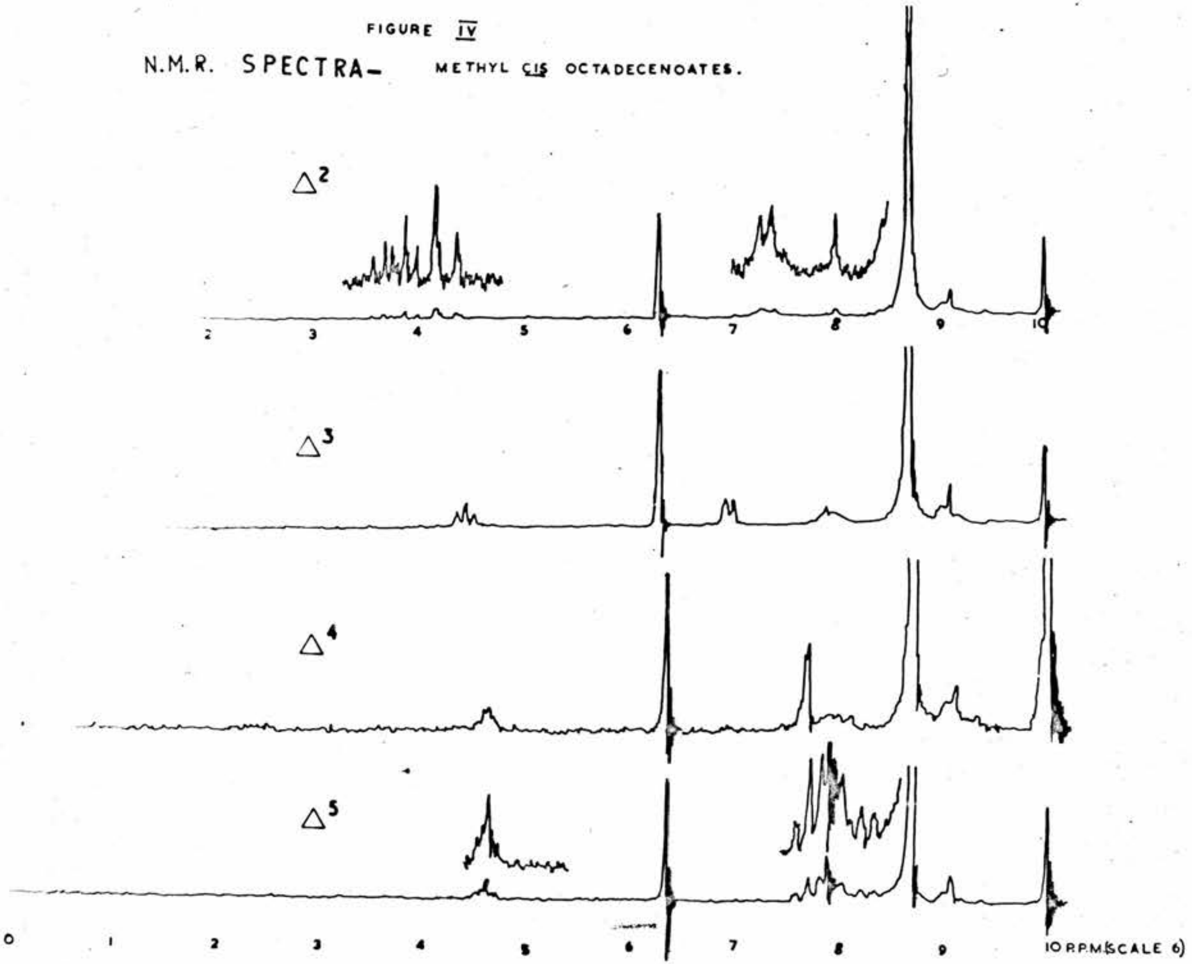


FIGURE IV CONT^{D}

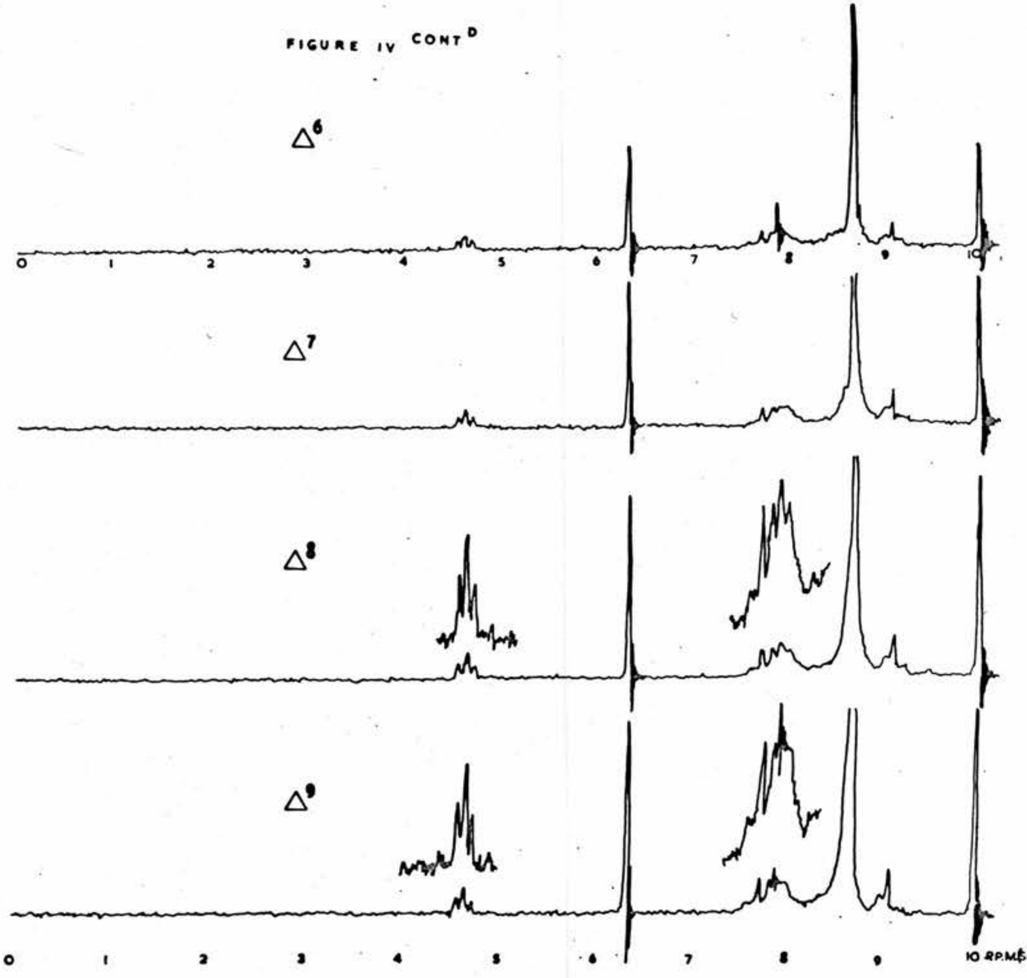


FIGURE IV CONT^{D}

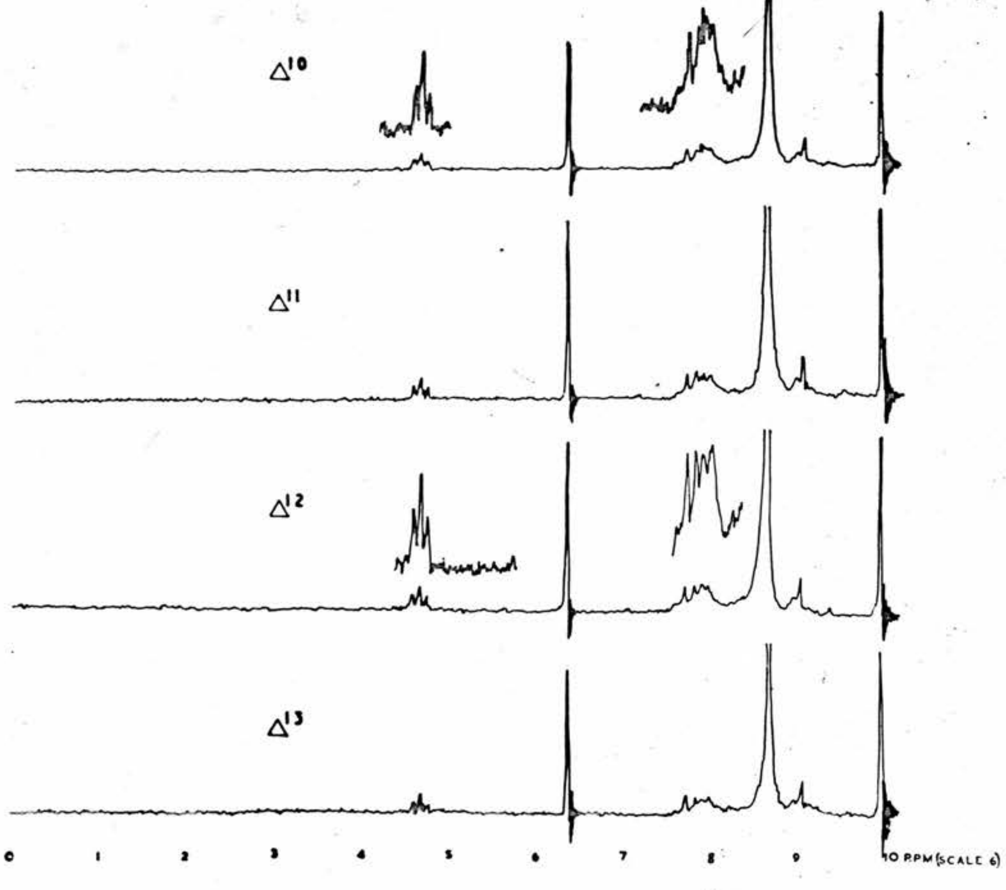


FIGURE IV CONT^{D}

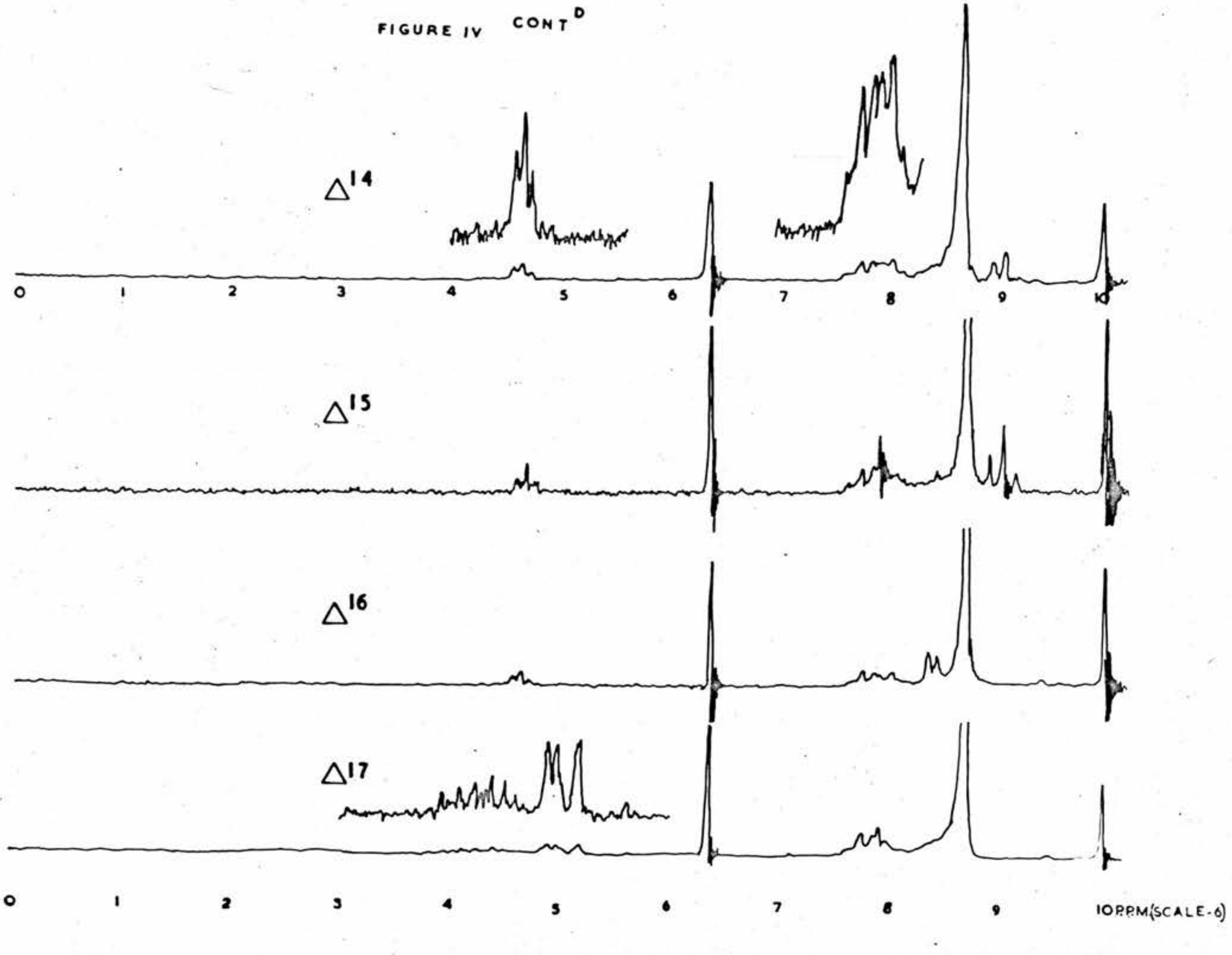


FIGURE V

ISOMERIC ACETYLENIC ESTERS

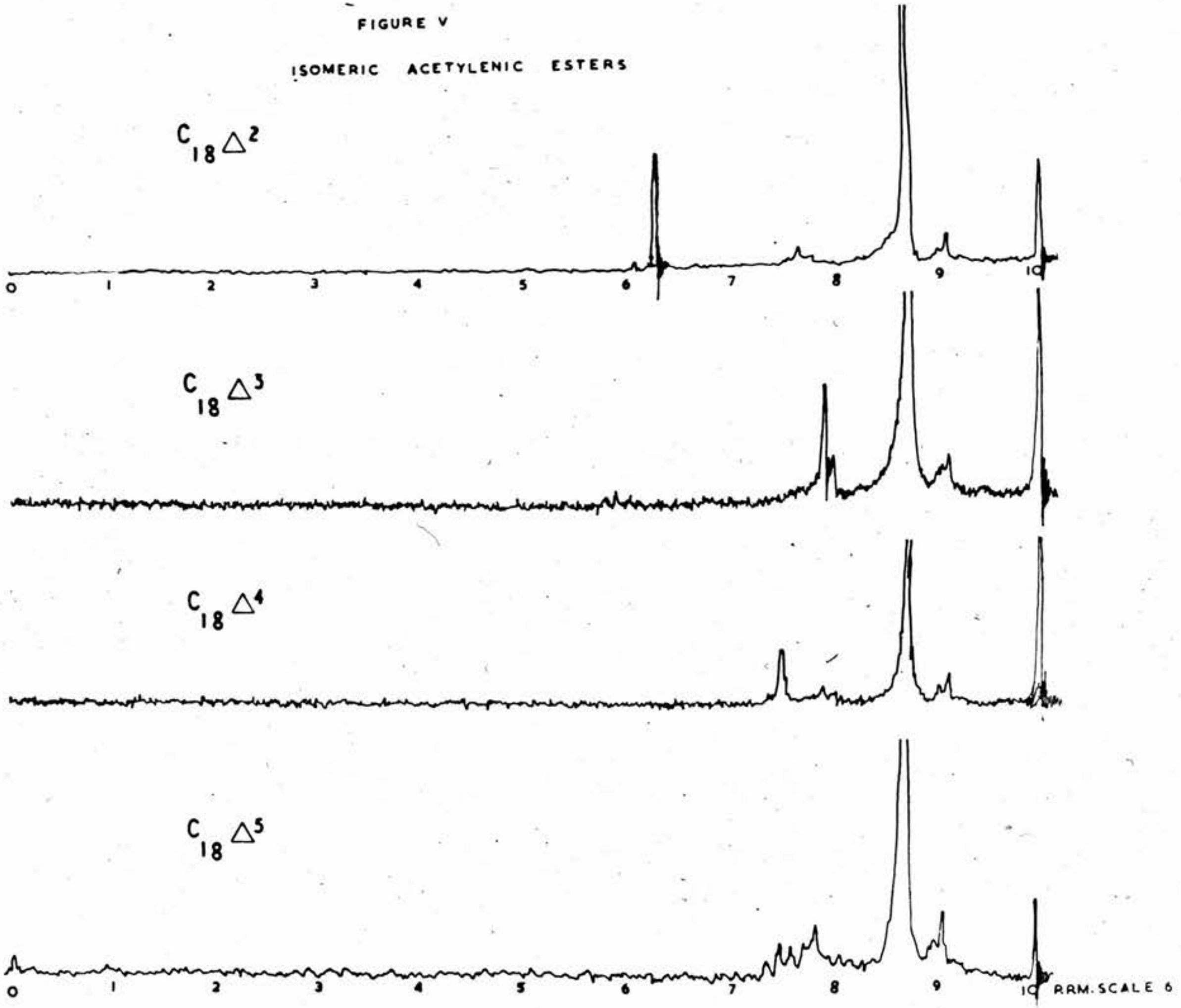
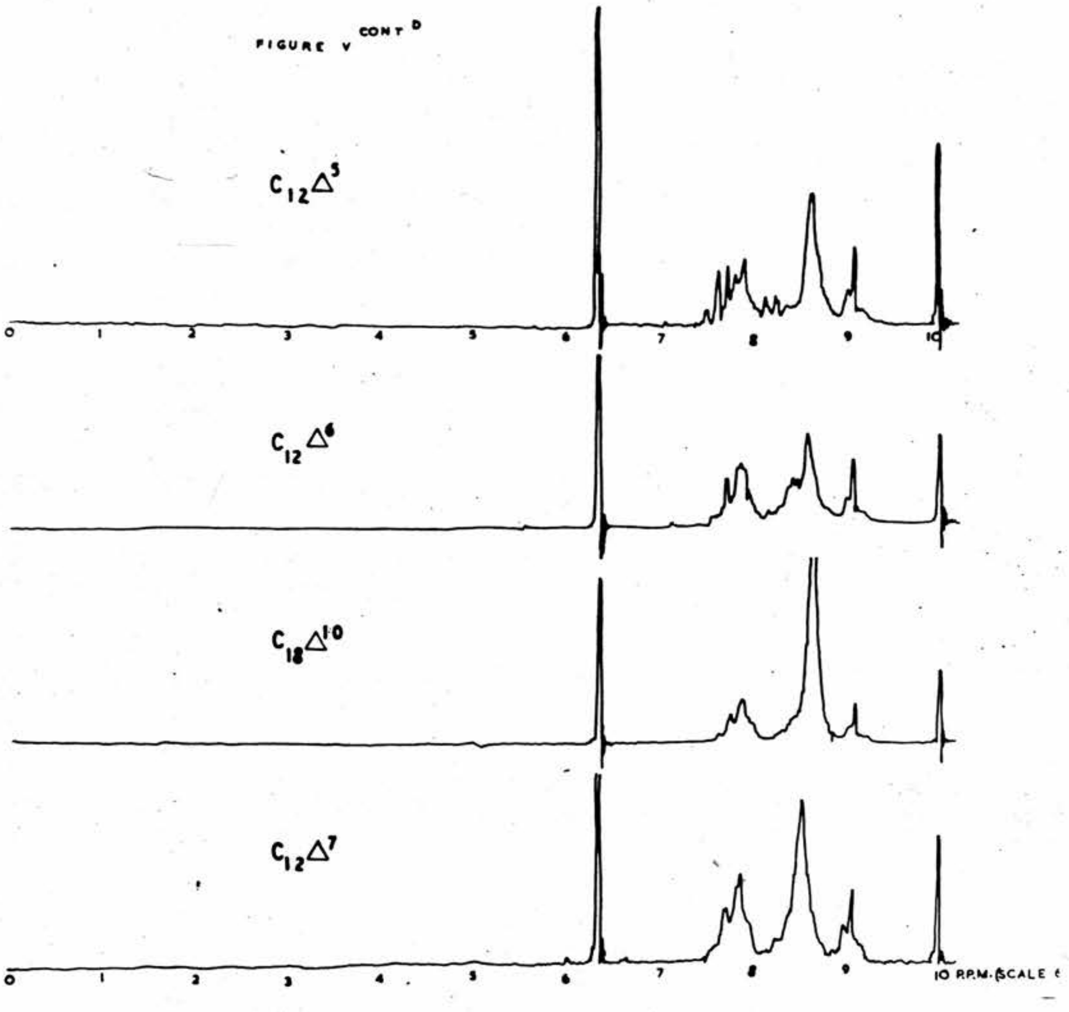
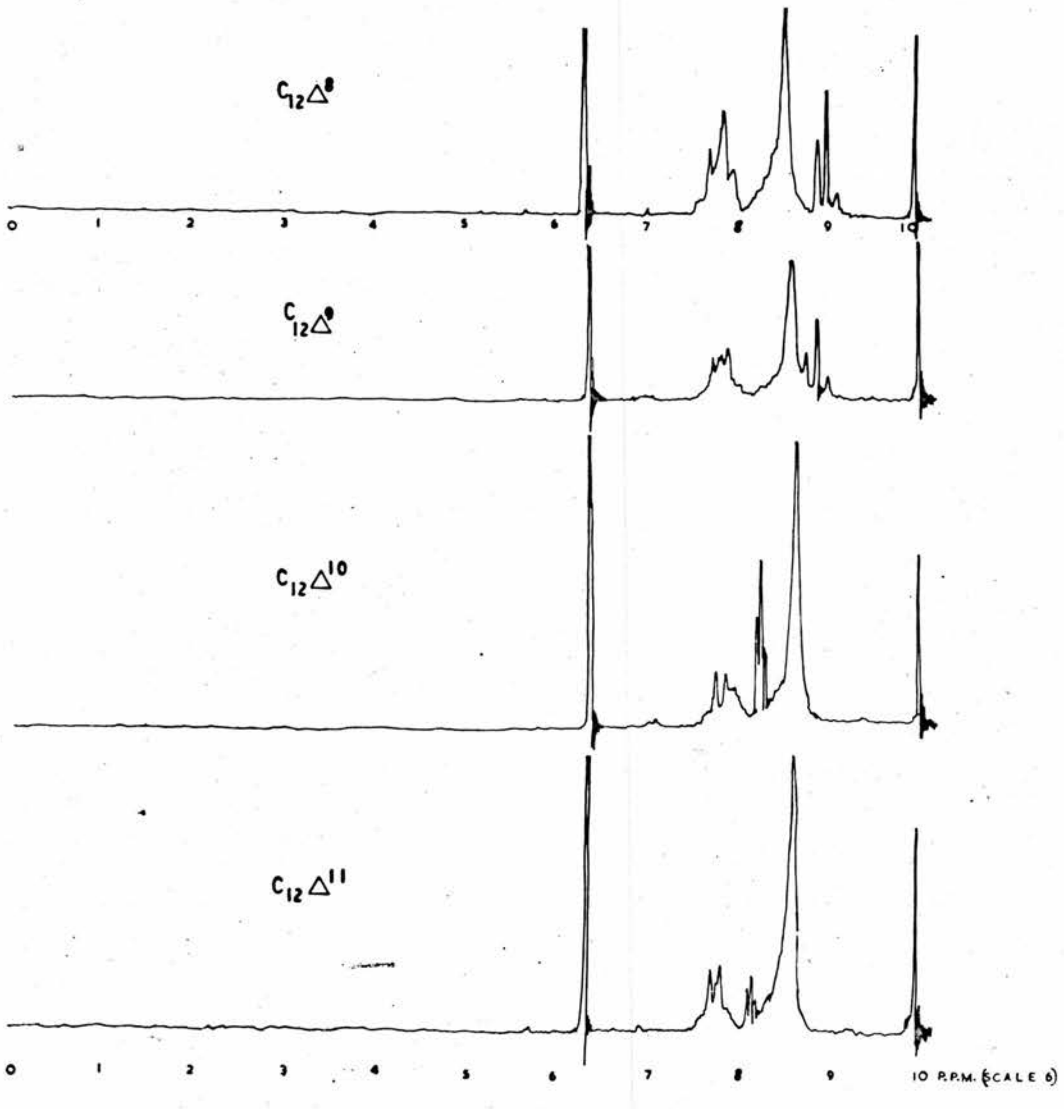


FIGURE V CONT^{D}




$C_{12}\Delta^{8}$
$C_{12}\Delta^{9}$
$C_{12}\Delta^{10}$
$C_{12}\Delta^{11}$
0
1
2
3
4
5
6
7
8
9
10 P.P.M. (SCALE δ)

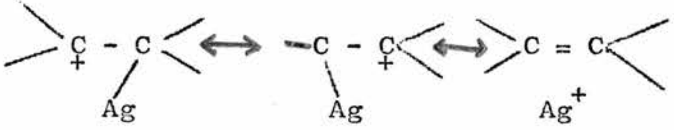
PART V - Chromatography

Thin Layer Chromatography

The nitrate, perchlorate, and halides of silver react directly with olefins to form metal-olefin complexes which are readily decomposed by water to the parent olefins.

By a comparison of the distribution of various olefins between aqueous silver nitrate/carbon tetrachloride with their distribution between potassium chloride, of the same ionic strength, and carbon tetrachloride, it was concluded that a 1:1 silver olefin $[\text{olefin Ag}]^+$ is always formed, sometimes accompanied by $[\text{olefin 2Ag}]^+$ and $[\text{2 olefin Ag}^+]$. The cis olefins complex more strongly than the trans isomers with silver ions.

The original concept,[162] that the $[\text{olefin Ag}]^+$ species was a resonance hybrid of 3 forms, has been superseded



by a proposal of Dewar,[163] who suggests that the bond is formed by overlap of the vacant 5s orbital of the silver with a filled π 2p orbital of the olefin. The metal ion, with the resulting decreased positive charge, tends to revert to its original form by overlap of one of its original orbitals with a vacant 2p antibonding orbital of the olefin.

The compounds formed between the silver ion and a variety of unsaturated hydrocarbons have been studied extensively by Lucas and co-workers.[164,165]

The prediction by Nichols (1952)[166] that the quantitative separation of cis and trans octadec-9-enoates was possible by counter-current distribution in the system iso-octane/0.2 M silver nitrate in 90% methanol was confirmed by Dutton[167] but de Vries[168] found that these isomers had more convenient partition coefficients of 3.2 and 4.8 respectively (ca. 20 and 40 respectively in Nichols system) if the system was changed to heptane/2 molar silver nitrate in glycol mono-ethyl ether and triethylene glycol, (9:1 respectively).

de Vries also used a column of silica gel impregnated with silver nitrate to separate triglycerides according to their unsaturation and Barrett and co-workers[169] extended this principle to thin layer chromatography.

Morris[170] separated cis and trans isomers of C_{18} Δ^6 and Δ^9 isomers using thin layer plates of silica treated with silver nitrate.

Bergelson and co-workers[171] showed that it was possible to separate, not only cis and trans isomers, but also the Δ^5, Δ^7, Δ^9, and Δ^{11} isomers of some long chain mono-ethylenic esters using plates coated with a mixture of silica and silver nitrate. They separated a mixture of unsaturated esters differing in position of the double bond and/or chain length by two dimensional thin layer chromatography first on silica (reverse phase) and then on silica impregnated with silver nitrate. The separated components were identified with the aid of standards or by their oxidation directly on the thin layer of the absorbent.

We have examined the change of R_f with double bond position on silica/silver nitrate layers in our complete series of cis and trans octadecenoates. Fig.VI shows the results with the cis esters alone, and Fig. VIa the results for both series.

For the cis olefinic esters, the Δ^2 isomer has the highest R_f value. This falls steeply through the Δ^3 and Δ^4 compounds and then more slowly to a minimum value for the Δ^6 ester. Thereafter the R_f value rises gently to a new maximum at Δ^{14} and then declines again.

The trans esters form weaker complexes and therefore have higher R_f values than their cis isomers. Again the Δ^2 ester has the greatest value and the Δ^6 the lowest; the values then rise to a maximum around the Δ^8 compound but remain fairly constant in the range Δ^8 - Δ^{16} with a final drop for the Δ^{17} ester. (There is, of course, only one Δ^{17} ester since this compound does not show geometric isomerism).

Our results show which isomeric esters can be separated by thin layer argentation and which cannot, at least in the solvent system we have used. Petroselenate can be separated from oleate, for example, as could several other mixtures, but the separation of Δ^4 from Δ^9, and Δ^{11} from Δ^{14}, to quote only two cases, would not be possible under our conditions. We believe Bergelson's claim to separate all olefinic esters according to their position of unsaturation, based on the separation of the Δ^7, Δ^9 and Δ^{11} octadecenoates only, to be unfounded.

A similar variation of R_f values have been observed among all the positional isomers of monohydroxy octadecanoic acids on thin layer chromatography of untreated silica but no explanation has been given for such a variation.[172]

Perhaps it is not surprising that the patterns given by the cis ethylenic esters on silica/silver nitrate and the monohydroxy C_{18} esters on silica are similar, for the forces which play a part between the silica and the hydroxy esters could possibly be paralleled by the attraction between the silver ion and the olefinic esters.

The marked dependency of the R_f values on the position of the functional group is, however, intriguing and an attempt will be made to explain this phenomenon with respect to the unsaturated esters.

We believe that three factors must be considered.

(i) Changes in availability of electrons in the olefinic bond due to electron withdrawal by the carbonyl function acting through the carbon chain.

(ii) Changes in availability of electrons in the olefinic bond due to electron donation from the ether oxygen of the ester group.

(iii) Steric factors arising from imbalance between the groups attached to the olefin-carbon atoms.

(i) The high R_f value of the Δ^2 isomer is almost certainly caused by reduced availability of electrons in the olefin bond through conjugation with the carbonyl function. This influence will be present to a lesser extent in the Δ^3 and Δ^4 isomers by inductive relay.

(ii) There is some resemblance between the plot of R_f value against position of double bond and curves reported for the ease of formation of alicyclic ring systems by several methods. Yields are greatest for the C_5-C_7 rings, decreases to a minimum at C_9 - C_{11} and rises gradually thereafter.

This similarity has led us to believe that some form of cyclic interaction of the carboxylate group and the double bond takes place. It is most probable that a chelate compound (shown below) is formed by the donation of the lone pair of electrons on the ether oxygen to the silver ion involved in the metal-olefin complex.

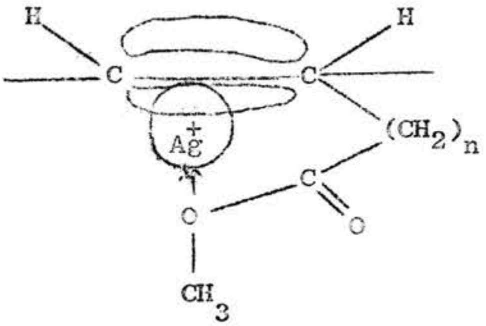
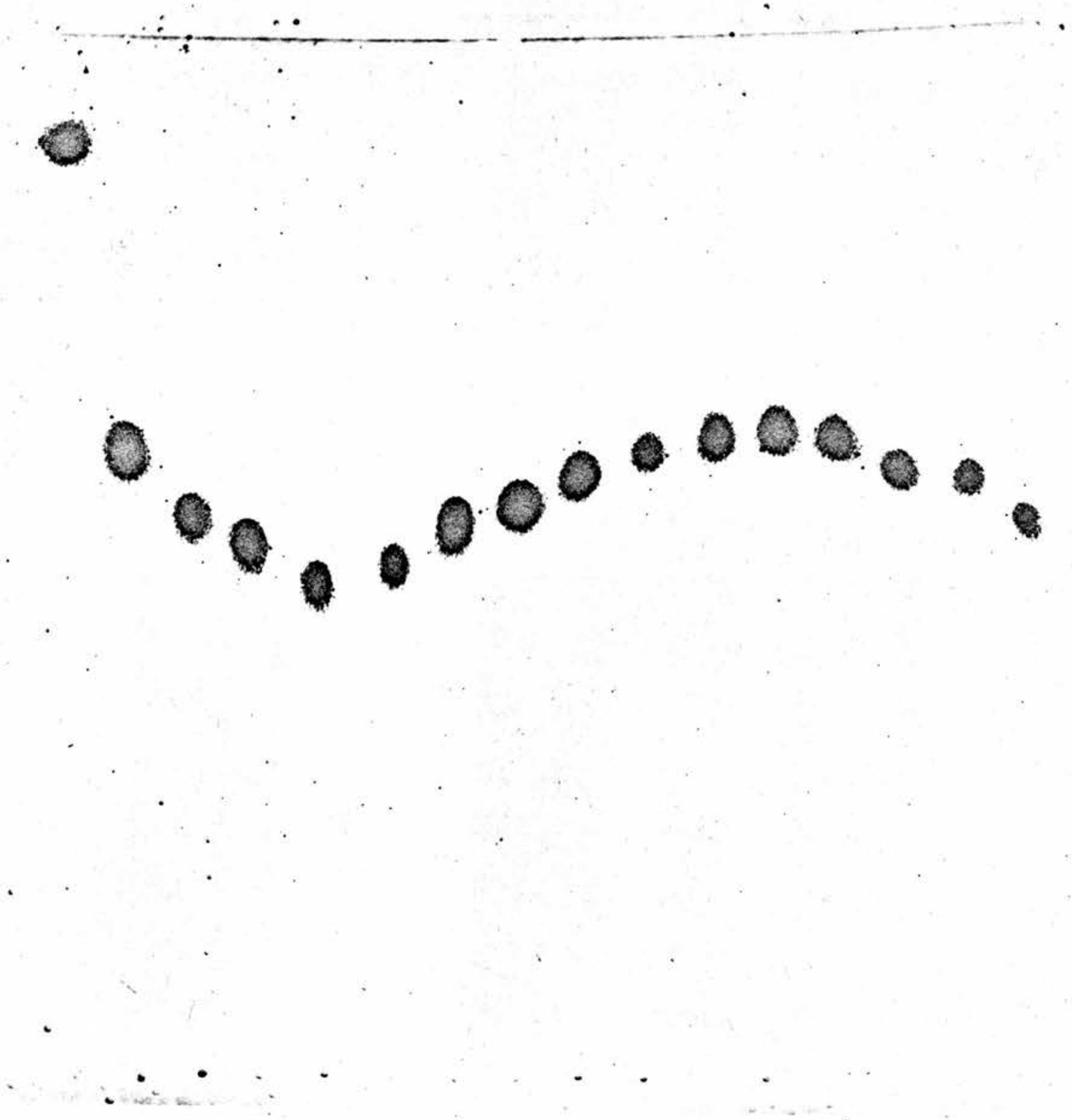


FIGURE VI

T.L.C. Methyl *cis* Octadecenoates.

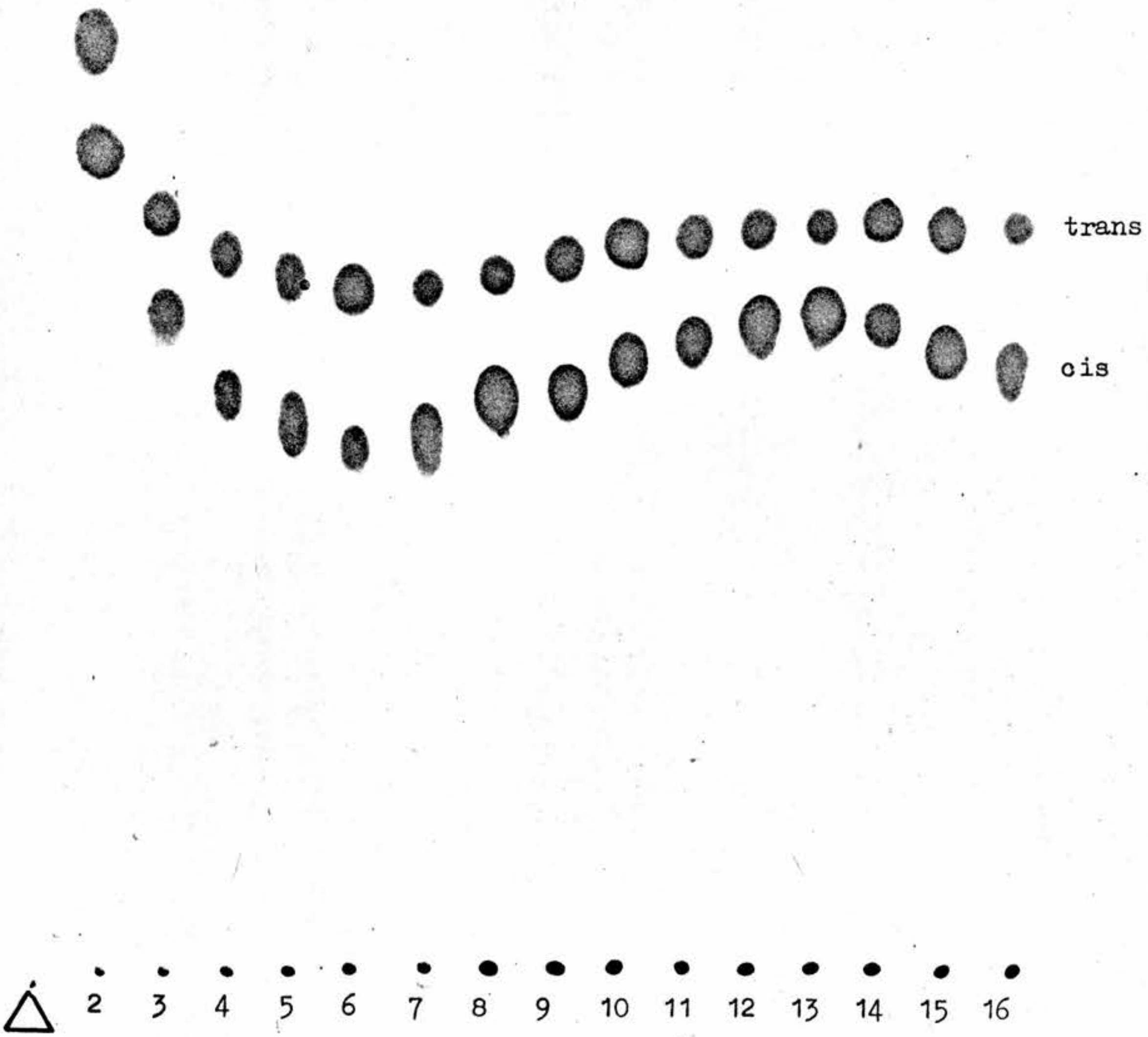


$\Delta^2 - \Delta^{17}$

SOLVENT dibutyl ether/hexane 40 : 60.

FIGURE VI a

T.L.C . Methyl cis and trans Octadecenoates.



SOLVENT - dibutyl ether/hexane 40 : 60.

Such a process will stabilize the silver-olefin complex and result in a decrease in the R_f value of the unsaturated ester.

Chelation giving rise to 5,6,7 nnd 8 membered rings, would occur more readily than for rings with 9-13 members, so that the location of double bonds at Δ^4, Δ^5, Δ^6 and Δ^7 will form more stable silver-olefin complexes and hence have lower R_f values, than the esters with the unsaturation between Δ^8 and Δ^{13}. Since alicyclic rings with fourteen or more carbons also form rings almost as easily as the 5 or 6 membered systems, it is not surprising that the R_f values begin to decrease from Δ^{14} - Δ^{17}.

(iii) It is possible that steric factors depending on the two alkyl groups attached to the olefinic carbons may affect the stability of the silver complex. These groups will be of similar size and weight for the Δ^7 and Δ^8 (allowing for carbon and oxygen atoms in the ester group) and will become more unequal as the double bond is moved from this position in either direction.

Gas Liquid Chromatography

Gas liquid chromatography has proved to be an indispensable tool in lipid research and has been extensively used for the analysis of fatty acids in both animal and plant fats. The introduction of capillary columns with theoretical efficiencies of greater than 40,000 plates has increased the scope of this technique to include the analysis of mixtures of cis and trans isomers[145,173] and more recently, the separation and identification of positional isomers of long chain mono-unsaturated fatty acids.[174,175]

We have examined the g.l.c. behaviour of all our octadecenoic esters and several mono-ynoic esters on polar and non-polar stationary phases and have used the procedure in our studies of the stereomutation process.

Analysis of cis-trans fatty acid esters.

James and Martin (1956)[176] separated cis and trans isomers of palmitoleate, oleate and octadec-4-enoate on packed columns coated with Apiezon M. In 1959 Lipsky and co-workers[177] demonstrated the separation of oleate and elaidate using capillary columns coated with Apiezon L. Extensive studies by Litchfield et al.[140,145] showed that mixtures of oleate and elaidate can be resolved on Apiezon L, diethyleneglycol succinate, and more recently[173] on three different nitrile silicones using high resolution capillary columns. The most efficient phase for such a separation was found to be β cyano-ethyl-methylsiloxane.

We have investigated the behaviour of the geometrical isomers of all the octadecenoic acids on 50 M. capillary columns coated with a polar phase (neopentylglycol succinate) and a non-polar (Apiezon L) and have obtained a separation of cis-trans isomers with all but the Δ^3 ethylenic esters on one or both of these phases.

Apiezon L separated the two isomers of all but the Δ^3, Δ^4, Δ^{12} and Δ^{13} octadecenoates and proved to be a better phase for the resolution of cis-trans isomers than the polar phase, which did, however, separate some of the isomeric pairs including the Δ^4, Δ^{12} and Δ^{13} esters . Although polyester phases are generally believed to be incapable of distinguishing between cis and trans isomers, Litchfield[178] resolved these isomers using diethyleneglycol succinate as the stationary phase but we were unable to achieve the separation of oleate and elaidate using columns coated with neopentylglycol succinate.

The order of elution of the cis and trans isomers of the different octadecenoates is interesting and is summarised in the following statement.

<u>Trans isomers on Apiezon L</u>

longer retention times than cis- Δ^2, Δ^5, Δ^6, Δ^7, Δ^8, Δ^9, Δ^{10}, Δ^{11}.

indistinguishable from cis Δ^3, Δ^4, Δ^{12}, Δ^{13}.

shorter retention times than cis Δ^{14}, Δ^{15}, Δ^{16}.

Trans isomers on neopentylglycol succinate

longer retention times than cis-	Δ^{2}
indistinguishable from cis	Δ^{3}, Δ^{5}, Δ^{6}, Δ^{7}, Δ^{8}, Δ^{9}, Δ^{10}, Δ^{11}
shorter retention times than cis	Δ^{4}, Δ^{12}, Δ^{13}, Δ^{14}, Δ^{15}, Δ^{16}.

Gas Liquid Chromatography of Positional Isomer

The behaviour of the positional isomers of methyl nonynoate on both packed and capillary columns of diethyleneglycol succinate and Apiezon L was investigated by Anderson and Rakoff[174] with packed columns, the results were not very useful; there was some separation on the polar phase but baseline separations were not achieved. With a 100 ft. Apiezon baseline separations were obtained only between Δ^{6} - Δ^{3} and Δ^{7} but a similar polar column separated all isomers except the Δ^{4} and Δ^{5} isomers.

We have obtained retention data on all the cis and trans methyl octadecenoates and on positional isomers of some acetylenic esters, viz., the methyl esters of the Δ^{5} - Δ^{11} dodecynoic acid and the Δ^{2} and Δ^{4} - Δ^{10} octadecynoic acids using capillary columns coated with

Apiezon L or neopentylglycol succinate. Retention data for some of these esters have also been obtained on packed diethyleneglycol succinate columns.

Acetylenic Esters (See Table VI. and Figure VII)

The octadecynoic esters (Δ^4 - Δ^{10}) show little variation either on an Apiezon column (17.91 - 17.83) or on a neopentylglycol succinate column (19.02 - 19.25) but on both columns the Δ^2 isomer has a much longer retention time.

The dodecynoic esters (Δ^5 - Δ^{11}) show little variation on the Apiezon L column (12.00 - 12.15) except for the Δ^{10} isomer (12.52) but on the polar column there is a fairly steady rise through the series (13.22 for Δ^5 to 14.00 for Δ^{11}) with the Δ^{10} isomer again being markedly higher (14.26).

Since the distance of the double bond from the methyl end has more control over the g.l.c. behaviour of methyl esters than the distance between the double bond and the carboxylate group (see later) the acetylenic C_{12} and C_{18} acids are not directly comparable. (The Δ^{10} dodecynoic ester should be compared with the Δ^{16} octadecynoic ester and not its Δ^{10} isomer).

Anderson and Rakoff's results for the nonynoic esters are qualitatively comparable with ours in that the Δ^2 isomer and that isomer containing the group $CH_3C\equiv C$ have longer retention times than the other isomers but cannot be compared more fully because of the different temperatures used for the three groups of esters.

Olefinic Esters (See Table VII.)

The cis olefinic esters have shorter retention times than their acetylenic analogues (at least for the range covered). Most of them behave very similarly to the trans compounds on the neopentylglycol succinate columns but have slightly shorter retention times on the Apiezon L column.

As in the acetylenic ester, the longest retention times are shown by the Δ^2 and Δ^{16} isomers. The only exception to this is on the neopentylglycol succinate column, where the Δ^2 cis isomer is eluted unusually quickly. In fact on both columns the Δ^2 cis isomer is very similar to the saturated ester but this effect is not noticed with the 2 trans isomer.

Relative Retention Times and Identification of Mono-ethenoid Esters.

It is an accepted rule in gas liquid chromatography that the retention times of homologues plotted on a log basis lie on a straight line and many authors have suggested that mono-olefinic esters and the various polyolefinic esters lie on separate lines parallel or approximately parallel to the line for saturated esters. It is clear from our results that the octadecenoic esters are not identical in their chromatographic behaviour and the question arises what is a homologue ?

Ackman[179,180,181] has made a very careful study of a few mono-enoic and many polyenoic esters (the latter are not very relevant to this discussion) and concludes that in a series of mono-enoic acids the distance between the double bond and the end CH_3 group is much more important than the distance between the double bond and carboxylic group. He, thus, considers that the C_{18} Δ^9, C_{20} Δ^{11} and C_{22} Δ^{13} esters are truly homologous and not the three Δ^9 isomers. Each series of true homologues will give retention data which lie on a straight line log plot though, in some cases, these separate lines may be so close as to be indistinguishable.

Panos,[175] on the other hand, has published a straight line for the log plot derived from 14:1 (9c), 16:1 (9c) and 18;1 (9c) and claims from these results to be able to identify unusual mono-enoic esters.

Since the results for C_9 (Ap. L. 126°; D.e.g.s. 136°), C_{12} (Ap. L. 150°; N.p.g.s. 150°; D.e.g.s. 150°) and C_{18} (Ap. L. 200°; N.p.g.s. 190°; D.e.g.s. 190°) were measured at quite different temperatures, it is not possible to distinguish between these divergent views.

Our more complete results on the C_{18} ethylenic esters show how far it is possible to determine double bond position by g.l.c. alone (given a knowledge of Cis or trans configuration). Distinction can easily be made between the group of esters having their double bond in the central region (Δ^4 - Δ^{15}) and those having a double bond close to either end of the molecule. Further recognition of the ester with a "central" double bond requires careful work, preferably with some suitable standards. Esters differing in carbon numbers by 0.05 can be distinguished. A suitable group of standard octadecenoic esters could be obtained by partial hydrogenation of linolenic acid with hydrazine hydrate and isolation by thin layer argentation, of the mixed Δ^9, Δ^{12} and Δ^{15} octadecenoates along with stearate (See Figure VIII).

C_{18} Ester	Ap. L	N.p.g.s.
Δ^9	17.63	18.15
Δ^{12}	17.73	18.27
Δ^{15}	17.89	18.46
stearate	18.00	18.00

TABLE VII - Acetylenic Esters

Position of triple bond	50 m. N.p.g.s. capillary		50 m. Ap. L. capillary		2 m. D.e.g.s. Packed	
	Carbon No.	Relative* retention time	Carbon No.	Relative* retention time	Carbon No.	Relative* retention time
Δ^2 C_{18}	20.47	2.23	18.60	1.28	–	–
Δ^4 C_{18}	19.02	1.42	17.91	0.97	–	–
Δ^5 C_{18}	19.07	1.42	18.87	0.95	–	–
Δ^6 C_{18}	19.16	1.48	17.85	0.94	—	—
Δ^7 C_{18}	19.19	1.48	17.84	0.94	–	–
Δ^8 C_{18}	19.23	1.49	17.83	0.93	–	–
Δ^9 C_{18}	19.23	1.48	17.83	0.93	–	–
Δ^{10} C_{18}	19.25	1.52	17.87	0.95	–	–
Δ^5 C_{12}	13.22	1.69	12.04	1.02	14.47	1.18
Δ^6 C_{12}	13.33	1.78	12.00	1.00	14.67	1.26
Δ^7 C_{12}	13.42	1.84	12.03	1.02	14.78	1.31
Δ^8 C_{12}	13.48	1.90	12.06	1.03	14.87	1.36
Δ^9 C_{12}	13.61	2.03	12.15	1.09	15.13	1.48
Δ^{10} C_{12}	14.26	2.73	12.52	1.33	16.00	2.03
Δ^{11} C_{12}	14.00	2.37	12.01	1.01	15.74	1.83

* C_{12} = 1.00 for Dodecynoates and C_{18} = 1.00 for octadecenoates

TABLE VII- Carbon Numbers of Methyl Octadecenoates

Position of double bond	50 m. N.p.g.s. capillary		50 m. Ap. L. capillary		2 m. D.e.g.s. Packed
	Cis	Trans	Cis	Trans	Cis
Δ^{2}	18.06	19.23	17.97	18.81	18.28
Δ^{3}	18.42	18.42	17.86	17.86	18.74
Δ^{4}	18.14	18.10	17.71	17.71	18.43
Δ^{5}	18.12	18.12	17.66	17.79	18.34
Δ^{6}	18.15	18.15	17.65	17.74	18.44
Δ^{7}	18.14	18.14	17.64	17.73	18.45
Δ^{8}	18.12	18.12	17.64	17.75	18.45
Δ^{9}	18.15	18.15	17.63	17.73	18.49
Δ^{10}	18.18	18.19	17.67	17.73	18.54
Δ^{11}	18.23	18.23	17.68	17.77	18.57
Δ^{12}	18.27	18.22	17.73	17.75	18.62
Δ^{13}	18.32	18.26	17.80	17.80	18.75
Δ^{14}	18.40	18.27	17.86	17.83	18.86
Δ^{15}	18.46	18.33	17.83	17.85	19.01
Δ^{16}	18.75	18.54	18.17	18.05	19.34
Δ^{17}	18.48	-	17.89	-	18.92

TABLEVIIa - Relative Retention Data* (C_{18} = 1.00) Cis

Methyl Octadecenoates

Position of double bond	50 m. N.p.g.s. capillary	50 m. Ap. L. capillary	2 m. D.e.g.s. Packed
Δ^{2}	1.02	0.99	1.08
Δ^{3}	1.15	0.94	1.26
Δ^{4}	1.05	0.89	1.14
Δ^{5}	1.04	0.87	1.11
Δ^{6}	1.05	0.86	1.14
Δ^{7}	1.05	0.86	1.15
Δ^{8}	1.04	0.86	1.15
Δ^{9}	1.05	0.86	1.16
Δ^{10}	1.07	0.87	1.18
Δ^{11}	1.08	0.88	1.19
Δ^{12}	1.10	0.90	1.21
Δ^{13}	1.12	0.92	1.26
Δ^{14}	1.15	0.94	1.30
Δ^{15}	1.17	0.96	1.36
Δ^{16}	1.30	1.05	1.60
Δ^{17}	1.18	0.99	1.32

* Retention times were measured from the apices of peaks.

FIGURE VII

G.L.C. METHYL DODECYNOATES

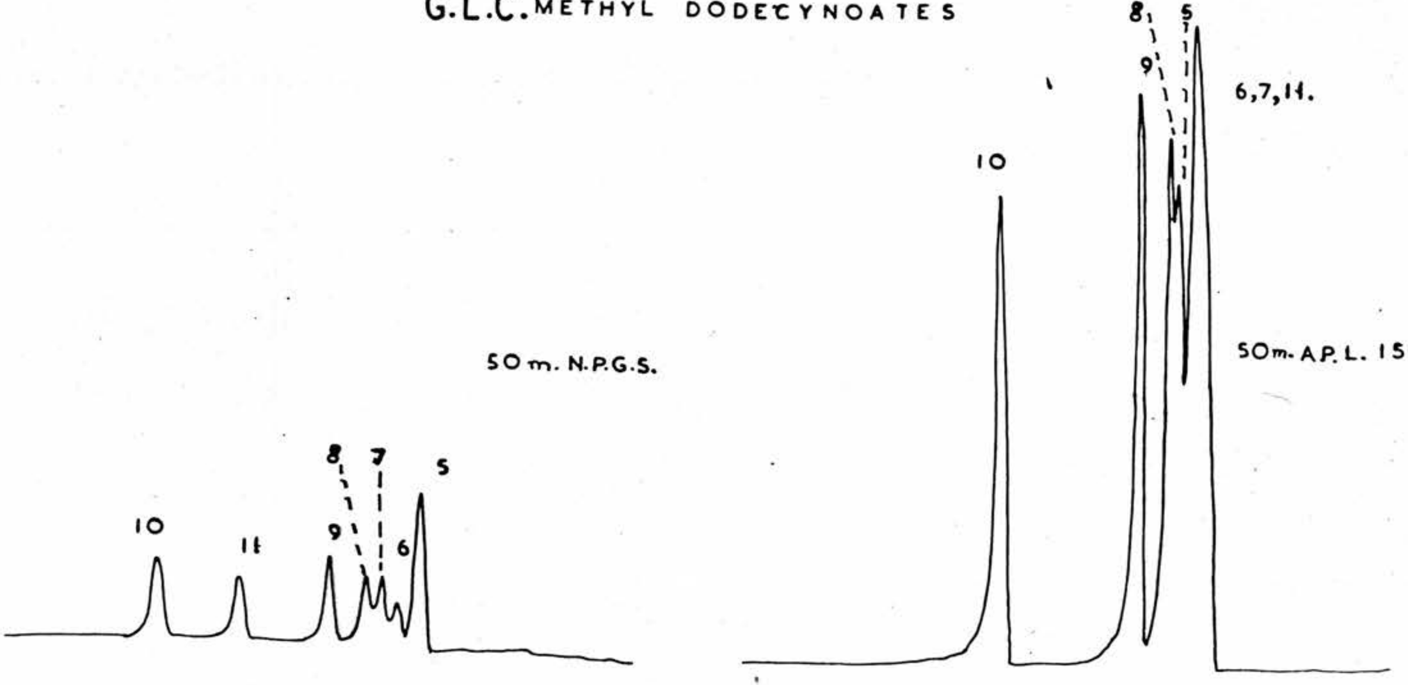
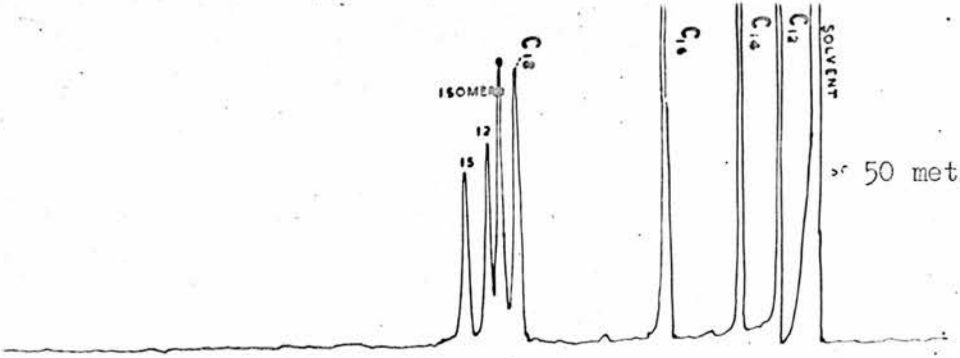
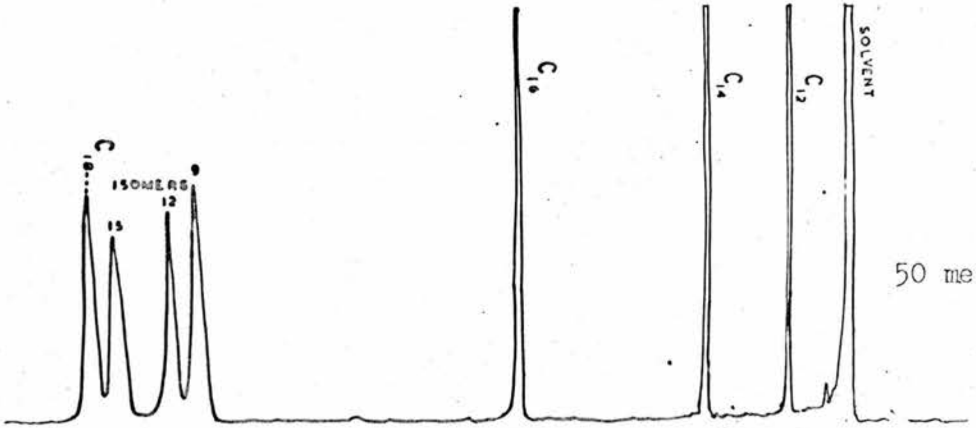


FIGURE VIII

G.L.C. of the methyl octadecenoates obtainable by the reduction of linolenic acid with hydrazine



50 metre N.P.G.S. column.



50 metre Ap.L column.

Evaluation of the physical methods for the determination of double bond position.

In the following table an attempt is made to show how far each of the cis octadecenoic acids or esters can be distinguished by the various physical methods which have been examined. The terms g.l.c. and t.l.c. refer respectively to chromatography with capillary columns using polar and/or non-polar phases and to chromatography on silica impregnated with silver nitrate. In the evaluation of these two techniques it is assumed that a standard mixture of the Δ^9, Δ^{12} and Δ^{15} isomers obtainable by hydrazine reduction of linolenic acid (see page 88) and methyl petroselenate are available.

The + sign indicates that the acid or ester can be differentiated from other isomers by the technique in question.

The trans acids (Δ^4- Δ^{16}) can be distinguished from each other by their infra-red spectra in the solid state (see page 64).

Position of double bond	acid m.p.	esters		
		g.l.c.	t.l.c.	n.m.r.
Δ^{2}	Δ^{3}	+	+	+
Δ^{3}	Δ^{2}	+	$\Delta^{10}, \Delta^{15}, \Delta^{16}$	+
Δ^{4}	+	$\Delta^{5}, \Delta^{7}, \Delta^{9}$	$\Delta^{5}, \Delta^{7} - \Delta^{9}, \Delta^{17}$	+
Δ^{5}	$\Delta^{7}, \Delta^{9}, \Delta^{11}$	$\Delta^{4}, \Delta^{7}, \Delta^{9}$	$\Delta^{4}, \Delta^{7} - \Delta^{9}$ Δ^{17}	
Δ^{6}	Δ^{12}, Δ^{13}	+	+	$\Delta^{7} - \Delta^{13}$
Δ^{7}	$\Delta^{5}, \Delta^{9}, \Delta^{11}$	$\Delta^{4}, \Delta^{5}, \Delta^{9}$	$\Delta^{4} - \Delta^{6}, \Delta^{8},$ Δ^{17}	$\Delta^{6}, \Delta^{8} - \Delta^{13}$
Δ^{8}	Δ^{10}	+	$\Delta^{4}, \Delta^{5}, \Delta^{7},$ Δ^{17}	Δ^{6}, Δ^{7} $\Delta^{9} - \Delta^{13}$
Δ^{9}	$\Delta^{5}, \Delta^{7}, \Delta^{11}$	$\Delta^{4}, \Delta^{5}, \Delta^{7}$	$\Delta^{4}, \Delta^{5}, \Delta^{17}$	$\Delta^{6} - \Delta^{8}$ $\Delta^{10} - \Delta^{13}$
Δ^{10}	Δ^{8}	+	$\Delta^{3}, \Delta^{15}, \Delta^{16}$	$\Delta^{6} - \Delta^{9},$ $\Delta^{11} - \Delta^{13}$
Δ^{11}	$\Delta^{5}, \Delta^{7}, \Delta^{9}$	+	$\Delta^{12} - \Delta^{14}$	$\Delta^{6} - \Delta^{10},$ Δ^{12}, Δ^{13}
Δ^{12}	Δ^{6}, Δ^{13}	+	$\Delta^{11}, \Delta^{13}, \Delta^{14}$	$\Delta^{6} - \Delta^{11},$ Δ^{13}

Position of double bond	acid m.p.	esters		
		g.l.c.	t.l.c.	n.m.r.
Δ^{13}	Δ^{6}, Δ^{12}	+	$\Delta^{11}, \Delta^{12}, \Delta^{14}$	Δ^{6}- Δ^{12}
Δ^{14}	Δ^{15}	+	Δ^{11}- Δ^{13}	+
Δ^{15}	Δ^{14}	+	$\Delta^{3}, \Delta^{10}, \Delta^{16}$	+
Δ^{16}	Δ^{17}	+	$\Delta^{3}, \Delta^{10}, \Delta^{15}$	+
Δ^{17}	Δ^{16}	+	$\Delta^{4}, \Delta^{5}, \Delta^{8},$ Δ^{9}	+

EXPERIMENTAL

Solvents

Ether and tetrahydrofuran were dried overnight with calcium chloride. The decanted solvent was refluxed with sodium wire for 1 hr., distilled and then redistilled from fresh sodium. Tetrahydrofuran dried in this way **was redistilled** from sodium immediately prior to use. Ether required for the preparation of phenyl lithium was further dried, just before use, with lithium aluminium hydride (using 1 g. of the reagent for about 50 ml. of ether).

Carbon tetrachloride and chloroform were refluxed with phosphorus pentoxide for 30 min. and distilled.

Petroleum ether(olefin-free) - Petroleum ether (60-80° 2 l.) was first washed with c. sulphuric acid, then with water and dried with sodium sulphate. Bromine (30 ml.) was added and the solution left aside for 48 hr. Further quantities of bromine were added if the solution decolourized within this period. The pale brown solution was then washed successively with 10% sodium sulphite, 2N sodium hydroxide, and water, and then dried. Distillation gave olefin-free petrol which was usedfor the preparation of either mono or dibromo undecanoic acid.

Methanol and Ethanol - Both these solvents were dried with magnesium methoxide made in situ with methanol and magnesium in the presence of catalytic amounts of iodine.

Drying

Solvent extracts of the different compounds were dried with "dried" magnesium sulphate or anhydrous sodium sulphate.

Melting Points.

Melting points were determined on a Gallenkamp micro-melting point unit and are uncorrected.

Distillation

Distillation of most of the intermediates was carried out on a ½ M. Fenske column with a Perkin triangle as made by Towers.

All the C_{18} cis ethylenic esters were distilled on an "Abeggs" spinning band column supplied by Buchi. A stainless steel band was used in all the distillations and the reflux ratio generally used was 1 in 20.

Methylation of small quantities of acids.

The acid (~ 50 mg.) was mixed with dry methanol (10 ml.) and boron-trifluoride methanol complex (10 ml., 14%) and refluxed for 5 min. on a waterbath. The product was poured into excess water (50 ml.) and extracted with ether, which was washed with water, dried and evaporated.

Infra-red spectroscopy

Routine samples were examined on a Perkin Elmer 137 spectrophotometer. The determination of the trans content on the cis ethylenic acids and the spectra of the cis esters and trans acids were investigated on a "grating infra-red spectrophotometer"- Perkin Elmer 621.

Gas Liquid Chromatography

The Perkin Elmer Fractometer 451 or the Pye Argon Chromatograph were used to examine the different compounds prepared. The stationary phases used included polyethylene glycol succinate and diethyleneglycol succinate (polar) and Apiezon L (non-polar). Capillary columns (50 m) with neopentyl glycol succinate or Apiezon L were used on the Perkin Elmer F11 gas chromatograph.

The attempted separation of N,N-dimethyl dodec-10-ynamide from the N,N-dimethyl undec-11-ynamide was carried out on the "Aerograph" Autoprep, Model A-700 made by Wilkens Instruments Inc.

Nuclear Magnetic Spectroscopy

The spectra of acids and/or their methyl esters and other intermediate compounds were recorded at 60 Mc/S with approximately 15% solutions in carbon tetrachloride on a Perkin Elmer R-10. Chemical shifts are in p.p.m. downfield from internal tetramethyl silane ($\tau = 10$).

Liquid ammonia syntheses

Sodamide.[182] Liquid ammonia was run in from an "upright" cylinder to a conical flask (1 l.) and transferred into a 3-necked flask (1 l.) equipped with a stirrer and dry ice condenser. The flask was placed within an empty Dewar flask.

Powdered ferric nitrate (0.5 g.) was added followed by sodium cut into small pieces ($\sim$ 0.5 g.). These were added at intervals as the blue colouration caused by each addition changed to grey or black. Stirring was continued for 30 min. after the addition of sodium was completed.

Sodium acetylide.[183] - An acetylene cylinder was connected to the inlet tube of the reaction flask through a mercury safety trap, a Drechsel bottle cooled with solid carbon dioxide (to condense out the acetone), a Drechsel bottle containing c. sulphuric acid and a reversed Drechsel bottle packed loosely with glass wool. Liquid ammonia was run into the flask and saturated with acetylene for 5 min. The flow of acetylene was continued (4 or 5 bubbles per sec.) and ferric nitrate (0.5 g.) was added, followed by pieces of sodium (0.5 g. each), which were introduced to the stirred liquid ammonia at a rate to maintain the grey/black colour of the reaction mixture. The acetylene was bubbled through for a further 30 min. after all the sodium had dissolved.

Von Rudloff Oxidation (Craig and Tulloch's modification)[184]

The unsaturated ester or acid (50 mg.) was dissolved in tertiary butanol (35 ml.), water (7 ml.) and potassium carbonate (0.5 M; 7 ml.). A solution of oxidant, (14 ml., made from potassium permanganate (0.0395 g.) and potassium periodate (2.24 g.) in water (100 ml.)), was then added and the whole shaken for 6 hr. at ambient temperature. The excess permanganate was then reduced with gaseous sulphur dioxide, the solution made alkaline with potassium carbonate and evaporated to dryness on a rotary film evaporator. The residue was acidified with the minimal volume of dilute hydrochloric acid and extracted with ether (75-100 ml.). The ether extract was washed with water (~ 10 ml.), dried and evaporated. The fission products were studied as their methyl esters by g.l.c.

Ozonolysis

Ozone was generated by passing dry oxygen through a laboratory ozonizer supplied by Griffin and George Ltd.

The unsaturated compound (25 mg.) was dissolved in dry methanol (15 ml.) and cooled to ~ 5° with ice. Ozone was bubbled through this solution until iodine was liberated by the effluent-gases from a mixture of potassium iodide and hydrochloric acid. The methanol was stripped off at room temperature under reduced pressure. Formic acid (2 ml.) and hydrogen peroxide (30%, 5 ml.) were added to the residue and the whole refluxed for 1 hr. on a water bath. The product was diluted with water, extracted with ether, washed with water, dried and evaporated. The fission products were examined as their methyl esters by g.l.c.

Semihydrogenation.

Lindlar's catalyst was made in the manner described in the original publication.[185]

The catalyst and distilled quinoline were dissolved in ethyl acetate and shaken in an atmosphere of hydrogen until no more gas was absorbed. The acetylenic compound in more ethyl acetate was then added and the mixture shaken in hydrogen until the rate of absorption decreased. Samples of the reaction mixture were occasionally removed and examined by g.l.c. Hydrogenation was continued until such time when g.l.c. showed that no acetylenic material remained in the product. The mixture was filtered on a Büchner funnel and the filtrate washed with 2N hydrochloric acid, then with water, dried and evaporated to give the desired ethylenic compound.

Pure Cis Acids - for melting point determination

The cis ethylenic ester($\sim$15 mg.) were run on thin layer plates (20 cm. x 20 cm) of silica (250μ thick) impregnated with silver nitrate (15%) and activated for 75 min. at 105°, using the solvent system petroleum ether/ether in the ratio 93:7 respectively. The plates were removed from the tank when the solvent front reached about an inch from the uppermost boundary of the plates, left for 30 min., and then redeveloped in the same solvent system. The bands corresponding to the cis isomer and the unwanted trans and saturated esters were detected with 2,7-dichlorofluorescein.

The absorbent with the cis ester was scraped off, transferred to a centrifuge tube and stirred for 2 min. with a mixture of ether, methanol and water (10 ml. of a 5:5:1 mixture). The mixture was then centrifuged over 2 min. and the solvent decanted from the residue. The solvent from 5 such extractions (50 ml.) was refluxed for 1 hr. with sodium hydroxide (4 g.). The product was acidified with dilute hydrochloric acid, and extracted with ether which was washed, dried and finally evaporated.

The crude acid (6-10 mg.) was dissolved in distilled petroleum ether (0.5 ml.) and placed in a "Craig tube"[186] where it crystallised at 10°. The solvent was removed by centrifuging and the crystallised acid dried in a vacuum desiccator.

PREPARATION OF TRANS ETHYLENIC ESTERS AND ACIDS.

Selenium isomerization

A mixture of the cis ethylenic ester (100 mg.) octanoic acid (200 mg. as solvent) and selenium (2 mg.) was sealed under nitrogen in a pyrex tube (2" x 0.25"). Four such capsules were attached to a glass stirrer with copper wire and rotated slowly for 4 hr. in an oil bath maintained at 200°. The capsules were cooled, opened, and the contents separated on thin layer chromatoplates (20 x 20 cm.) using silica (1 mm. thick) with the solvent system, ether,petroleum ether, ammonia(1.880 s.g.) in the ratio 50:48:2 respectively. The ester band; detected with dichlorofluorescein and ultra violet light, was scraped off and extracted with ether alone in a manner similar to that described for the preparation of cis ethylenic acids. The combined ether extracts were washed with water, dried and evaporated to give the cis-trans equilibrium mixture.

The recovery of organic material varied between 84-102%.

The relative amounts of the cis-trans isomers from the different positional isomers were determined by gas liquid chromatography using capillary columns with a polar (Neopentylglycol succinate) and non-polar phase (Apiezon L).

A portion of this equilibrium mixture (25 mg.) was oxidised by the Von Rudloff procedure to determine the extent of double bond migration during the isomerisation.

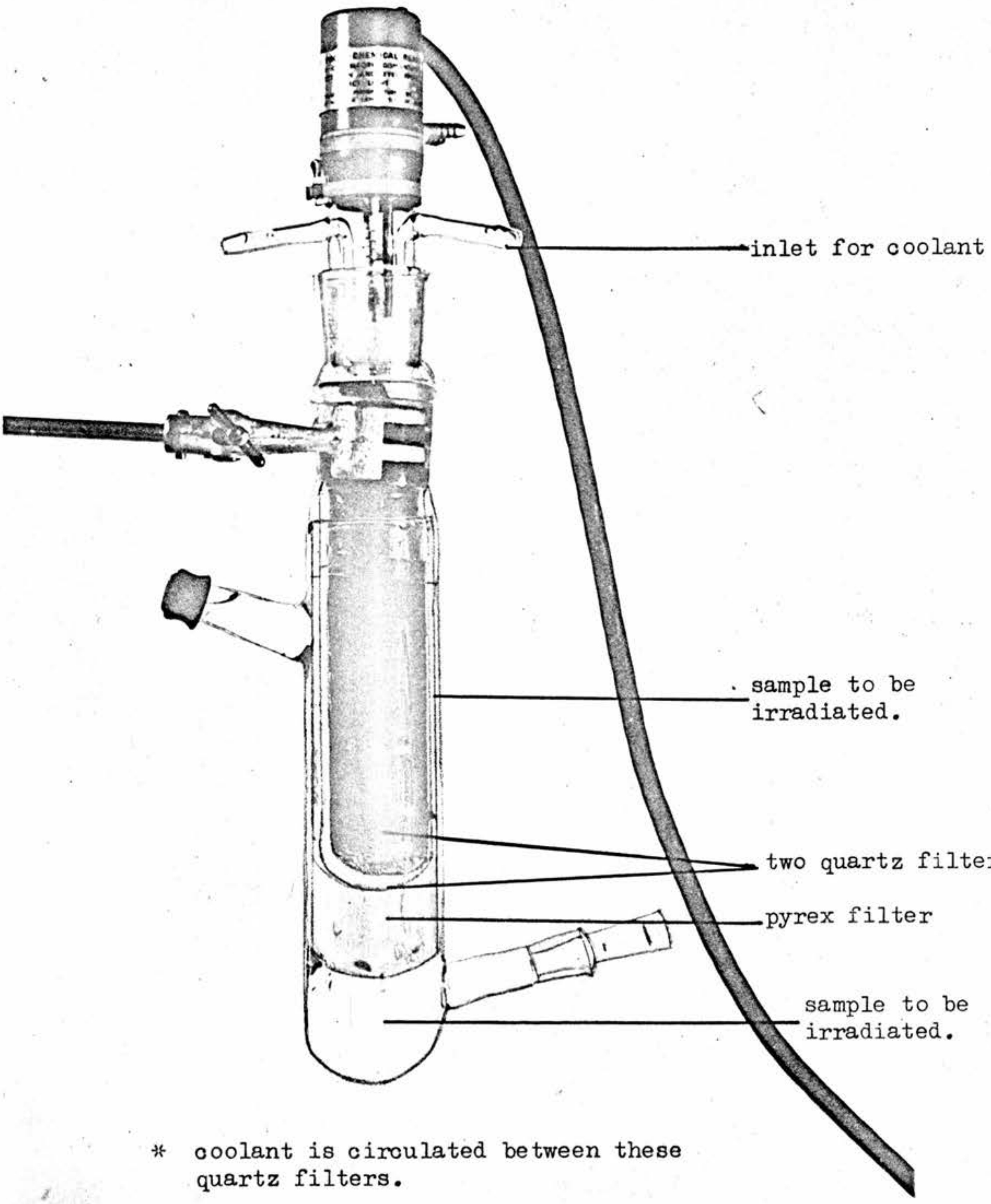
Cis/trans isomerization using ultra-violet radiation.[142]

The light source was a 125 w. "Hanovia" portable ultra-violet lamp with a quartz mantle and facilities for cooling by circulating water.

The solution to be irradiated was contained in an annular reaction vessel (15 cm x 1 cm., see figure IX) which surrounded the mercury lamp assembly. Radiation reaching the reactants was cut off at 280 mμ by interposing a 2.0 mm. thick walled pyrex cylinder between the quartz mantle and

FIGURE IX

U.V. REACTION VESSEL FOR cis - trans ISOMERIZATION



* coolant is circulated between these quartz filters.

the solution. The outer reaction vessel was separated all-round from the pyrex cylinder by a gap of about 1.0 mm. except at the bottom where a separation of one inch was deliberately allowed to make provision for a teflon stirrer.

The cis ethylenic ester (100 mg.) with diphenyl sulphide (100 mg.) in benzene (120 ml.) was introduced into the reaction vessel through a side arm and stirred with a magnetic stirrer. The solution was irradiated for 3 hr. after which it was freed of benzene on a rotary film evaporator.

The mixture, of the cis-trans esters, residual diphenyl sulphide and the side products, was separated by thin layer chromatography. The procedure adopted for this separation and the conversion of the trans esters, obtained thereby, to their corresponding ethylenic acids was similar to that described for the preparation of pure cis acids from the cis ethylenic esters (p. 95).

Infra red spectroscopy

Progression bands in the region 1180-1350 cm^{-1}

The trans ethylenic acid (1.5 - 2 mg.) and potassium chloride (150 mg.) were taken in an agate capsule and finely powdered in a vibrating mill (Grubb-Parsons) and then pressed into a disc at a pressure of 5000 p.s.i. using a 30 ton press H30-1 Mk. 2 supplied by Research and Industrial Instruments Company. The spectrum was recorded on the Perkin Elmer 621.

Trans isomer content in cis ethylenic esters

The method used by O'Conner[187] was used to determine the trans content of the distilled cis ethylenic esters.

The spectra in the region 9.5 - 11μ were recorded on a Perkin-Elmer 621 instrument using solution cells with a path length of 0.1 mm. Measurements were carried out on solutions of esters in carbon disulphide (16%) and pure methyl elaidate was taken as the standard.

Methyl Octadec-2-enoate

$$CH_3(CH_2)_{14}COOH \xrightarrow{1} CH_3(CH_2)_{14}Br \xrightarrow{2} CH_3(CH_2)_{14}C{\equiv}CH$$

$$\xrightarrow{3} CH_3(CH_2)_{14}C{\equiv}C.COOH \xrightarrow{4} CH_3(CH_2)_{14}C{\equiv}CCOOMe \xrightarrow{5}$$

$$CH_3(CH_2)_{14}CH\overset{cis}{=}CHCOOMe$$

1, $AgNO_3$; Br_2 2 , NaC≡CH, liquid ammonia

3 , EtMgBr; CO_2 4 , MeOH, HCl 5 , H_2, Lindlar

METHYL OCTADEC-2-ENOATE.

Silver Palmitate.[188]

Palmitic acid (100 g., 0.39 mole) was added to a solution of potassium hydroxide (24 g., 0.43 mole) in distilled water (1100 ml.) contained in a flask (3 l.) with a stirrer. When the acid dissolved, silver nitrate (70 g., 0.41 mole) in distilled water (750 ml.) was added over 10 min. The precipitated silver palmitate was collected on a Büchner funnel, washed with methanol and dried in an oven at 70° for 8 hr. The granular silver salt was crushed to a fine powder, transferred to a 3-necked flask (1 l.) and dried at 70° under oil pump pressure for 8 hr. Silver palmitate (128.5 g., 91%) was obtained as a light brown powder, melting with decomposition between 202-209° (lit.[189] 209°).

1-Bromopentadecane.

Dry bromine (58 g., 0.72 mole) was added to the mixture of silver salt (128 g., 0.35 mole) and dry carbon tetrachloride (300 ml.). When the addition was complete, the mixture was heated for an hour on a steam bath. The precipitated silver bromide was centrifuged from the solution from which the crude bromide was then isolated. Distillation through a ½-metre Fenske column gave 1-bromopentadecane (65 g., 63.8%), b.p. 136-136.5°/0.5 mm. (lit.,[190] b.p. 127-128°/0.5 mm.).

Heptadec-1-yne.

Sodium acetylide made from sodium (9.4 g., 0.4 mole) in liquid ammonia (500 ml.) was transferred from the reaction flask to an autoclave of 1 l. capacity. 1-Bromopentadecane (65.g., 0.22 mole) in dry tetrahydrofuran (75 ml.) was added rapidly over 3-5 min. and the autoclave sealed. The mixture was stirred for 24 hr., and the ammonia allowed to escape through a needle valve. The product was diluted with water, acidified with 2N hydrochloric acid, and extracted with ether. Distillation gave heptadec-1-yne (44 g., 84.4%), b.p. 116-118°/0.6 mm. (lit.[191] b.p. 171°/17 mm.). It contained about 5% of unreacted starting material.

Methyl Octadec-2-ynoate.

Heptadec-1-yne (40 g., 0.17 mole) in dry ether (100 ml.) was added over 1 hr. to a well-stirred solution of ethyl magnesium bromide, prepared from magnesium (8.2 g.) and ethyl bromide (32.7 g.), in dry ether (400 ml.). The mixture was maintained at 5° during the addition and was then heated under reflux for an hour. The reaction mixture was cooled to room temperature and poured into an autoclave containing solid carbon dioxide (about 200 g.). The autoclave was sealed for 12 hr., during which time the pressure rose to 20 atmospheres. The product was diluted with water, acidified with 2N sulphuric acid, extracted with ether and then converted to its methyl ester. The crude ester was distilled to give methyl octadec-2-ynoate (30.3 g.) b.p. 143-146°/0.5 mm. with a diethylglycol succinate column, g.l.c. showed the product to be 98.5% ester with 1.5% of unchanged heptadec-1-yne.

Methyl Octadec-2-enoate.

A mixture of Lindlar's catalyst (12 g.), quinoline (3.0 g.) and ethyl acetate (180 ml.) was vigorously shaken in hydrogen until saturated. A solution of methyl octadec-3-ynoate (15 g.) in ethyl acetate (60 ml.) was then added and the mixture shaken until the reduction to the ethylenic acid was complete as shown by g.l.c. The catalyst was filtered off, and the filtrate, after washing with 2N hydrochloric acid and water, was dried and evaporated. The residue was distilled through a spinning band column to give methyl octadec-2-enoate.(11.3 g.) b.p. 165-167°/1 mm. (Octadec-2-ynoic acid. Found:C, 77.24 ; H, 11.78 . $C_{18}H_{32}O_2$ requires C,77.07; H, 11.53). M.p. of cis olefinic acid 49-50 ° (lit.[46] 50-50.5), m.p. of acetylenic acid 56-57 ° (lit.[46] 56.7 - 57.5) .

Purity of Olefinic Acid.

The cis ester contained no detectable amount of the saturated acid (g.l.c.) and contained the trans isomer (2.0 % by i.r.) Von Rudloff oxidation gave hexadecanoic acid (96 .8%) along with pentadecanoic acid

(3.2%). The pure Δ^2 ethylenic ester was obtained by thin layer chromatography on silica impregnated with silver nitrate (see page 95).

Octadec-3-enoic Acid

$$\mathrm{CH_3(CH_2)_{13}OH} \xrightarrow{1} \mathrm{CH_3(CH_2)_{13}Br} \xrightarrow{2} \mathrm{CH_3(CH_2)_{13}C{\equiv}CH}$$

$$\xrightarrow{3} \mathrm{CH_3(CH_2)_{13}C{\equiv}CCH_2CH_2OH} \xrightarrow{4} \mathrm{CH_3(CH_2)_{13}\overset{cis}{CH{=}CH}CH_2CH_2OH}$$

$$\xrightarrow{5} \mathrm{CH_3(CH_2)_{13}\overset{cis}{CH{=}CH}CH_2COOH}$$

1, Br_2, red phosphorus 2, NaC≡CH, liquid ammonia

3, PhLi, ethylene oxide, liq. NH_3 4, H_2, Lindlar

5, CrO_3, H_2SO_4, acetone.

METHYL OCTADEC-3-ENOATE

1-Bromotetradecane.

Bromine (48 g., 0.60 mole) was added over an hour to a stirred, warm (40-50°) mixture of tetradecanol (107 g., 0.5 mole) and red phosphorus (3.4 g.). The mixture was then heated for 2 hr. at a temperature which allowed gentle reflux of the excess bromine. The product was then poured into ice and water and extracted with ether. The extract was washed free of bromine with dilute sodium bicarbonate, washed with water, dried and distilled to give 1-bromotetradecane (101.5 g., 73.3%) b.p. 165.5°/10 mm. containing about 6% C_{12} bromide and some C_{16} bromide. This mixture was carefully distilled through a ½ metre Fenske column to obtain 1-bromotetradecane (78 g.) b.p. 122-124°/0.7 mm (lit.[116] 178.5 - 179.5°/20 mm.) which was shown to be pure by g.l.c.

Hexadec-1-yne.

1-Bromotetradecane (157 g., 0.57 mole) in dry ether (50 ml.) was poured into an autoclave (1 l.) containing sodium acetylide made from sodium (22.8 g., 0.97 mole) in liquid ammonia (600 ml.). The autoclave was sealed and the mixture stirred for 24 hr. at room temperature, after which the ammonia was allowed to escape. Hexadecyne (106 g., 84%) b.p. 100°/0.6 mm (lit.[191] 144°/10 mm.) was obtained from the reaction product as in the case of the C_{17} homologue (see preparation of methyl octadec-2-ynoate). The distilled compound was shown by g.l.c. to be better than 99% pure.

Octadec-3-yn-1-ol

Freshly dried bromobenzene (52.5 g., 0.33 mole) in ether (dried first over sodium and then distilled from $LiAlH_4$, 100 ml.) was added dropwise to freshly cut lithium (5.3 g.) kept under an atmosphere of nitrogen. When the lithium began to react (the metal turns a bright gold) the rate of addition was altered to maintain a gentle reflux of the reaction. When the addition was complete stirring was continued for another 90 min. to dissolve all the lithium. Hexadec-1-yne (60 g., 0.27 mole) in dioxan (100 ml.) was added over 30 min. and the mixture stirred for an hour and transferred into a 1 l. autoclave followed by ethylene oxide (74 g., 0.52 mole) and dioxan (50 ml. used to rinse the reaction flask). Liquid ammonia (600 ml.) was then added carefully, the autoclave sealed and the mixture stirred overnight at room temperature. Next day the ammonia was allowed to escape through a needle valve, the autoclave then opened and the reaction product diluted with water. The mixture was acidified with dilute sulfuric acid and extracted with ether which was washed with water, dried and evaporated to give crude octadec-3-yn-1-ol (84 g.).

Column chromatography of this material on silicic acid with petroleum ether (40-60°) removed the unreacted hexadecyne and bromobenzene. The more polar alcohol was eluted subsequently with ether. The separated alcohol (61.2 g., 87%) was shown to be about 98% pure by g.l.c.

Octadec-3-ynoic Acid

Chromium trioxide (2.0 g., 0.020 mole) in c. sulphuric acid (0.3 ml.) and water (1.2 ml.) was added dropwise to a solution of octadec-3-yn-1-ol (4.0 g., 0.015 mole) in acetone (62 ml.) maintained at 10°. The mixture was stirred for 4 hr. more at 15-20°, diluted with water (125 ml.), and extracted with ether. The extract was first washed free of inorganic salts and washed again with dilute ammonium hydroxide. The alkaline solution was acidified and extracted with ether to give an acidic product.

Ozonolysis and von Rudloff oxidation of the material did not give consistent results within or between the methods. The oxidation of the alcohol was repeated 5 times and in some cases the content of the Δ^4 isomer was as high as 33.8% but the Δ^2 isomer was consistently below 5%.

Octadec-3-en-1-ol.

The acetylenic alcohol (67 g.) with Lindlar's catalyst (25 g.) and quinoline (5.9 g.) in ethyl acetate (450 ml.) was shaken vigorously in an atmosphere of hydrogen. The reduction was followed by g.l.c. and the conversion to the octadec-3-en-1-ol took about 4 hr.

The alcohol, examined both by ozonolysis and von

Rudloff oxidation, was about 95% pure. The results on oxidation were not reproducible.

Octadec-3-enoic Acid.

A solution of chromium trioxide (31.5 g., 0.315 mole) in c. sulphuric acid (4.7 ml.) and water (18.3 ml.) was added dropwise over an hour to a solution of octadec-3-en-1-ol (62 g., 0.233 mole) in acetone (960 ml.) maintained at 10°. When the addition was complete, the mixture was stirred for 4 hr. at 15-20°, then poured into water (1800 ml.) and extracted with ether. The extract was washed free of inorganic acid and extracted with 2N ammonium hydroxide (six portions of 300 ml. each) to which 3% sodium chloride had been added. The combined alkaline extracts were washed three times with ether, acidified with 2N sulphuric acid and extracted with more ether. This was washed with water, dried and evaporated to give crude octadec-3-enoic acid (34 g.). Distillations under high vacuum gave the acid (28 g.) b.p. 150-158°/2.5×10^{-4} mm. (Octadec-3-enoic acid:

m.p. of cis isomer 49.5-50.5

Von Rudloff oxidation of the acid showed it to be only 93 % pure and contained 6.5% of the Δ^2 isomer and 0.5 % of the Δ^4 isomer.

Small amounts of the methyl ester were purified by thin layer chromatography using silica impregnated with silver nitrate. The Δ^2 isomer had an appreciably higher R_f value than the Δ^3 isomer thereby making the separation very easy (n_D^{25} 1.4521).

Purity of olefinic acid.

The cis ester contained the corresponding saturated acid ($\sim$ 0.2% by g.l.c.) and the trans isomer (2.0 % by i.r.). Von Rudloff oxidation gave the products mentioned above.

Attempted syntheses of Ethyl Octadec-3-ynoate.

(i) Lithium hexadecyne made from hexadecyne (4.44 g., 0.02 mole) and lithium (0.40 g., 0.022 mole) in dioxan (25 ml.) was added slowly over an hour to ethyl bromo-acetate (5.01 g., 0.03 mole) in dioxan (25 ml.) and then refluxed for 3 hr. The product was acidified and extracted with ether, which was washed with water, dried, and evaporated. The product gave a number of peaks on g.l.c. but none of them corresponded to a C_{18} ester.

(ii) Hexadecyne (2.22 g., 0.01 mole) in dry ether (25 ml.) was added to ethyl magnesium bromide made from magnesium (0.4 g., 0.016 mole) and ethyl bromide (1.10 g., 0.01 mole) in ether (25 ml.). The Grignard complex was added over 30 min. to a solution of ethyl bromo-acetate (2.0 g., 0.013 mole) in dry ether (25 ml.)

and then heated under reflux for 8 hr. The product was diluted with water acidified and extracted with ether. Examination of the recovered product by g.l.c. did not show any ethyl octadec-3-ynoate.

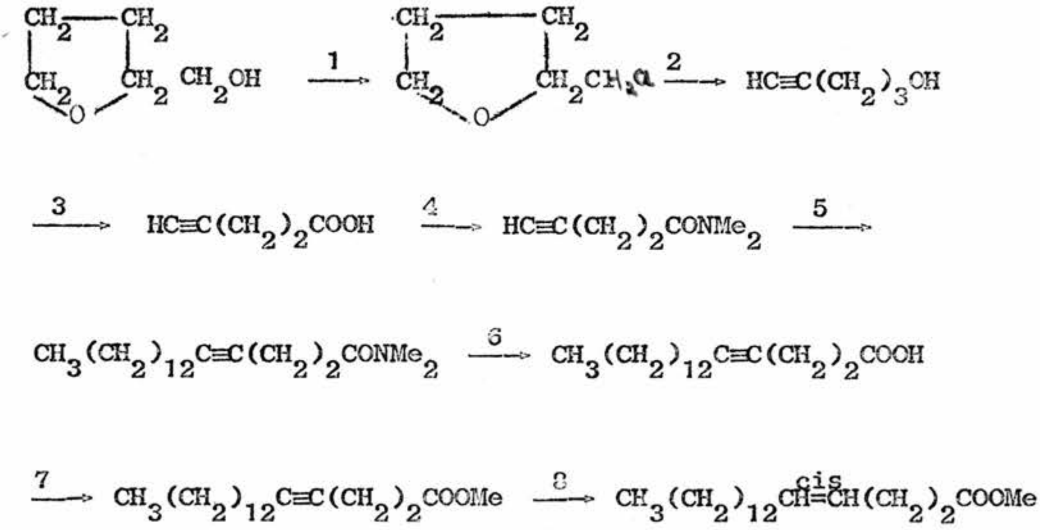
Hydrolysis of Methyl trans octadec-3-enoate

The Δ^3 trans ester (see page 98) was refluxed for 15 min. with sodium hydroxide (0.4 g.) in ethanol (80% 10 ml.).

The acidic product was isolated and recrystallised 4 times from a mixture of hexane and acetone (9:1) at -10°.

A small sample of the purified acid, re-esterified with boron-trifluoride/methanol complex was shown to contain only the Δ^3 isomer by g.l.c. using a capillary column coated with neopentylglycol succinate.

Methyl Octadec-4-enoate



1, $SOCl_2$, pyridine   2, $NaNH_2$, liquid ammonia

3, CrO_3, H_2SO_4, acetone   4, $SOCl_2$; $HNMe_2$

5, $NaNH_2$, liquid ammonia; 1-Bromotridecane

6, NaOH, EtOH; HCl   7, MeOH, HCl   8, H_2, Lindlar

METHYL OCTADEC 4-ENOATE

Silver myristate.

Pure myristic acid (99.5% by g.l.c. 91.2 g., 0.4 mole) was dissolved in a solution of potassium hydroxide (22.4 g., 0.4 mole) in water (1200 ml.). Silver nitrate (68 g., 0.40 mole) in water (800 ml.) was added rapidly over 10 min. to a stirred solution. After stirring vigorously for a further 2 hr., the precipitated silver salt was filtered on a Büchner funnel, washed with methanol and dried in an oven at 80° for 6 hr. The cake was finely powdered in a mechanical crusher and dried at 110° for 72 hr. leaving the silver salt (116 g., 87%) as a light brown powder which decomposed at 196° and became liquid at 214°. (lit.[189] 211°).

1-Bromotridecane.

To an efficiently stirred mixture of the dry silver salt (101 g.) and dry carbon tetrachloride (150 ml.), dry bromine (53 g., 0.66 mole) was added dropwise over an hour. The mixture was then heated on a boiling water bath and stirred for a further hour. After centrifuging, the residual silver bromide was washed thoroughly with more carbon tetrachloride. The combined extracts were washed with dilute sodium carbonate and water, dried, and evaporated. Distillation of the residue gave pure 1-bromotridecane (55.4 g., 70%) b.p. 104-106°/0.35 mm.

n_D^{25} 1.4592. (lit.[192] b.p. 135-136°/4 mm.).

Tetrahydrofurfuryl chloride.[111]

Distilled tetrahydrofurfuryl alcohol (208 g., 0.203 mole b.p. 92-98°/15 mm.) and pyridine (181 ml.) were placed in a 3-necked flask (2 l.) fitted with a mechanical stirrer, dropping funnel and thermometer. Thionyl chloride (255.9 g., 0.215 mole) was added dropwise to the rapidly stirred and ice-cooled mixture. When about half of the thionyl chloride was added, a pasty crystalline mass began to separate, the temperature rose rapidly, and the rate of addition was controlled to keep the temperature below 60°. When the addition was complete, the mass was stirred for 4 hr. at room temperature and extracted with ether (10 times with 250 ml. portions of ether). The ether was evaporated and the residue washed 3 times with water (100 ml. portions), dried, and distilled to give tetrahydrofurfuryl chloride (148 g., 60.5%) b.p. 149-150°, n_D^{25} 1.4549 (lit.[111] 47-48°/15 mm).

Pent-4-yn-1-ol.[111]

Tetrahydrofurfuryl chloride (120.5g., 1 mole) was added over 30 min., to a suspension of sodamide made from sodium (80.5 g., 3.42 mole) in liquid ammonia (1.5 l.). Liquid ammonia was added to keep the volume constant whilst the mixture was stirred for an additional hour, after which ammonium chloride (177 g.) was added in portions that permitted control of the resulting exothermic reaction. After the ammonia evaporated, the residue was extracted thoroughly with ether (10 x 250 ml.). The combined ether extract was filtered through a Büchner funnel and the filtrate evaporated. The residue was distilled through a ½ metre Fenske column with a reflux ratio of (1:10) to give pent-4-yn-1-ol (57.8 g. 69%) b.p. 60-61°/15 mm. n_D^{25} 1.4414. (lit.[111] 70 -71°/29 mm).

Pent-4-ynoic Acid.[110]

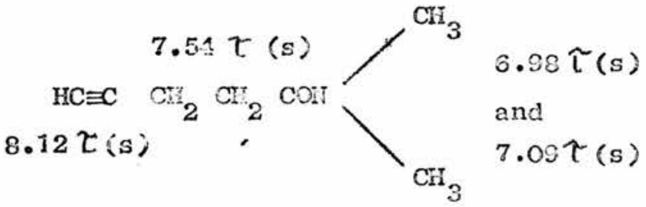
A solution of chromium trioxide (128 g., 1.9 eq.) and c. sulphuric acid (208 ml.) in water (418 ml.) was added during an hour to a cooled (below 20°) solution of pent-4-yn-1-ol (75 g., 0.89 mole) in water (520 ml.). After stirring for 16 hr., the acidic fraction (43.4 g.) was extracted with ether. Two recrystallisations from petroleum ether gave pure pent-4-ynoic acid (34 g., 39%) m.p. 57-58 °C. (Lit.[110] 57-58°).

The methyl ester (0.8 g.,) was prepared by refluxing the acid (1.0 g.) with methanol (10 ml.) and c. sulphuric acid (0.4 g.) with both Apiezon L and polyethyleneglycol succinate phase g.l.c. showed only one peak.

N,N-Dimethylpent-4-ynamide. based on 17

Pent-4-ynoic acid (20.6 g., 0.18 mole) was treated with thionylchloride (47.6 g., 0.4 mole) to give the crude acid chloride. The excess reagent was distilled off at atmospheric pressure with the bath temperature at 120°. Distillation was stopped when the vapour temperature rose to 98°. The acid chloride in ether (75 ml.) was added over 45 min., to a well stirred solution of dimethylamine (27 g., 0.6 mole) in ether (400 ml.) cooled in ice and salt. The mixture was stirred for 2 hr. and then left overnight. Next day the dimethylamide was extracted with ether and recrystallised from ethanol/water to give dimethylpent-4-ynamide (19 g., 76%).

N.M.R. of the sample was in keeping with the structure.



N,N-Dimethyloctadec-4-ynamide.

based on 17

N,N-Dimethylpentynamide (23.7 g., 0.17 mole) in tetrahydrofuran (26 ml.) was added to sodamide made from sodium (4.25 g., 0.18 mole) in liquid ammonia (600 ml.) and the mixture stirred for 3 hr., after which 1-bromotridecane (39 g., 0.148 mole) in tetrahydrofuran (50 ml.) was rapidly introduced over 5 min. The mixture was stirred for 15 hr. and during the evaporation of ammonia (6 hr.) T.L.C. showed the reaction product

(42.5 g.) to contain similar compounds to those produced from reaction of other alkyl bromides and acetylenic amides but the relative amount of octadecynamide was much less in this preparation.

Methyl Octadec-4-enoate.

The crude amide (42 g.) was refluxed with a mixture of ethanol (450 ml.) and 5N sodium hydroxide (470 ml.) for 8 hr. and the acidic product (17.8 g.) was isolated with ether.

The methyl ester showed 3 peaks examined by g.l.c. using a diethylene glycol succinate column one of them corresponding to octadec-4-ynoic ester (45%).

The crude acetylenic ester was hydrogenated in the presence of Lindlar's catalyst and distilled through a spinning band column to give a fraction (7.4 g.) b.p. 150-152°/1 mm.

T.L.C. still showed the presence of the same 3 components but pure methyl octadec-4-enoate was obtained by preparative thin layer chromatography of silica impregnated with silver nitrate (n_D^{25}, 1.4514). (Octadec-4-ynoic acid. Found: C, 76.50; H, 11.28 . $C_{18}H_{32}O_2$ requires C, 77.07; H, 11.53). m.p. of cis ethylenic acid 45.5-46.5°C(Lit.[54] 44.5-45.5°) m.p. of acetylenic acid 74.0-75.0°C (lit.[54] 75.0-76.0°).

Methyl Octadec-5-enoate

$$\mathrm{Br(CH_2)_3Cl \xrightarrow{1} HC{\equiv}C(CH_2)_3Cl \xrightarrow{2} HC{\equiv}C(CH_2)_3COOH \xrightarrow{3}}$$

$$\mathrm{HC{\equiv}C(CH_2)_3CONMe_2 \xrightarrow{4} CH_3(CH_2)_{11}\ C{\equiv}C\ (CH_2)_3CONMe_2 \xrightarrow{5}}$$

$$\mathrm{CH_3(CH_2)_{11}C{\equiv}C(CH_2)_3COOH \xrightarrow{6} CH_3(CH_2)_{11}C{\equiv}C(CH_2)_3COOMe}$$

$$\mathrm{\xrightarrow{7} CH_3(CH_2)_{11}CH\overset{cis}{=}CH(CH_2)_3COOMe}$$

1, NaC≡CH, liquid ammonia 2, NaI, NaCN; KOH; HCl

3 , $SOCl_2$; $HNMe_2$ 4, $NaNH_2$, liquid ammonia; 1-bromododecane

5, NaOH, EtOH 6 , MeOH, HCl 7, H_2, Lindlar

METHYL OCTADEC-5-ENOATE

5-Chloropent-1-yne.[193]

To a suspension of sodium acetylide prepared from sodium (36.7 g., 1.57 mole) in liquid ammonia (1200 ml.), 1,3-bromochloropropane (227 g., 1.44 mole) in dry ether (75 ml.) was added over 45 min. The flask was equipped with a dry-ice condenser which was replaced with an ordinary condenser after 2 hr. stirring. Next day, the ammonia was allowed to evaporate and the product diluted with water, acidified, and extracted with ether. The dried extract was evaporated and distilled to give the chloro-alkyne (74.8g., 50.7%), b.p. 110-112° (lit.[193] 88°/350 mm.)

Hex-5-ynoic Acid.

A mixture of 5-chloropent-1-yne (74 g., 0.72 mole), sodium iodide (125 g.) and sodium cyanide (125 g.) in ethanol (80%, 1310 ml.) was refluxed for 48 hr. Potassium hydroxide (418 g.) in water (1440 ml.) was then added and refluxing continued for a further 48 hr. Hex-5-ynoic acid (60 g., 74%) b.p. 112-116° n_D^{25} 1.4494) was isolated in the usual manner. (lit.[110] b.p. 106°/9 mm. n_D^{17} 1.4500

N,N-Dimethylhex-5-ynamide.[17]

Thionyl chloride (95.2 g., 0.8 mole) was added dropwise over an hour to stirred hex-5-ynoic acid (44.8 g., 0.4 mole). The mixture was stirred for 1 hr. and then heated under reflux for 30 min. The crude acyl chloride, freed of excess thionyl chloride under reduced pressure, and dissolved in ether (200 ml.), wss transferred into a dropping funnel and added to a stirred solution of dimethyl amine (54 g., 1.2 mole) in ether (400 ml.) maintained at 0-5°. The product was extracted with ether as usual and distilled to give N,N-dimethylhexynamide (37 g., 67%), b.p. 68-69°/0.5 mm., n_D^{25} 1.4720 (lit.[17] b.p. 75°/0.5 mm., n_D^{21} 1.4739).

1-Bromododecane.

Bromine (39g., 0.49 mole) was added dropwise to a well stirred mixture of dodecanol (80 g., 0.43 mole) and red phosphorus (3.75 g.). The mixture was stirred for 1 hr. at room temperature and refluxed for a further hour. The product was extracted with ether, dried over potassium carbonate, and distilled to give 1-bromododecane (91 g.) shown by g.l.c. to contain small amounts of C_{12} and C_{14} homologues. The mixture was redistilled through a ½ metre Fenske column and the fraction (52 g.) boiling at 134-137°/ 10 mm. collected. G.L.C. still showed an impurity (~ 2%) as a peak having a retention time similar to the C_{12} alcohol but not removed by rebromination. The bromide was purified by column chromatography using silicic acid with the solvent system, petroleum ether/ether in the ratio 10:1. Pure 1-bromododecane was isolated from the eluent and distilled through a ½ metre Fenske column b.p. 134-137°/10 mm.

n_D^{25} 1.4570 (lit.[194] b.p. 130.0°/5.7 mm. n_D^{20} 1.45807.

N,N-Dimethyl Octadec-5-ynamide.[17]

N,N-Dimethylhex-5-ynamide (36.2 g., 0.26 mole) in dry tetrahydrofuran (25 ml.) was added over 45 min. to sodamide prepared from sodium (7.2 g., 0.31 mole) and excess of liquid ammonia (500 ml.). The mixture was stirred for 3 hr. and 1-bromododecane (70.3 g., 0.28 mole) in dry tetrahydrofuran (50 ml.) was then added over 5 min. After stirring for a further 12 hr., the ammonia was allowed to evaporate. Crude C_{18} amide(58 g.) was obtained as a yellow oil.

Methyl Octadec-5-enoate Acid.

The crude dimethylamide (55 g.) was refluxed in ethanol (625 ml.) and 5N sodium hydroxide (625 ml.) for 8 hr. Water (625 ml.) was added and 600 ml. of the ethanol removed on a rotary film evaporator. The residue was extracted with ether to remove non-acidic material, then poured into ice and dilute sulphuric acid and extracted with ether. The extract was washed with water, dried and evaporated to give crude octadec-5-ynoic acid (41.5 g.). This was crystallised from ethanol and water and the first crop of crystals gave pure octadec-5-ynoic acid (21 g.) when recrystallised. (Found: C,77.01; H,11.84. $C_{18}H_{32}O_2$ requires C,77.07, H,11.53).

The acetylenic acid (18 g.) was converted to its methyl ester and hydrogenated in the presence of Lindlar's catalyst. The reduced ester was distilled through a spinning band column to give methyl octadec-5-enoate (16.2 g.) b.p. 152-153°/1 mm. n_D^{25} 1.4516. m.p. of cis ethylenic acid -12.5-13.5° (lit.[51] f.p. 13°) m.p. of acetylenic acid 51.5 - 52.5 (lit.[51] 51-52°).

Purity of Olefinic Acid.

The cis olefinic ester contained no detectable amounts of the saturated acid (g.l.c.) or the trans isomer (g.l.c. and i.r.).

Von Rudloff oxidation gave a tridecanoic acid as the only monobasic acid.

Methyl Octadec-6-enoate

$$HO(CH_2)_4OH \xrightarrow{1} Cl(CH_2)_4Cl \xrightarrow{2} I(CH_2)_4Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_4Cl \xrightarrow{4} HC{\equiv}C(CH_2)_4COOH \xrightarrow{5} HC{\equiv}C(CH_2)_4CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4CONMe_2 \xrightarrow{7} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOH$$

$$\xrightarrow{8} CH_3(CH_2)_{10}C{\equiv}C(CH_2)_4COOMe \xrightarrow{9} CH_3(CH_2)_{10}\overset{cis}{CH{=}CH}(CH_2)_4COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4 , NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$
6, $NaNH_2$, liquid ammonia; 1 bromo-undecane 7, NaOH, EtOH
8, MeOH, HCl 9, H_2, Lindlar.

METHYL OCTADEC-6-ENOATE.

1-Bromo-undecane.[116]

Bromine (25.9 g., 0.32 mole) was added dropwise over 30 min. to a mixture of undecanol (55 g., 0.32 mole) and purified red phosphorus (2.48 g.). The mixture was stirred for a further hour, then diluted with water and extracted with ether. The extract was washed with dilute sodium carbonate, water, and dried. Distillation gave bromoundecane (58 g. 77%) b.p. 134-137°/18 mm. n_D^{25} 1.4557. (lit.[194] 114°/5 mm. n_D^{25} 1.456977).

1,4-Dichlorobutane. based on 112

Thionyl chloride (357 g.) was added to 1,4-butane diol (67.6 g., 0.75 mole) and dry pyridine (14 ml.) at such a rate that the temperature rose to, but did not exceed 25°. The mixture was refluxed for 2 hr. and the product isolated as usual (c.f. dichlorohexane p. 134) to give 1,4-dichlorobutane (76 g., 80%) boiling at 72-75°/15 mm. n_D^{25} 1.4530 (lit.[195] b.p. 55-56.5°/14 mm.).

1,4-Chloro-iodobutane.

1,4-Dichlorobutane (75 g., 0.59 mole) was added to a solution of sodium iodide (84 g., 0.56 mole) in acetone (500 ml.). The efficiently stirred mixture was refluxed for 6 hr. and 1,4-chloro-iodobutane (55 g., 42.7%) b.p. 92-94°/11 mm. n_D^{25} 1.5392 (lit.[9] b.p. 93-94.5°/17 mm.) was isolated in the usual manner.

6-Chlorohex-1-yne .

1,4-Chloro-iodobutane (54 g., 0.25 mole) in dry ether (25 ml.) was added dropwise over 30 min. to sodium acetylide prepared from sodium (7.0 g., 0.3 mole) in liquid ammonia (500 ml.). The mixture was stirred for 12 hr. and the ammonia then allowed to evaporate. The product was extracted with ether to give 6-chlorohex-1-yne (26.4 g.)(lit.[13] b.p. 143-144°).

Hept-6-ynoic Acid.

The crude 6-chlorohex-1-yne (25.4 g.), sodium iodide (44.5 g.), sodium cyanide (44.5 g.) and ethanol (80%, 437 ml.) were refluxed for 48 hr. and refluxed for a further 48 hr. with potassium hydroxide (149 g.) in water (37 ml.). The acidic material was extracted as usual and distilled to give heptynoic acid (24 g., 79.1% based on chloro-iodo-butane) b.p. 70-70.5°/0.5 mm. n_D^{25} 1.4512 (lit.[110] b.p. 89-92°/0.05 mm.).

N,N-Dimethyl hept-6-ynamide.

based on 17

Thionyl chloride (35.7 g., 0.3 mole) was added dropwise over 30 min. to heptynoic acid (20 g., 0.16 mole). The mixture was stirred for 1 hr. at room temperature and then refluxed for 30 min. The crude acid chloride, was freed of thionyl chloride, dissolved in ether (150 ml.) and added dropwise to a solution of dimethylamine (21 g., 0.45 mole) in ether (450 ml.). The product was isolated as usual to give N,N-dimethylhept-6-ynamide (15.2 g., 62%) b.p. 79-80°/0.4 mm. n_D^{25} 1.4768.

N,N-Dimethyl Octadec-6-ynamide.

N,N-Dimethylhept-6-ynamide (14.6 g., 0.09 mole) in dry tetrahydrofuran (25 ml.) was added dropwise to a suspension of sodamide prepared from sodium (2.5 g., 0.11 mole) in liquid ammonia (600 ml.). Stirring was continued for 3 hr., after which 1-bromoundecane (24 g., 0.1 mole) in dry tetrahydrofuran (50 ml.) was added rapidly over 5 min. to prevent the bromide crystallising out of solution. The mixture was stirred for a further 12 hr. and the ammonia allowed to evaporate. Extraction with ether in the usual manner gave the crude amide (22 g.).

Methyl Octadec-6-ynoate.

The crude C_{18} amide (20 g.) was refluxed for 8 hr. with ethanol (225 ml.) and 5N sodium hydroxide (225 ml.) to give octadec-6-ynoic acid (12.7 g.) and crystallised from ethanol/water.

Methyl Octadec-6-enoate.

The acetylenic acid (9.5 g.) was converted to its methyl ester and partially reduced in the presence of Lindlar's catalyst. Distillation through a spinning band column gave methyl octadec-6-enoate. (6.9 g.) b.p. 143-144°/ 1 mm. n_D^{25} 1.4516. (Found: C,76.69; H,12.06. $C_{19}H_{35}O_2$ requires C,76.95; H,12.06.). m.p. of cis ethylenic acid

28.0-29.0° (lit.[16] m.p. 29-29.5° m.p. of acetylenic acid 50.0-51.0° (lit.[16] m.p. 50-51°).

Purity of olefinic acid.

The cis olefinic ester contained no detectable amounts of saturated acid (g.l.c.) or trans isomer (g.l.c. and i.r.).

Von Rudloff oxidation gave only lauric and adipic acids as shown both on polar and non-polar phases.

Methyl Octadec-7-enoate

$$HO(CH_2)_5OH \xrightarrow{1} Cl(CH_2)_5Cl \xrightarrow{2} I(CH_2)_5Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_5Cl \xrightarrow{4} HC{\equiv}C(CH_2)_5COOH \xrightarrow{5} HC{\equiv}C(CH_2)_5CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_9C{\equiv}C(CH_2)_5CONMe_2 \xrightarrow{7} CH_3(CH_2)_9C{\equiv}C(CH_2)_5COOH$$

$$\xrightarrow{8} CH_3(CH_2)_9C{\equiv}C(CH_2)_5COOMe \xrightarrow{9} CH_3(CH_2)_9CH\overset{cis}{=}CH(CH_2)_5COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4, NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$ 6, $NaNH_2$, liquid ammonia; 1-bromodecane 7, NaOH, EtOH 8, MeOH, HCl 9, H_2, Lindlar

METHYL OCTADEC-7-ENOATE.

1,5-Dichloropentane.

1,5-Dichloropentane was prepared from the diol (152 g., 1.46 mole), pyridine (21 ml.) and thionyl chloride (403 g.) as described for 1,6-dichlorohexane. The dihalide (160 g., 78%) has a boiling point of 68-70°/10 mm. and n_D^{25} 1.4554. (lit.[196] b.p. 76-78°/21 mm.).

1,5-Chloro-iodopentane.

1,5-Dichloropentane (155 g., 1.1 mole) was added to sodium iodide (164 g., 1.1 mole) in dry acetone (850 ml.) and the efficiently stirred mixture heated under reflux for 5 hr. The product was isolated as usual (c.f. chloro-iodohexane p. 134). Distillation gave 1,5-chloro-iodopentane (116.5 g., 45.6%) b.p. 94-98°/8 mm. n_D^{25} 1.5272 (lit.[15] b.p. 125-127°/36 mm. n_D^{25} 1.5297).

7-Chlorohept-1-yne.[61]

1,5-Chloro-iodopentane (116 g., 0.5 mole) in ether (50 ml.) was added over 45 min. to sodium acetylide made from sodium (14 g., 0.6 mole) in liquid ammonia (750 ml.). After stirring the mixture for 10 hr., the chloro-alkyne was isolated with ether. Distillation gave 7-chlorohept-1-yne (53.8 g., 82.5%) b.p. 78-79°/28 mm. n_D^{25} 1.4530 (lit.[13] 166°, n_D^{25} 1.4501).

Oct-7-ynoic Acid.[61]

7-Chlorohept-1-yne (53 g., 0.41 mole) was refluxed with a mixture of sodium iodide (70 g.), sodium cyanide (70 g.) and ethanol (80%, 700 ml.) for 48 hr., and for a further 48 hr. after potassium hydroxide (230 g.) in water (680 ml.) was added. Distillation of the recovered acidic product gave oct-7-ynoic acid (48 g., 83.6%) b.p. 81-84°/ 0.5 mm., n_D^{25} 1.4510 (lit.[13] 123°/2 mm. n_D^{25} 1.4502).

based on 17

N,N-Dimethyloct-7-ynamide.

Thionyl chloride (71 g., 0.6 mole) was added over an hour to oct-7-ynoic acid (42 g., 0.3 mole) and the mixture after stirring for a further hour was heated under reflux for 30 min. The excess of thionyl chloride was removed under reduced pressure, and the crude acid chloride in ether (300 ml.) was added to dimethylamine (41.4 g., 0.92 mole) in ether (300 ml.). After stirring for 8 hr., the crude amide was recovered with ether. Distillation gave the C_8 amide (35 g., 70%) b.p. 82-84°/0.4 mm. n_D^{25} 1.4710.

1-Bromodecane.[116]

Bromine (50 g., 0.63 mole) was added over 30 min. to a mixture of n-decanol (80 g., 0.51 mole) and purified red phosphorus (4.75 g.). Crude bromodecane (80.4 g., 71%) was recovered in the usual manner. Both C_{12} and C_{14} bromides were present as minor impurities (~ 6%). Pure 1-bromodecane (57 g.) was obtained by careful fractionation through a ½ metre Fenske column. b.p.

116-117°/11 mm., n_D^{25} 1.4547 (lit.[194] b.p. 102.5°/5.9 mm., n_D^{20} 1.45527).

N,N-Dimethyloctadec-7-ynamide. based on 17

N,N-Dimethyloct-7-ynamide (33 g., 0.19 mole) in dry tetrahydrofuran (25 ml.) was added over 30 min. to sodamide prepared from sodium (5.8 g., 0.25 mole) in liquid ammonia (600 ml.). After stirring for 4 hr. 1-bromodecane (55 g., 0.25 mole) in dry tetrahydrofuran (25 ml.) was added over 30 min. Stirring was continued for 10 hr., after which the ammonia was allowed to evaporate. Isolation of the reaction product gave the crude dimethylamide (45 g.).

Methyl Octadec-7-ynoate.

The C_{18} amide (44 g.) was refluxed with ethanol (575 ml.) and 5N sodium hydroxide (575 ml.) for 8 hr. The resulting acidic material was isolated and distilled as its methyl ester to give methyl octadec-7-ynoate (20.5 g.) b.p. 148-151°/0.6 mm.

Methyl Octadec-7-enoate.

The acetylenic ester (19 g.) was hydrogenated in the presence of Lindlar's catalyst and distilled through a spinning band column to give methyl octadec-7-enoate (15.2 g.) b.p. 158-159°/1 mm. n_D^{25} 1.4513. Found: C,76.81; H,12.08. $C_{19}H_{35}O_2$ C,76.95; H,12.23 . M.p. of cis ethylenic acid 12.0-13.0° (lit.[15] b.p. 11.8 - 12.5°) m.p. of acetylenic acid 48.0-49.0 (lit,[15] m.p. 48.5-49.5°).

Purity of olefinic acid.

The cis olefinic ester contained no detectable amount of saturated acid (g.l.c.) or the trans isomer (g.l.c. and i.r.).

Von Rudloff oxidation gave only undecanoic acid and pimelic acid.

Methyl Octadec-8-enoate

$$HO(CH_2)_6OH \xrightarrow{1} Cl(CH_2)_6Cl \xrightarrow{2} I(CH_2)_6Cl \xrightarrow{3}$$

$$HC\equiv C(CH_2)_6Cl \xrightarrow{4} HC\equiv C(CH_2)_6COOH \xrightarrow{5} HC\equiv C(CH_2)_6CONMe_2$$

$$\xrightarrow{6} CH_3(CH_2)_8C\equiv C(CH_2)_6CONMe_2 \xrightarrow{7} CH_3(CH_2)_8C\equiv C(CH_2)_6COOH$$

$$\xrightarrow{8} CH_3(CH_2)_8C\equiv C(CH_2)_6COOMe \xrightarrow{9} CH_3(CH_2)_8\overset{cis}{CH=CH}(CH_2)_6COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, $NaC\equiv CH$,
liquid ammonia 4, NaI, NaCN; KOH; HCl 5, $SOCl_2$; $HNMe_2$
6, $NaNH_2$, liquid ammonia; 1-bromononane 7, NaOH, EtOH
8, MeOH, HCl 9, H_2, Lindlar.

METHYL OCTADEC-8-ENOATE.

1,6-Dichlorohexane.[112]

1,6-Hexanediol (150 g., 1.27 mole) and dry pyridine (17.7 ml.) were melted together and thionyl chloride (30.7 g.) added to lower the melting point. To the cooled, stirred mixture, thionyl chloride (355 g.) was added dropwise at such a rate to maintain the reaction temperature at 25°. After the addition, the mixture was heated under reflux for 2 hr. and poured carefully into ice and water. The precipitated oil was recovered with petroleum ether, and the extract washed with c. sulphuric acid, aqueous sodium bicarbonate, water, and then dried. Evaporation of the solvent and distillation gave the product 1,6-dichlorohexane (175 g., 89%) b.p. 86°/15 mm., n_D^{25} 1.4562 (lit.[112] b.p. 99°/28 mm. n_D^{25} 1.4576).

1,6-Chloro-iodohexane.[112]

1,6-Dichlorohexane (225 g., 1.45 mole) was added to a solution of sodium iodide (225 g., 1.5 mole) and dry acetone (1525 ml.) and the vigorously stirred mixture heated under reflux for 4 hr., poured into water 1.5 l., and extracted with petroleum ether. The extract was washed with water, dried, and evaporated. Distillation through a ½ metre Fenske column gave a middle fraction b.p. 76-78°/0.7 mm. which was redistilled to give 1,6-chloro-iodohexane (164.2 g., 46%) b.p. 76-78°/0.7 mm.

n_D^{25} 1.5212 (lit.[112] 73-74°/0.7 mm. n_D^{24} 1.5248.

The redistilled material was shown by g.l.c. to be 98.5% pure.

8-Chloro-oct-1-yne.

1,6-Chloro-iodohexane (9.42 g., 0.38 mole) was dissolved in dry ether (75 ml.) and added dropwise over 45 min. to a suspension of sodium acetylide prepared from sodium (10.2 g., 0.44 mole) and liquid ammonia (600 ml.) The mixture was stirred overnight and the product isolated in the usual manner. Distillation gave 8-chloro-oct-1-yne (48 g., 87.4%), b.p. 34°/0.2 mm., n_D^{25} 1.4525 (lit.[112] 73-74°/10 mm., n_D^{25} 1.4590).

Non-8-ynoic acid.

8-Chloro-oct-1-yne(46 g., 0.32 mole) was refluxed with sodium iodide (42 g.), and sodium cyanide (42 g.) in ethanol (80%, 410 ml.). After 48 hr., potassium hydroxide (138 g.) in water (310 ml.) was added, and the mixture refluxed for a further 48 hr. Recovery of the acidic material and distillation gave non-8-ynoic acid (43.8 g., 88.9%) b.p. 96-97°/0.8 mm. n_D^{25} 1,4545 (lit.[14] b.p. 128°/4 mm.

N,N-Dimethylnon-8-ynamide. based on 17

Thionyl chloride (66.6 g., 0.56 mole) was added over an hour to non-8-ynoic acid (43 g., 0.28 mole) which was well stirred.. The mixture was allowed to stand for another hour at room temperature, and refluxed for 30 min. The excess thionyl chloride was removed under reduced pressure, and the crude acid chloride in ether (300 ml.) was added to a solution of dimethylamine (37.8 g., 0.84 mole) in dry ether (300 ml.); the reaction temperature was maintained between 0-5° during the addition. After stirring for a further 8 hr., the crude amide was isolated with ether. Distillation gave N,N-dimethylnon-8-ynamide (44.1 g., 87%) b.p. 100-102°/0.7 mm., n_D^{25} 1.4708.

1-Bromononane.

1-Bromononane obtained from Koch Light was distilled through a ½ metre Fenske column to give a product shown to be pure by g.l.c. b.p. 98°/11 mm., n_D^{25} 1.4536 (lit.[194] 219.5°/745 mm., n_D^{20} 1.45417.

based on 17

N,N-Dimethyloctadec-8-ynamide.

N,N-Dimethylnonynamide (40 g., 0.22 mole) in dry tetrahydrofuran (50 ml.) was added dropwise to a suspension of sodamide made from sodium (6.32 g., 0.27 mole) and liquid ammonia (600 ml.). After stirring for 3 hr., nonyl bromide (56.9 g., 0.27 mole) in dry tetrahydrofuran was added over 30 min., and the stirring was continued for 10 hr. After the ammonia had evaporated, the product was isolated in the usual manner with ether, to give crude N,N-dimethyl octadec-8-ynamide (54 g.) as a yellow oil.

Methyl Octadec-8-ynoate.

The crude amide (48 g.) was added to a solution of ethanol (600 ml.) and 5N sodium hydroxide (600 ml.) and the mixture heated under reflux for 8 hr. Isolation of the acidic material and distillation of its methyl ester gave methyl octadec-8-ynoate (24.6 g.) b.p. 142-144°/ 0.4 mm. (The acid - Found: C, 76.86 ; H, 11.20 $C_{18}H_3O_2$ requires C, 77.07; H, 11.53).

Methyl Octadec-8-enoate.

Methyl octadec-8-ynoate (17.5 g.) was reduced with Lindlar's catalyst and distilled through a spinning band column to give methyl octadec-8-enoate (14.2 g.) b.p. 165-166°/1 mm. n_D^{25} 1.4515. m.p. of cis ethylenic acid 23.0-24.0° (lit.[15] 22.7 - 23.8°) m.p. of acetylenic acid 47-47.5 corr. (lit.[15] 46.5 - 47.5°).

Purity of olefinic acid.

The cis olefinic ester contained no detectable amounts of saturated acid (g.l.c.) or trans isomer (g.l.c. and i.r.) Von Rudloff oxidation gave only decanoic and suberic acids.

Methyl Octadec-9-enoate

$$HO(CH_2)_6OH \xrightarrow{1} Cl(CH_2)_6Cl \xrightarrow{2} I(CH_2)_6Cl \xrightarrow{3}$$

$$HC{\equiv}C(CH_2)_6Cl \xrightarrow{4} HC{\equiv}C(CH_2)_6CH(COOEt)_2 \xrightarrow{5}$$

$$HC{\equiv}C(CH_2)_6CH_2COOH \xrightarrow{6} HC{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{7}$$

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{8} CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH$$

$$\xrightarrow{9} CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOMe \xrightarrow{10} CH_3(CH_2)_7CH\overset{cis}{=}CH(CH_2)_7COOMe$$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, $NaC{\equiv}CH$, liquid ammonia 4, NaI, $HC(Na)(COOEt)_2$, EtOH 5, NaOH; HCl; 160°, 6, $SOCl_2$; $HNMe_2$ 7, $NaNH_2$, liquid ammonia; 1-bromo-octane 8, NaOH, EtOH- HCl 9, MeOH, HCl 10, H_2, Lindlar.

METHYL OCTADEC-9-ENOATE

Ethyl Oct-7-ynylmalonate.

Freshly cut sodium (9.2. g., 0.39 mole) was added in small amounts to absolute alcohol (250 ml.) contained in a flask (1 l.) fitted with a stirrer and reflux condenser. After the sodium dissolved, freshly distilled diethyl malonate (70.4 g., 0.44 mole) was added gradually and the mixture then refluxed for 1 hr. The reaction mixture was cooled to room temperature, sodium iodide (65.5 g., 0.44 mole) and 8-chloro-oct-1-yne(57.8 g., 0.40 mole) added, and the whole mixture refluxed for 24 hr. Water (250 ml.) was then added and the volume reduced to half on a rotary film evaporator. The solution was acidified with cold dilute hydrochloric acid and extracted with ether which was subsequently washed with water, dried, and evaporated. Distillation yielded ethyl oct-7-ynylmalonate (78 g., 73%) b.p. 180-184°/0.5 mm. n_D^{25} 1.4465.

Oct-7-ynylmalonic Acid.

The ester (75 g., 0.28 mole) was refluxed with potassium hydroxide (62.7 g., 1.12 mole) in ethanol (80%; 600 ml.) for 2 hr. Water (600 ml.) was added and the volume reduced to half on a rotary film evaporator. Neutral material was extracted with ether and the remaining aqueous layer, acidified, and extracted with ether to give the malonic acid (56.3 g., 95%).

Dec-9-ynoic acid.

The malonic acid (55 g., 0.26 mole) was heated to 180-190° under an atmosphere of nitrogen for 8 hr., until the evolution of carbon dioxide ceased. The product was diluted with ether, dried and distilled to give dec-9-ynoic acid (40.2 g., 92%) b.p. 110-114°/0.6 mm. (lit.[99] b.p. 88°/0.1 mm.).

N,N-Dimethyldec-9-ynamide. based on 17

Dec-9-ynoic acid (38 g., 0.227 mole) was treated with thionyl chloride (33.5 g., 0.28 mole) to give the crude acid chloride after the excess thionyl chloride was removed under reduced pressure. Acid chloride dissolved in dry ether (100 ml.) was then added dropwise to dimethylamine (31 g., 0.68 mole) in dry ether (500 ml.) maintained at 0-5°. After stirring for 6 hr. longer, the reaction product was isolated in the usual manner. Distillation gave N,N-dimethyl dec-9-cyamide (38.3 g., 86%) b.p. 95-100°/0.1 mm. n_D^{25} 1.4740.

1-Bromo-octane.[116]

Technical octanol distilled through a ½ metre Fenske column gave n-octanol shown to be pure by g.l.c.

Dry bromine (56 g., 0.7 mole) was added over an hour to a stirred mixture of octanol (82 g., 0.63 mole) and red phosphorus (5 g.). After stirring for another hour, the product was extracted with ether and distilled to obtain 1-bromo-octane (94.3 g., 78%) b.p. 199.5°/765 mm.

n_D^{25} 1.4516. (lit.[194] 200°/768 mm. n_D^{20} 1.45267).

based on 17

N,N-Dimethyloctadec-9-ynamide.

N,N-Dimethyldec-9-ynamide (29.25 g., 0.15 mole) in dry tetrahydrofuran (25 ml.) was added to a suspension of sodamide prepared from sodium (4.6 g., 0.2 mole) and liquid ammonia (500 ml.). When the mixture had been stirred for 3 hr., 1-bromo-octane (38.6 g., 0.2 mole) in tetrahydrofuran (25 ml.) was added dropwise over 30 min. Crude N,N-dimethyloctadec-9-ynamide(35.7 g.) was isolated as before.

Methyl Octadec-9-enoate.

The crude amide (35 g.) was heated under reflux with ethanol(350 ml.) and 5N sodium hydroxide (350 ml.) for 8 hr. The acidic product (22 g.) was isolated and converted to the methyl ester (22 g.). This acetylenic ester was partially reduced with hydrogen in the presence of Lindlar's catalyst to give methyl octadec-9-enoate (8.2 g.) b.p. 145-147°/1 mm. n_D^{25} 1.4515. (Found: C,76.80; H,12.05. $C_{19}H_{35}O_2$ requires C,76.95; H,12.26). purified by distillation through a spinning band column. m.p. of cis ethylenic acid 10.0-11.0° (lit.[15] m.p. 10.9 - 11.5°) m.p. of acetylenic acid 45.5-46.5° (lit.[15] m.p. 46.4 - 47.6).

Purity of olefinic acid.

The cis olefinic ester contained no detectable amounts of saturated acid (g.l.c.) or trans isomer (g.l.c. and i.r.) Von Rudloff oxidation gave only nonanoic and azelaic acids.

Methyl Octadec-10-enoate

$$HOOC(CH_2)_8COOH \xrightarrow{1} HOOC(CH_2)_8COOMe \xrightarrow{2} Br(CH_2)_8COOMe$$

$$\xrightarrow{3} Br(CH_2)_8COOH \xrightarrow{4} Br(CH_2)_8CONMe_2 \xrightarrow{5} I(CH_2)_8CONMe_2$$

$$\xrightarrow{\quad 6 \quad} CH_3(CH_2)\ C{\equiv}C.(CH_2)_8CONMe_2 \xrightarrow{7} CH_3(CH_2)_6C{\equiv}C(CH_2)_8COOH$$

$$\xrightarrow{8} CH_3(CH_2)_6C{\equiv}C(CH_2)_8COOMe \xrightarrow{9} CH_3(CH_2)_6\overset{cis}{CH{=}CH}(CH_2)_8COOMe$$

1, diethyl sebacate, EtOH 2 , KOH; $AgNO_3$; Br_2,CCl_4

3, 0.5N NaOH 4, $SOCl_2$; $HNMe_2$ 5, NaI, acetone

6, $NaNH_2$, liquid ammonia; nonyne 7, NaOH,EtOH; HCl

8, MeOH, HCl 9, H_2, Lindlar

METHYL OCTADEC-10-ENOATE

1-Bromoheptane.[116]

Bromine (88 g., 1.1 mole) was added over 1 hr. to a stirred mixture of heptanol (116 g., 1 mole) and red phosphorus (8.2 g.). Distillation of the isolated product gave 1-bromoheptane (138 g., 77%) b.p. 178-179°/753 mm. n_D^{25} 1.4497. (lit.[194] 177.5°/758 mm. n_D^{20} 1.45052).

Non-1-yne.

1-Bromoheptane (125 g., 0.7 mole) was added to a suspension of sodium acetylide made from sodium (20.6 g., 0.875 mole), in liquid ammonia (700 ml.) and the mixture stirred for 10 hr. Distillation of the product gave non-1-yne (78.8 g., 91%) b.p. 148-150°, n_D^{25} 1.4214. (lit.[197] 148-150° n_D^{20} 1.4250).

Ethyl Hydrogen Sebacate.

A mixture of ethyl sebacate (132 g., 0.51 mole), sebacic acid (178.5 g., 0.88 mole), c. hydrochloric acid (sp. gr. 1.19, 22.5 g.) and dibutyl ether (44 ml.) was heated under reflux at 160-170° for 30 min., in a 1 l. flask fitted with a long condenser. The mixture became completely homogeneous and the temperature of the bath was lowered to 120-130°; dry ethanol (53 ml.) was added and refluxing continued for 2 hr. A further volume of ethanol (17 ml.) was introduced and the mixture refluxed for another 2 hr. The temperature of the bath was reduced to 75° and the water removed azeotropically with toluene using a water separator. The residue was distilled through a ½ metre Fenske column. The first fraction of diethyl sebacate was followed by pure ethyl hydrogen sebacate (105.2 g., 89%) b.p. 162-164°/0.6 mm. m.p. 36.3 - 37°(corr.) (lit.[198] b.p. 183-187°/6 mm. m.p. 34-36°).

Ethyl Silver Sebacate.

Ethyl hydrogen sebacate (203 g., 0.88 mole) was well stirred with a solution of potassium hydroxide (54.2 g., 0.96 mole) in water (1800 ml.). Silver nitrate (164.5 g., 0.97 mole) in water (900 ml.) was rapidly added over 15 min. and the whole stirred for a further 2 hr. The precipitated silver salt was filtered on a Büchner funnel, washed with methanol and dried in an oven at 70° for 6 hr. The mass was finely divided in a mechanical crusher and dried in a vacuum oven at 80° for 72 hr. to give the silver salt (279 g., 94%) melting at 208-213°(corr.) with decomposition.

Ethyl-9-Bromononanoate.

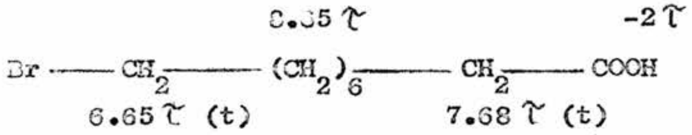
Bromine (128g., 1.6 mole) was added dropwise, over an hour to a well stirred mixture of the silver salt (269 g., 0.8 mole) in dry carbon tetrachloride (400 ml.). After the addition was complete, the mixture was stirred for a further hour. The bromo-ester was extracted from the precipitated silver bromide with more carbon tetrachloride. Careful fractionation through a ½ metre Fenske column gave a forerun

(38 g.) containing 6% of the lower homologues and pure methyl-9-bromononanoate (68 g.) b.p. 164-168°/11 mm., n_D^{25} 1.459 (lit.[199] b.p. 180°/30 mm., n_D^{20} 1.4610.

9-Bromononanoic Acid.

The bromo-ester (1.6 g.) was added to 0.5 N-sodium hydroxide in ethanol (60%, 25 ml.) and the mixture left at 0° for 10 hr. On isolating the product, 9-bromononanoic acid (1.35 g., 92.8%) m.p. 36-36.5° (from dilute acetic) (lit.[115] m.p. 36°) was obtained.

T.L.C. showed absence of hydroxy acid and n.m.r. was in keeping with the structure.



$$\mathrm{Br} - \underset{6.65\,\tau\ (t)}{\mathrm{CH_2}} - \overset{8.35\,\tau}{(\mathrm{CH_2})_6} - \underset{7.68\,\tau\ (t)}{\mathrm{CH_2}} - \overset{-2\,\tau}{\mathrm{COOH}}$$

9-Hydroxynonanoic acid (with bromononanoic acid.

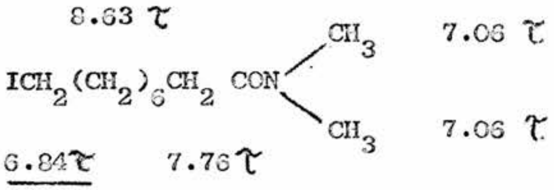
The bromo-ester (67 g., 0.25 mole) was added to a solution of potassium hydroxide (14.3 g.) in ethanol (60% 450 ml.) and the mixture left at 0° over 10 hr. The product (43.8 g.) m.p. 43-46° was a mixture of bromo and hydroxy- acids. Since both could be used to prepare the iodo-amide, no attempt was made to separate the components.

9-Bromo(chloro-N,N-dimethylnonanamide.

The bromo(hydroxy) acid(35 g.) was treated with thionyl chloride (52.8 g.) to give the acid chloride, after the excess reagent was removed under reduced pressure. The acid chloride was transfered to a 1 l. 3-necked flask and diluted with dry ether (500 ml.). This solution was cooled to 0° and dimethylamine (27 g., 0.6 mole) in dry ether (200 ml.) added dropwise. After 2 hr. further stirring, the mixture was allowed to remain overnight. Extraction and distillation gave a neutral substance (36.5 g.) b.p. 100-105°/0.4 mm.

N,N-Dimethyl-9-iodononanamide.

The bromo(chloro) amide (34 g.) was dissolved in a solution of sodium iodide (35.4 g., 0.24 mole) in dry acetone (265 ml.), and refluxed with stirring for 6 hr. After evaporating most of the acetone, diluting with water, iodo-amide (40 g.,) was extracted with ether.



$ICH_2(CH_2)_6CH_2CON(CH_3)_2$

based on 17

N,N-Dimethyl Octadec-10-ynamide.

Nonyne (17.8 g., 0.143 mole) in tetrahydrofuran (25 ml.) was added over 30 min. to sodamide prepared from sodium (3.5 g., 0.15 mole) in liquid ammonia 600 ml., and the mixture stirred for 4 hr. N,N-Dimethyl-9-iodononamide (35 g., 1.13 mole) in tetrahydrofuran (50 ml.) was rapidly added over 5 min., and stirring continued for 10 hr., after which the ammonia was allowed to evaporate. Crude octadec-10-ynamide (34.8 g.) was isolated with ether. (The acid-

Methyl Octadec-10-enoate.

The crude C_{18} amide (33 g.) was refluxed with ethanol (330 ml.) and 5N potassium hydroxide (330 ml.) for 8 hr. The acidic product (22 g.) was isolated and most (19 g.) of this was converted to its methyl ester (18.4 g.). The crude ester (18.2g.) was hydrogenated in the presence of Lindlar's catalyst and the product distilled through a spinning band column to give methyl octadec-10-enoate (12.4 g.) b.p. 167-168°/1 mm. n_D^{25} 1.4519 m.p. of cis ethylenic acid 22.5-23.5° (lit.[15] m.p. 22.2 - 22.8°) m.p. of acetylenic acid 45.5-46.5°)(lit.[15] m.p. 45.5 - 46.5°).

Purity of olefinic acid.

The cis olefinic ester contained no detectable amounts of saturated acid (g.l.c.) and the trans isomer (g.l.c. and i.r.) Von Rudloff oxidation gave only C_{10} dibasic acid.

Methyl Octadec-11-enoate

$$CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} Br(CH_2)_{10}COOH \xrightarrow{2} Br(CH_2)_9COOH$$

$$\xrightarrow{3} Br(CH_2)_9CONMe_2 \xrightarrow{4} CH_3(CH_2)_5C{\equiv}C(CH_2)_9CONMe_2 \xrightarrow{5}$$

$$CH_3(CH_2)_5C{\equiv}C(CH_2)_9COOH \xrightarrow{6} CH_3(CH_2)_5C{\equiv}C(CH_2)_9COOMe$$

$$\xrightarrow{7} CH_3(CH_2)_5\overset{cis}{CH{=}CH}(CH_2)_9COOMe$$

1, HBr, petroleum ether, O_2 2 , Barbier-Wieland R^n
3 , $SOCl_2$; $HNMe_2$ 4 , $NaNH_2$, liquid ammonia; octyne
5, NaOH, EtOH; HCl   6, MeOH,HCl   7, H_2, Lindlar

METHYL OCTADEC-11-ENOATE

11-Bromo-undecanoic Acid.[113]

Hydrogen bromide (prepared from tetrahydronaphthalene and bromine) was rapidly passed into a solution of commercial undec-10-enoic acid (62.3 g., 0.34 mole) in purified petroleum ether (60-80°, 400 ml.) maintained at 0° in a 1 l. conical flask. After an hour a solid appeared and the flask was shaken frequently for another hour while the gas was passed in. The solid was filtered off, after cooling the reaction mixture to -12°, and dried in a vacuum desiccator over P_2O_5. Two crystallisations of the crude product (22g.) gave pure 11-bromo-undecanoic acid (48 g., 53%) m.p. 47-48° (Lit.[113] m.p. 45-48°).

N.m.r. of the recrystallised sample showed no methyl peak indicating the absence of 10-bromo-undecanoic acid. G.L.C. of the methyl ester on both polar and non-polar phases showed only one component.

Ethyl 11-Bromo-undecanoate.

11-Bromo-undecanoic acid (68 g.) was mixed with a solution of ethyl alcohol (300 ml.) and c. sulphuric acid (22 ml.) and the solution heated under reflux for 6 hr. The product was diluted with water (600 ml.) and after reducing its volume by a half, extracted with ether. The extract was freed of any unreacted acid and distilled to give ethyl 11-bromo-undecanoate (66.3 g., 89%) b.p, 122-124°/0.5 mm. n_D^{25} 1.4612

1,1-Diphenyl-11-bromo-undec-1-ene.[114]

A solution of bromo-ester (87.6 g., 0.3 mole) in dry ether (390 ml.) was added dropwise over an hour to an ethereal solution (390 ml.) of phenylmagnesium bromide made from bromobenzene (104.2 g., 0.6 mole) and magnesium (14.4 g., 0.6 mole). The solution was refluxed for 4 hr. and then poured into a mixture of dilute sulphuric acid (10%; 600 ml.) and ice (∼150 g.). The ether layer was separated and together with ether extracts of the remaining aqueous layer, washed with water, dried, and evaporated, to give an alcohol. The latter was heated directly to 220° for 30 min. and distilled to give 1,1-diphenyl-11-bromo-undec-1-ene (88.8 g., 77%) b.p. 167-177°/0.2 mm. n_D^{25} 1.5568 (lit.[114] b.p. 190°/0.5 mm., n_D^{25} 1.557).

10-Bromodecanoic Acid.

A solution of chromium trioxide (68 g.) in water (80 ml.) was added over 2½ hr. to a well stirred warm (55-60°) solution of 11-bromo-1,1-diphenylundec-1-ene (132 g.) in acetic acid (1000 ml.). After the mixture had been stirred overnight at 20°, most of the solvent was evaporated under reduced pressure and the residue warmed with 2N sulphuric acid (800 ml.) on a boiling water bath for an hour. A saturated aqueous solution of sodium chloride (2400 ml.) was added to the cooled mixture which was then extracted with ether. Isolation and distillation of the acidic product yielded 10-bromodecanoic acid (48.5 g., 56%) b.p. 138-142°/0.5 mm. (lit.[114] m.p. 35-38°).

N,N-Dimethyl-10-bromodecanamide.

Thionyl chloride (25.6 g., 0.22 mole) was added to the bromo-acid (43 g., 0.172 mole) over an hour. After another hour, the mixture was refluxed for 30 min. and the excess thionyl chloride removed under reduced pressure. The crude acid chloride was diluted with dry ether (400 ml.) and dimethylamine (0.38 mole) in dry ether (150 ml.) was added over 90 min. The product was extracted with ether to give N,N-10-bromo-dimethyldecanamide (40.3 g., 85%) b.p. 125-132°/0.4 mm.

1-Bromohexane.[116]

Bromine (70.5 g., 0.88 mole) was introduced dropwise over 1 hr. to hexanol (81.6 g., 0.8 mole) and red phosphorus (5.7 g.). The mixture was stirred for another hour and extracted with ether. 1-Bromohexane (103.5 g., 78.4%) b.p. 156° n_D^{25} 1.4478 (lit.[194] 153°/751 mm. n_D^{20} 1.4476) was recovered in the usual manner.

Oct-1-yne.

1-Bromohexane (98 g., 0.6 mole) in dry ether (25 ml.) was added to sodium acetylide prepared from sodium (17.3 g., 0.74 mole) and liquid ammonia (600 ml.). The

The acidified reaction product was extracted with ether, dried and distilled to give oct-1-yne (52.8 g., 80%), b.p. 123-126°, n_D^{25} 1.4179 (lit.^{200} 126.3°/760 mm., n_D^{20} 1.4159).

N,N-Dimethyloctadec-11-ynamide. based on 17

Octyne (15.4 g., 0.14 mole) in tetrahydrofuran (25 ml.) was added to sodamide prepared from sodium (3.5 g., 0.15 mole) and liquid ammonia (750 ml.). The mixture was stirred for 3 hr. and the bromo- amide(38 g., 0.137 mole) in tetrahydrofuran (50 ml.) added rapidly over 5 min. Stirring was continued overnight and extraction with ether gave the crude C_{18} amide (34.8 g.).

Methyl Octadec-11-enoate.

The amide (30 g.) in ethanol (310 ml.) and 5N-sodium hydroxide (310 ml.) was refluxed for 8 hr. The mixture was acidified and extracted with ether to give crude octadec-11-ynoic acid (24 g.), which was converted with methanolic hydrogen chloride (1.5%) to its ester. The crude acetylenic ester (22 g.) was hydrogenated in the presence of Lindlar's catalyst and distilled through a spinning band column to give methyl octadec-11-enoate (14.8 g.). b.p. 154°/1 mm., n_D^{25} 1.4517.

m.p. of cis acid 12.5-13.5° (lit.^{15} 13.0-14.0°)

m.p. of acetylenic acid 46.5-47.5°, (lit.^{15} 46.0-47.3)

Purity of Olefinic Acid.

The cis olefinic ester contained no detectable amounts of saturated or trans acid.

Von Rudloff oxidation gave the C_{11} dibasic acid with no C_{10} or C_9 homologues.

Methyl Octadec-12-enoate

$$\mathrm{CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} Br(CH_2)_{10}COOH \xrightarrow{2} Br(CH_2)_{10}CONMe_2}$$

$$\mathrm{\xrightarrow{3} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}CONMe_2 \xrightarrow{4} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}COOH}$$

$$\mathrm{\xrightarrow{5} CH_3(CH_2)_4C{\equiv}C(CH_2)_{10}COOMe \xrightarrow{6} CH_3(CH_2)_4\overset{cis}{CH{=}CH}(CH_2)_{10}COOMe}$$

1, HBr, petroleum ether, O_2 2, $SOCl_2$; $HNMe_2$

3, $NaNH_2$, liquid ammonia; Heptyne 4, NaOH, EtOH; HCl

5, MeOH, HCl 6, H_2, Lindlar

METHYL OCTADEC-12-ENOATE

1-Bromopentane.

n-Pentanol was obtained free from 4-methyl butan-1-ol by distilling commercial amyl alcohol through a $\frac{1}{2}$ metre Fenske column. b.p. 138°.

Bromine (88 g., 1.1 mole) was added over an hour to a mixture of n-pentanol (96 g., 1.1 mole) and red phosphorus (8.0 g.). The mixture was stirred for another hour, diluted with water (250 ml.) and extracted with ether. The extract was washed with dilute sodium carbonate, water, then dried and evaporated. Distillation gave 1-bromopentane (103 g., 63%) b.p. 129°, n_D^{25} 1.4440 (lit.[194] 128.5°/762 mm., n_D^{20} 1.44460).

Hept-1-yne.

1-Bromopentane (100 g., 0.66 mole) in dry ether (25 ml.) was added dropwise over 45 min. to a suspension of sodium acetylide prepared from sodium (22 g., 0.94 mole) and liquid ammonia (750 ml.). The mixture was stirred for 6 hr., and the ammonia then allowed to evaporate. The product was diluted with water, acidified, and extracted with ether. The extract was washed twice with water, dried, and distilled through a $\frac{1}{2}$ metre Fenske column to give first, ether, then a mixture of heptyne and ether, and finally heptyne (54.7 g., 85.5%), b.p. 99-100°, n_D^{25} 1.4084 (lit.[200] 99.8°/760 mm. n_D^{20} 1.4048.

N,N-Dimethyl 11-Bromo-undecanamide.

11-Bromo-undecanoic acid (35 g., 0.132 mole) was treated with thionyl chloride (19.6 g., 0.165 mole) to give the crude acid chloride. This was freed from excess reagent by heating to 50° under reduced pressure and dissolved in dry ether (300 ml.). The solution was cooled to 0-5° and dimethylamine (17.5 g., 0.39 mole) in dry ether (100 ml.) added over 45 min. The crude bromo-amide was isolated with methylene chloride and recrystallised from ethanol/water to give N,N-dimethyl-11-bromo-undecanamide (35.4 g., 92%) based on 17

N,N-Dimethyloctadec-12-ynamide.

Heptyne (22.8 g., 0.22 mole) in dry tetrahydrofuran (25 ml.) was added over 30 min. to a suspension of sodamide prepared from sodium (6.6.g., 0.28 mole) and liquid ammonia (500 ml.). After stirring the mixture for 3 hr. the C_{11} amide (43,5 g., 0.149 mole) in tetrahydrofuran (50 ml.) was added rapidly over 5 min., and stirring continued overnight. Next day the ammonia was allowed to evaporate and the acidified reaction product extracted with ether to give crude N,N-dimethyloctadec-12-ynamide (52 g.).

Octadec-12-ynoic Acid.

The crude C_{18} amide (45 g.) was refluxed with potassium hydroxide (153 g.) in a solution of ethanol (560 ml.) and water (560 ml.) for 8 hr. Isolation of the acidic product (37.5 g.) followed by crystallisation from ethanol /H_2O gave an octadec-12-ynoic acid (20.2 g.) as the first crop of crystals.

Methyl Octadec-12-enoate.

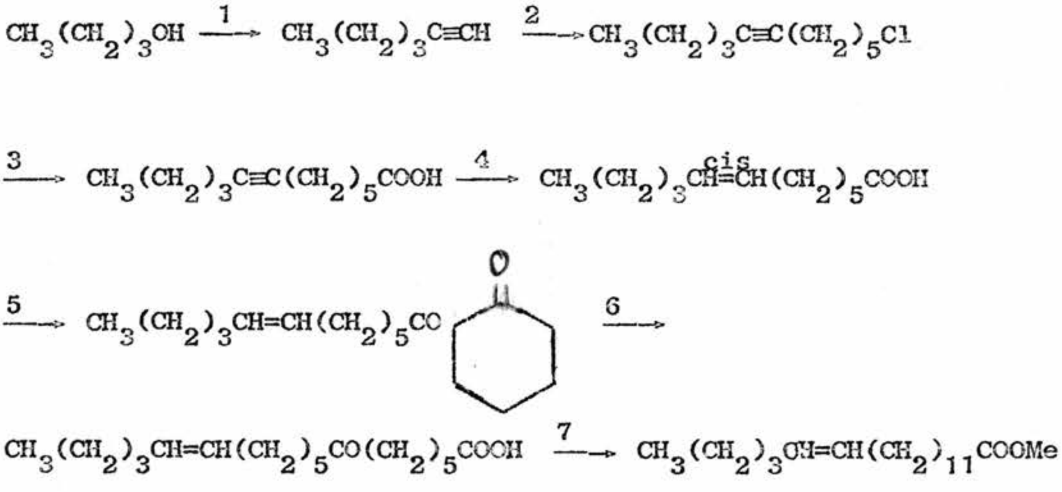
The crystalline Δ^{12} acetylenic acid (20 g.) was esterified with methanolic hydrogen chloride (1.5%, 250 ml.) and the resulting methyl ester partially reduced in the presence of Lindlar's catalyst (12 g.). The methyl octadec-12-enoate was purified by distillation through a spinning band column (17.8 g.) b.p. 150°/1 mm., n_D^{25} 1.4517.

m.p. of cis acid -27.0-28.0° (lit.[15] m.p. 26.8 - 27.6°) m.p. of acetylenic acid 46 - 47° (lit.[15] m.p. 46.2 - 47.2°).

Purity of Olefinic acid.

The cis ester contained no detectable content of saturated acid or the trans isomer. Von Rudloff oxidation showed only the C_{12} dibasic acid.

Methyl Octadec-13-enoate



$$CH_3(CH_2)_3OH \xrightarrow{1} CH_3(CH_2)_3C{\equiv}CH \xrightarrow{2} CH_3(CH_2)_3C{\equiv}C(CH_2)_5Cl$$

$$\xrightarrow{3} CH_3(CH_2)_3C{\equiv}C(CH_2)_5COOH \xrightarrow{4} CH_3(CH_2)_3\overset{cis}{CH{=}CH}(CH_2)_5COOH$$

$$\xrightarrow{5} CH_3(CH_2)_3CH{=}CH(CH_2)_5CO \xrightarrow{6}$$

$$CH_3(CH_2)_3CH{=}CH(CH_2)_5CO(CH_2)_5COOH \xrightarrow{7} CH_3(CH_2)_3CH{=}CH(CH_2)_{11}COOMe$$

1, Br_2, red phosphorus; NaC≡CH, liquid ammonia

2, $NaNH_2$, liquid ammonia; $I(CH_2)_5Cl$ 3, NaI, NaCN;

KOH 4, H_2, Lindlar 5, $SOCl_2$; morpholino-cyclohex-1-ene;

HCl 6, KOH, HCl 7, N_2H_4, ethanolamine; KOH; HCl;

MeOH, HCl.

METHYL OCTADEC-13-ENOATE.

1-Bromobutane. [116]

Bromine (96 g., 1.2 mole) was added over 1 hr., to butanol (88.2 g., 9.2 mole) and red phosphorus (9 g.) in a flask fitted with a mechanical stirrer, dry ice-condenser, and dropping funnel. The fuming product was diluted with water and extracted with ether. The extract was washed successively with 10% sodium carbonate solution, water, dilute hydrochloric acid and water and then dried. Distillation through a ½ metre Fenske column gave pure 1-bromobutane (115 g., 70%) b.p. 100-101°, n_D^{25} 1.4397. (lit.[194] 101°/768 mm., n_D^{20} 1.43993).

Hex-1-yne.

Butyl bromide (109 g., 0.8 mole) in dry ether (25 ml.) was added to sodium acetylide made from sodium (23.5 g., 1 mole) in liquid ammonia (700 ml.) contained in a flask. This was equipped with a dry ice-conddnser, which was replaced by an ordinary condenser after stirring for 2 hr. Stirring was continued for another 2 hr. and 2N-ammonium hydroxide (200 ml.) was added dropwise to the mixture and the organic layer separated. The aqueous layer was extracted with ether which together with the organic layer was washed with 2N hydrochloric acid, with water, dilute sodium carbonate, again with water and dried. Distillation gave hexyne (39.5 g., 60%) b.p. 70-71° n_D^{25} 1.3992 (lit.[200] 71.4°, n_D^{20} 1.3990 .

1-Chloro-undec-6-yne.

Hexyne (27.2 g., 0.33 mole) in dry ether (25 ml.) was added over 30 min., to sodamide made from sodium (9.2 g., 0.39 mole) in liquid ammonia (100 ml.). When the mixture had been stirred for 3 hr., 1,5-chloro-iodopentane (82 g., 0.35 mole) in ether (50 ml.) was added over 3/4 hr. The reaction mixture was stirred overnight and the ammonia, then, allowed to evaporate. 1-Chloro-undec-6-yne (47.4 g., 76%) b.p. 64°/0.7 mm. n_D^{25} 1.4518 (lit.[61] 77-79°/1 mm. n_D^{25} 1.4502) was obtained in the usual manner.

Dodec-7-ynoic Acid.

1-Chloro-undec-6-yne (47 g., 0.25 mole) was refluxed for 48 hr. with sodium iodide (42 g.) and sodium cyanide (42 g.) in ethanol (80%, 410 ml.). Potassium hydroxide (138 g.) in water (340 ml.) was then added and refluxing continued for a further 48 hr. Isolation of the acidic product and distillation gave dodec-7-ynoic acid (43.8 g., 89%) b.p. 118-120°/0.4 mm. n_D^{25} 1.4592 (lit.[61] 142-143°/1 mm. n_D^{25} 1.4568).

Dodec-7-enoic Acid.

A mixture of Lindlar's catalyst (15 g.), quinoline (3.7 g.) and ethyl acetate (175 ml.) was vigorously shaken in hydrogen until absorption was complete. The acetylenic acid (38 g.) in ethyl acetate (50 ml.) was added and hydrogenation continued till the conversion to the ethylenic acid was complete as shown by g.l.c. The reduction took much longer than usual (about 12 hr.) and may be the reason for the higher content of saturated acid (2.1 % by g.l.c.). Distillation gave dodec-7-enoic acid (36.2 g., 94%) b.p. 124-126°/0.5 mm. $n_D^{24.5}$ 1.4510 (lit.[61] $n_D^{27.5}$ 1.4486).

based on 98

2-Dodec-7-enoyl cyclohexanone.

Dodec-7-enoic acid (33 g., 0.17 mole) was converted to the corresponding acid chloride (30 g., 82%; b,p. 84-85°/ 0.4 mm. with thionyl chloride (40.5 g., 0.34 mole).

The acid chloride (30 g., 0.14 mole) in dry chloroform (140 ml.) was added over 90 min., to a solution of morpholinocyclohex-1-ene (26 g.) and freshly distilled triethylamine (20 ml.) in dry chloroform (175 ml.) maintained at 35°. The reaction mixture was stirred for 2 hr. Next day c. hydrochloric acid (46 ml.) in water (23 ml.) was added and the mixture refluxed for 5 hr. on a water bath. The chloroform layer was then washed 5 times with water until the aqueous layer had a pH of 5.5. The water washings were brought up to a pH of 5.5 with dilute sodium hydroxide and extracted 3 times with chloroform. The combined chloroform extracts were washed with water, dried and evaporated to give the crude diketone (38.4 g.) λ_{max} 272.8 mμ(methanol).

7-Keto-octadec-13-enoic Acid.

The diketone (37.5 g.) was heated with sodium hydroxide (4.65 g.) and water (93 ml.) on an oil bath at

150° for 4 hr. The mixture was poured into ice and 2N hydrochloric acid and extracted with ether. Evaporation of the ether gave the crude keto-acid (32.8 g.) .

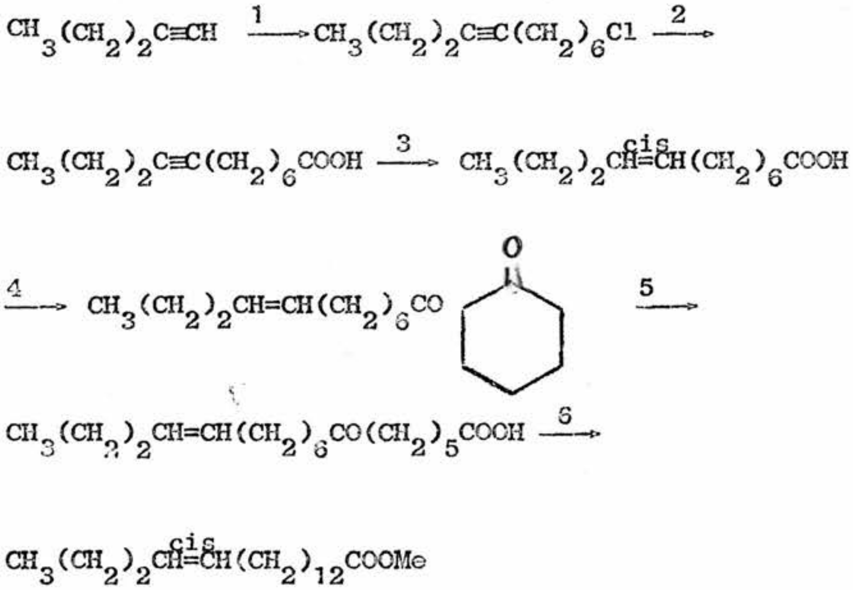
Methyl Octadec-13-enoate.

The crude keto-acid (32 g.) in ethanolamine (175 ml.) was refluxed with hydrazine hydrate (85%, 24 g.) and potassium hydroxide (5.2 g.) for 1 hr. at 150°. The reflux condenser was removed, potassium hydroxide (29 g.) and ethanolamine (175 ml.) added, and the temperature of the reaction mixture raised to 175° ($\sim$ 45 min.), with the bath temperature at 190°. A jet of nitrogen was directed towards the contents to break up the foam. The reflux condenser was replaced and the mixture heated under reflux for 90 min. The product was poured into ice and 2N hydrochloric acid and the solid acidic material extracted with ether. Evaporation of the dried extract gave crude octadec-13-enoic acid (24.7 g.) which was converted to its methyl ester and distilled through a spinning band column to give methyl octadec-13-enoate (12.2 g.) b.p. 160-162°/1 mm., n_D^{25} 1.4517. m.p. of cis ethylenic acid 26.5° - 27.0°. (Found: C, 77.14; H, 11.93. $C_{19}H_{35}O_2$ requires C, 76.95; H, 12.26.).

Purity of olefinic acid.

The cis olefinic ester contained the corresponding saturated acid (2.2% by g.l.c.) and the trans isomer (7.6% by g.l.c.,   % by i.r.). Von Rudloff oxidation gave tridecanedioic acid (~ 93%) with dodecanedioic (~ 5%) and tetradecanedioic(~ 0.5%).

Methyl Octadec-14-enoate



$CH_3(CH_2)_2C\equiv CH \xrightarrow{1} CH_3(CH_2)_2C\equiv C(CH_2)_6Cl \xrightarrow{2}$

$CH_3(CH_2)_2C\equiv C(CH_2)_6COOH \xrightarrow{3} CH_3(CH_2)_2\overset{cis}{CH=CH}(CH_2)_6COOH$

$\xrightarrow{4} CH_3(CH_2)_2CH=CH(CH_2)_6CO$

$\xrightarrow{5}$

$CH_3(CH_2)_2CH=CH(CH_2)_6CO(CH_2)_5COOH \xrightarrow{6}$

$CH_3(CH_2)_2\overset{cis}{CH=CH}(CH_2)_{12}COOMe$

1, $NaNH_2$, liquid ammonia; $I(CH_2)_6Cl$ 2 , NaI, NaCN; KOH; HCl 3 , H_2, Lindlar 4 , $SOCl_2$; morpholinocyclohex-1-ene; HCl 5, KOH, H_2O; HCl 6 , N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl.

METHYL OCTADEC-14-ENOATE.

Pent-1-yne. based on 201

Sodium acetylide was prepared from sodium (23.5 g., 1 mole) and liquid ammonia (750 ml.) in a 3-necked flask (1 l.) equipped with a stirrer, dropping funnel and cardice-condenser. Propyl bromide (123 g., 1 mole) was added dropwise over 30 min. The condenser was constantly replenished with dry ice. The mixture was stirred for 3 hr., after which cold petroleum ether (100-120°, 50 ml.) was added slowly to the mixture. 2N ammonium hydroxide (75 ml.) cooled to 5° was then introduced dropwise. The ammonia escaping through the dry ice-condenser was passed through two Drechsel bottles containing petroleum ether (100-120°). Water (300 ml.) was added and the organic layer separated. The latter, together with the petroleum ether from the traps, was washed with water (300 ml.) 6N hydrochloric acid till acid to litmus, with water, dilute sodium carbonate and finally with water. The extract was dried, distilled and the fraction boiling between 39-40° collected and redistilled to give pent-1-yne (41.1 g., 60.5%) b.p. 39-40° $n_D^{21.5}$ 1.3992 (lit.[201] b.p. 39-40°; n_D^{25} 1.3850).

11-Chloro-undec-4-yne.

Pentyne (12.8 g., 0.19 mole) in dry ether (25 ml.) was added over 30 min. to sodamide prepared from sodium

(4.7 g., 0.2 mole) suspended in liquid-ammonia (500 ml.). After stirring the mixture for 3 hr., 1,6-chloro-iodo hexane (44.1 g., 0.18 mole) in dry ether (25 ml.) was added over 45 min. and stirring was continued overnight. Solid ammonium chloride (10 g.) was then added to the mixture and the ammonia allowed to evaporate and the residue extracted with ether. This was washed with water, dilute sulphuric acid, with water and then dried. Distillation gave 11-chloro-undec-4 -yne (25.4 g., 76%) b.p. 57°/0.3 mm. n_D^{25} 1.4610. G.L.C. showed ~ 0.5% of unreacted material and ~ 0.5% of 10-chloro-2-methyl dec-3-yne.

Dodec-8-ynoic Acid.

11-Chloro-undec-4-yne (25 g., 0.134 mole) was refluxed with sodium iodide (21 g.) and sodium cyanide (21 g.) in ethanol (80%, 210 ml.) for 48 hr., and for a similar period after further addition of potassium hydroxide (72 g.) and water (102 ml.). Distillation of the isolated acidic fraction gave dodec-8-ynoic acid (19.8 g., 75 4%) b.p. 118-5 - 119.5°/0.4 mm. $n_D^{24.5}$ 1.4605 p-bromophenacyl ester m.p. 55.3 (Found: C,61.37; H,6.22. $C_{20}H_{25}O_2Br$ requires C,61.06; H,6.41%).

In another experiment to obtain more of the acetylenic acid, the chloro-undecyne was not distilled but converted in its crude form to the acid in a yield of 84% based on pent-1-yne.

Dodec-8-enoic Acid.

Dodec-8-ynoic acid (40 g.) was hydrogenated in the presence of Lindlar's catalyst (23 g.) to give dodec-8-enoic acid (40.5 g.).

The reduction was followed by g.l.c. which showed the final product to contain ~ 1.5% saturated acid.

Dodec-8-enoyl chloride.

Thionyl chloride (47.5 g., 0.4 mole) was added over an hr. to dodec-8-ynoic acid (40 g., 0.2 mole) and the mixture stirred for a further hour, after which it was refluxed for 30 min. The excess thionyl chloride was removed and the acid chloride distilled (42.4 g., 97%) b.p. 88-90°/ 0.7 mm.

2-Dodec-8-enoylcyclohexanone.

The acid chloride (42.4 g., 0.2 mole) in dry chloroform (182 ml.) was added dropwise over 90 min. to morpholinocyclohex-1-ene (36,4 g.) and triethylamine (30.5 ml.) in dry chloroform (257 ml.). The reaction was carried out as before (cf. the Δ^{13} acid) to give the crude diketone (65 g.) λ_{max} 274 mμ (methanol).

7-Keto-octadec-14-enoic Acid.

The crude diketone (63 g.) was hydrolysed with sodium hydroxide (8.7 g.) and water (175 ml.) for 4 hr. at 150°. Crude 7-keto-octadec-14-enoic acid (52.8 g.) was isolated as usual (cf. the Δ^{13} acid)

Methyl Octadec-14-enoate.

The crude keto-acid (50 g.) was refluxed for 1 hr. with hydrazine (85%, 37.4 ml.) and potassium hydroxide (8.1 g.) in ethanolamine (197 ml.). The reflux condenser was removed and potassium hydroxide (42.9 g.) together with ethanolamine (197 ml.) was added. The temperature of the reaction mixture was raised to 176° (∽ 45 min.) the condenser replaced and the mixture heated under reflux for another 30 min. Crude octadec-14-enoic acid (40.7 g.) was isolated (cf. the Δ^{13} acid). The ethylenic ester (30 g.) was distilled through a spinning band column to give methyl octadec-14-enoate (18.3 g.) b.p. 149-150°/9 mm. n_D^{25} 1.4515.

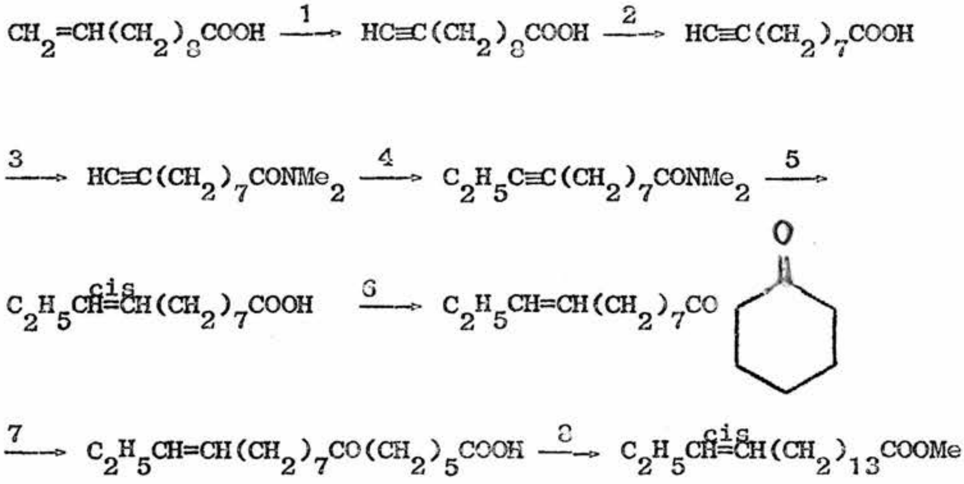
m.p. of cis acid 41.5-42.5°

Purity of olefinic acid.

The cis ester contained the corresponding saturated acid (1.1% by g.l.c.) and the trans isomer 3.3% by g.l.c., 2.5 % by i.r.)

Von Rudloff oxidation gave tetradecanedioic acid (∼ 99%) along with tridecanedioic and pentadecanedioic acids (in ∽ 0.5% each).

Methyl Octadec-15-enoate



$CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} HC{\equiv}C(CH_2)_8COOH \xrightarrow{2} HC{\equiv}C(CH_2)_7COOH$

$\xrightarrow{3} HC{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{4} C_2H_5C{\equiv}C(CH_2)_7CONMe_2 \xrightarrow{5}$

$C_2H_5CH\overset{cis}{=}CH(CH_2)_7COOH \xrightarrow{6} C_2H_5CH{=}CH(CH_2)_7CO$

$\xrightarrow{7} C_2H_5CH{=}CH(CH_2)_7CO(CH_2)_5COOH \xrightarrow{8} C_2H_5CH\overset{cis}{=}CH(CH_2)_{13}COOMe$

1, Br_2, petroleum ether; KOH 2, Barbier-Wieland R^n
3, $SOCl_2$; $HNMe_2$ 4 , $NaNH_2$, liquid ammonia; ethyl iodide
5 , NaOH,EtOH; HCl; H_2, Lindlar 6, $SOCl_2$, morpholinocyclohex-1-ene; HCl 7, NaOH; HCl 8, N_2H_4, ethanolamine; KOH; HCl; MeOH,HCl

METHYL OCTADEC-15-ENOATE

10,11-Dibromo-undecanoic Acid [202]

Undec-10-enoic acid (170 g., 0.92 mole) was dissolved in purified olefin-free petroleum ether (60-80°, 500 ml.) in a 3 necked flask fitted with a stirrer, reflux condenser and dropping funnel. Bromine (150 g., 1.87 mole) was added over 90 min. while cooling the flask in a mixture of ice and salt. When 3/4 of the bromine was added, the dibromo-acid began to separate. The mixture was stirred vigorously for a further hour and the precipitate filtered at the pump and washed with cold petroleum ether (100 ml.) The cake was broken up and dried in a vacuum dessicator. Crude dibromo-undecanoic acid (227 g., 72%) was obtained. A portion was crystallised from petroleum ether and found to melt at 38.5° (lit.[202] m.p. 38.5°).

Undec-10-ynoic Acid

The dibromo-acid (227 g., 0.66 mole) was mixed with a solution of potassium hydroxide (554 g.) in water (315 ml.) in a R.B. flask(**2 l.**) equipped with reflux condenser and the whole heated for 8 hr. The product was cooled below 100°, diluted with water (1000 ml.) and poured into ice and 2 N sulphuric acid. The mixture was then extracted with ether, and the extract dried and evaporated. Distillation of the residue gave undec-10-ynoic acid (85.2 g., 71%) b.p. 178-182°/12 mins. m.p. 41-42° (lit.[99] 177-182/15 mm. m.p. 42°).

This experiment has been repeated several times and von Rudloff oxidation show the products to contain 89-93% of the Δ^{10} acid, accompanied by the Δ^{9} isomer.

Ethyl Undec-10-ynoate

Undec-10-ynoic acid (290 g.) was refluxed with a mixture of dry ethanol (1250 ml.) and c. sulphuric acid (100 g.) for 6 hr. Water (1250 ml.) was added and the organic layer separated. The volume of the aqueous layer was reduced to half and extracted with ether. The ether extracts and the separated organic layer together were washed with water, dried and distilled to give ethyl undec-10-ynoate (278 g., 84%) b.p. 140-145°/ 10 mm. n_D^{25} 1.4612 (lit.[202] 145°/15 mm.) G.L.C. of the distilled ester showed one major peak (95%) and three minor peaks, one of them probably being the Δ^9 isomer.

1,1-Diphenylundec-1-en-10-yne.

Ethyl undec-10-ynoate (144 g., 0.69 mole) in ether (700 ml.) was added over 90 min. to a stirred solution of phenyl magnesium bromide preformed from magnesium (59.2 g., 2.45 mole) and bromobenzene (375 g., 2.4 mole) in ether (700 ml.). The mixture was heated under reflux for 2½ hr. before the Grignard complex was decomposed by the addition of ice and 2 N sulphuric acid. Extraction with ether in the usual manner gave the alcohol which was dehydrated, without purification, by heating to 220° for 30 min. Distillation gave 1,1-diphenylundec-1-en-10-yne (144 g., 70%) b.p. 172°/0.6 mm. (lit.[99] 240-245°/17 mm.).

Dec-9-ynoic Acid[99]

A solution of chromium trioxide (98 g., 1.47 eq.) in water (115 ml.) was added during 2½ hr. to a well stirred warm (50-60°) solution of 1,1-diphenylundec-1-en-10-yne (144 g., 0.48 mole) in acetic acid (1440 ml.). After the mixture had been stirred overnight at 20°, most of the solvent was evaporated under reduced pressure. The residue was warmed on a water bath at 100° for an hour with 2 N sulphuric acid (1600 ml.), then cooled and diluted with a saturated aqueous solution of sodium chloride (1800 ml.) Isolation and subsequent distillation gave dec-9-ynoic acid (37.6 g., 47%) b.p. 92-93°/0.7 mm. (lit.[99] b.p. 88°/0.1 mm.).

N,N-Dimethyldec-9-ynamide

Thionyl chloride (154 g., 1.3 mole) was added dropwise to dec-9-ynoic acid (108.9 g., 0.64 mole). The crude acyl chloride, freed of excess thionyl chloride, was dissolved in dry ether (100 ml.) and added dropwise over 45 min. to a well stirred solution of dimethylamine (86.4 g., 192 mole) in dry ether (600 ml.) maintained at 0-5°. The acid chloride was added at such a rate that the temperature of the reaction remained at this temperature during the addition. The mixture was stirred for a further 2 hr. and allowed to stand overnight. Extraction in the usual way gave N,N-dimethyldec-9-ynamide (99.4 g., 79.6%) b.p. 120-122°/1 mm. ([illegible]

With an S.E.30 column, G.L.C. showed that the amide was only 70% pure. Three other peaks, close to the main peak, accounted for the remaining 30%.

based on 17

N,N-Dimethyldodec-9-ynamide

The C_{10} amide (88.1 g., 0.45 mole) in tetrahydrofuran (50 ml.) was added dropwise over 15 min. to sodamide prepared from sodium (11.7 g., 0.5 mole) in liquid ammonia (700 ml.). After stirring for a further 3 hr., ethyl iodide (80.6 g., 0.52 mole) in tetrahydrofuran (50 ml.) was added over 45 min. The mixture was stirred for 12 hr. and the ammonia subsequently allowed to evaporate over 6 hr. The product, (90.1 g. along with 11 g. from another experiment) was distilled to give N,N-dimethyldodec-9-ynamide (63.1 g.) b.p. 146-148°/0.8 mm., containing <5% of impurities. (The C_{10} starting material being the largest). Other fractions distilling first were:-

1. 3.8 g., b.p. 126-130°/0.8 mm. - almost entirely C_{10} amides.
2. 7.0 g., b.p. 130-136°/0.8 mm. - " " " "
3. 14.8 g., b.p. 136-142°/0.8 mm. - 10% of C_{12} amides.
4. 8.9 g., b.p. 142-146°/0.8 mm. - 50% of C_{12} amides.

Dodec-9-ynoic Acid

The amide (62.3 g.) was refluxed with a mixture of ethanol (1300 ml.) and 5 N sodium hydroxide (1300 ml.) for 10 hr. The acidic product was isolated and distilled to give dodec-9-ynoic acid (51.3 g.) b.p. 121.5°/0.4 mm.

Dodec-9-enoic Acid.

The acetylenic acid (48 g.) was reduced with hydrogen in the presence of Lindlar's catalyst (12 g.) over 4 hr., to give dodec-9-enoic acid (48 g.).

G.L.C. of the methyl ester of a sample showed the presence of ~ 1.5% saturated acid together with the 5% impurity corresponding to that present at the amide stage.

The acid was redistilled carefully through a ½ metre Fenske column with a reflux ratio of 1:10 to give very pure dodec-9-enoic acid (37.5 g.) with ~ 1.5% saturated acid and none of the other impurities, b.p. 119-121°/0.4 mm.

7-Keto-octadec-15-enoate.

Dodec-9-enoic acid (34 g., 0.172 mole) was treated with thionyl chloride (41.7 g., 0.35 mole) and the product distilled to give dodec-9-enoyl chloride (33.1 g., 89%) boiling between 88-92°/0.6 mm. The acid chloride (33.1 g.) in dry chloroform (140 ml.) was added dropwise over 90 min., to a mixture of morpholino-cyclohex-1-ene (28 g.) and triethylamine (23.5 ml.) in dry chloroform (198 ml.) at 35°. After stirring for 2 hr., the contents were allowed to stand overnight. C. Hydrochloric acid (46 ml.) in water (23 ml.) was then added, the mixture refluxed for 5 hr., and the diketone (53 g.) isolated as in the previous case (cf. the Δ^{13} acid).

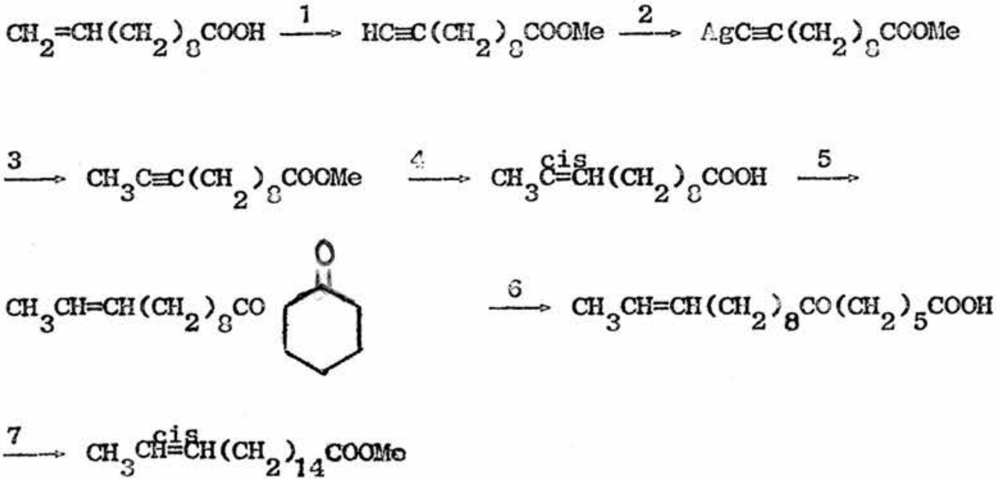
The crude keto-acid (37.5 g.) was refluxed for an hour, with hydrazine hydrate (90%, 27 ml.) and potassion hydroxide (5.8 g.) in ethanolamine (184 ml.). The oil bath was kept at 150-160°. The reflux condenser was removed and potassium hydroxide (29 g.) and ethanolamine (184 ml.) added and the temperature of the contents raised to 176° (45 min.). The condenser was replaced and the refluxing was continued for 90 min. Crude octadec-15-enoic acid (34,2 g.) was isolated as before. The crude acidic product (33.5 g.) was distilled as its methyl ester through a spinning band column to give pure methyl octadec-15-enoate (18,8 g.) b,p. 145°/1 mm., n_D^{25} 1.4518. (Found C,76.92; H,12.14. $C_{19}H_{35}O_2$ requires C,76.95; H,12.26) m.p. of cis ethylenic acid 40.5 - 41.5°.

Purity of Olefinic Acid.

The cis ester contained the corresponding saturated acid (1.5% by g.l.c.) and the trans isomer (2.5% by g.l.c.; 3.2 % by i.r.).

Von Rudloff oxidation gave pentadecanedioic acid (~ 99.5%) with tetradecanedioic acid 0.5% and no detectable amount of hexadecanedioic acid.

Methyl Octadec-16-enoate



$CH_2{=}CH(CH_2)_8COOH \xrightarrow{1} HC{\equiv}C(CH_2)_8COOMe \xrightarrow{2} AgC{\equiv}C(CH_2)_8COOMe$

$\xrightarrow{3} CH_3C{\equiv}C(CH_2)_8COOMe \xrightarrow{4} CH_3\overset{cis}{C{=}C}H(CH_2)_8COOH \xrightarrow{5}$

$CH_3CH{=}CH(CH_2)_8CO$ $\xrightarrow{6} CH_3CH{=}CH(CH_2)_8CO(CH_2)_5COOH$

$\xrightarrow{7} CH_3\overset{cis}{CH{=}C}H(CH_2)_{14}COOMe$

1, Br_2, petroleum ether; KOH   2, $AgNO_3/NH_4OH$

3, CH_3I 4, H_2, Lindlar; NaOH; HCl   5, $SOCl_2$;

morpholinocyclohex-1-ene; HCl   6, NaOH; HCl

7, N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl.

METHYL OCTADEC-16-ENOATE

Silver methyl undec-10-ynoate

Ammonium hydroxide (1 N) was added to a solution of silver nitrate (106.5 g., 0.63 mole) in water (250 ml.)until the initial precipitate just dissolved. This solution, made up to 2125 ml. with water, was added rapidly over 15 min. to methyl undec-10-ynoate (115 g., 0.58 mole) which was stirred vigorously. The stirring was continued overnight after which the precipitated silver salt was filtered on a Büchner funnel. The salt was dried in an oven at 80° for 5 hr. and under vacuum (1.mm.) for 5 hr., at 80° and dissolved in benzene (about 200 ml.). This solution was diluted with petroleum ether (200 ml.) when the silver salt crystallized out (60 g.). The filtrate was evaporated on a rotary film evaporator and the residue converted again to the silver salt (40 g.) with ammoniacal silver nitrate. Repeating this procedure,more silver salt (20 g.) was obtained. The silver salt from the three different crystallizations was dried in a vacuum dessicator over P_2O_5 (100 g.) m.p. 78-78.5°. (lit.[101] m.p. 76-78°).

Von Rudloff oxidation of the original methyl undec-10-ynoate showed it to contain 6.4% of the Δ^9 isomer together with traces of the Δ^8 and Δ^7 isomers. The residual organic material (22 g.) left after precipitating the silver salt contained 28% of the Δ^9 isomer.

Oxidative fission on the hydrolyzed silver salt showed the ester to contain exclusively the Δ^{10} isomer.

Methyl Dodec-10-ynoate[101]

The dry silver salt (95 g.) and methyl iodide (95 ml.) were introduced into an autoclave (1 l.) which was then sealed. The temperature was maintained at 80° for 24 hr. and then cooled down to room temperature. The reaction product was thoroughly extracted with ether which was centrifuged free of the fine precipitate of silver iodide. The product (64 g.) obtained on evaporating the ether was found to contain only 1.5% of the C_{11} ester.

Distillation through a ½ metre Fenske column first gave a forerun (10g., containing about 5% of the C_{11} ester) and the required methyl dodec-9-ynoate (35 g.) b.p. 110-112°/0.5 mm. was obtained as the second fraction. The residue (15 g.) recovered from the distillation flask and column was found to be methyl dodec-9-ynoate.

Methyl Dodec-10-enoate

The acetylenic ester (34.5 g.) in ethyl acetate (400 ml.) was hydrogenated with Lindlar's catalyst (14.0 g.) and quinoline (4 g.). The reduction which was monitored by g.l.c. took about 5 hr., methyl dodec-10-enoate (32.6 g., 94.5%) was recovered.

Dodec-10-enoic Acid

The ester (34.5 g., 0.163 mole) and sodium hydroxide (18 g.) in ethanol (8.5%, 370 ml.) was refluxed for 3 hr. Recovery of the acidic product and distillation yielded dodec-10-enoic acid. (30 g., 93%, b.p. 120-124°/0.4 mm.

Dodec-10-enoyl chloride

Dodec-10-enoic acid (29 g., 0.146 mole) was treated with thionyl chloride (35 g., 0.29 mole) as usual, and the acid chloride distilled (29.4 g., 94%) b.p. 124-127°/8 mm.

based on 98

2-Dodec-10-enoylcyclohexanone

The acid chloride (29.4 g., 0.136 mole) in dry chloroform (120 ml.) was added over 90 min. to a stirred mixture of triethylamine (20 ml.) and morpholinocyclohex-1-ene (26 g.) in chloroform (175 ml.) maintained at 35°. The solution was stirred for a further 2 hr. and left overnight. C. Hydrochloric acid (46 ml.) and water (23 ml.) were added and the mixture refluxed on a water bath for 5 hr. to give the diketone (39 g.): λ max - 292.7.

7-Keto-octadec-16-enoic Acid

The diketone (38 g.) was heated under reflux with sodium hydroxide (6.5 g.) and water (130 ml.) for 4 hr. The mixture was acidified with dilute hydrochloric acid and extracted with ether to give the crude keto-acid (31 g.) . . .

Methyl Octadec-16-enoate

The crude keto-acid (29 g.) was refluxed with hydrazine hydrate (85%, 21 ml.) and potassium hydroxide (5.5 g.) in ethanolamine (175 ml.) for an hour at 160°. The reflux condenser was removed and more potassium hydroxide (29 g.) and ethanolamine (175 ml.) were added and the bath temperature raised to 200°. (A jet of nitrogen was directed towards the mixture to control the frothing of the contents. When the temperature of the reaction mixture reached 176° (1 hr.) the condenser was replaced and refluxing continued for another 80 min.

The product was poured into ice and dilute hydrochloric acid and the crude octadec-16-enoic acid extracted. The acid was distilled as its methyl ester through a spinning band column and methyl octadec-16-enoate (20 g.) was obtained. b.p. 164-164.5°/1 mm. (Found C, 77.18; H, 12.24. $C_{19}H_{35}O_2$ requires C, 76.95; H, 12.26). m.p. of cis ethylenic acid. 53.5-54.5°.

Purity of olefinic acid

The cis olefinic ester contained the corresponding saturated acid (<0.2% by g.l.c.) and the trans isomer (<1.5% by g.l.c.;and 2.5 % by i.r.). The slow rise of the peak recorded on g.l.c. suggests an impurity which could only be roughly assessed at 3%. This impurity is removed by thin layer chromatography using silica.

Von Rudloff oxidation gave hexadecanedioic acid (~98.5%) along with the Δ^{15} and Δ^{17} homologues in equal proportion.

First Attempt to obtain dodec-10-ynoic acid

N,N-dimethyl undec-10-ynamide (40 g., 0.191 mole, 71% pure by g.l.c. b.p. 115-117°/0.5 mm. lit[17] 125-130°/1 mm. in dry tetrahydrofuran (50 ml.) was added rapidly over 10 min. to sodamide prepared from sodium (5.0 g., 0.22 mole) in liquid ammonia (500 ml.). After stirring for 3 hr., methyl iodide (32.3 g., 0.26 mole) in dry tetrahydrofuran (25 ml.) was added dropwise over 45 min., and stirring continued for another 12 hr. The ammonia was allowed to escape and a mixture (37.1 g.) of dodec-10-ynamide and starting material in the ratio 55:44 was isolated with ether.

Separation of the C_{11} starting material and the C_{12} amide was not possible on a ½ metre Fenske column. The two components were separated by g.l.c. (using a 2 metre 20% Apiezon L at 210° with a flow rate of 200 ml./min. of Helium) but the long retention times made their large scale separation impracticable.

Methyl Dodec-10-enoate and undec-10-enoate

The amides (37 g.) were boiled for 8 hr. with ethanol (649 ml.) and 5 N sodium hydroxide (649 ml.). The crude acid (30.2 g.) was converted to its methyl esters (29.5 g.) with methanolic hydrogen chloride (1.5%, 300 ml.).

The conditions used to separate the methyl esters on the "Autoprep" were as follows:--

Column: 2 metre, 20% Apiezon L.

Temperature: 200°

Flow rate: 200 ml./min.

Optimum sample size - 0.3 ml.

Retention time of methyl dodec-10-enoate - 18 min.

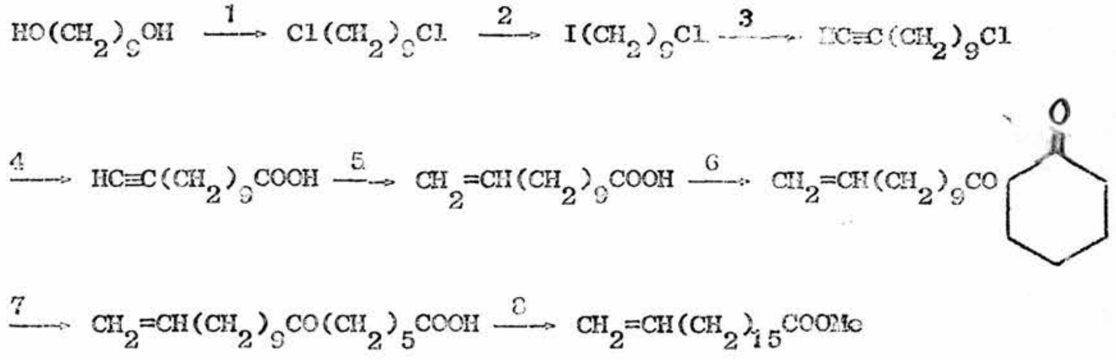
The attempted separation was given up when only 3.4 g.,of the ester was collected after 30 hr.

Attempt to remove C_{11} components from mixture

The amides(4.5 g.) were added to sodamide prepared from sodium (0.56 g.) in liquid ammonia (100 ml.) and stirred for 2 hr. Dry carbon dioxide was passed through the mixture for 30 min., and the white solid mass left overnight.

The product was diluted with water, acidified, and extracted with ether which was then washed with dilute alkali. The extract was washed with water, dried and evaporated. The neutral amides obtained were shown by g.l.c. to contain almost the same proportion of C_{11} components as the original mixture of amides.

Methyl Octadec-17-enoate



$HO(CH_2)_9OH \xrightarrow{1} Cl(CH_2)_9Cl \xrightarrow{2} I(CH_2)_9Cl \xrightarrow{3} HC{\equiv}C(CH_2)_9Cl$

$\xrightarrow{4} HC{\equiv}C(CH_2)_9COOH \xrightarrow{5} CH_2{=}CH(CH_2)_9COOH \xrightarrow{6} CH_2{=}CH(CH_2)_9CO$

$\xrightarrow{7} CH_2{=}CH(CH_2)_9CO(CH_2)_5COOH \xrightarrow{8} CH_2{=}CH(CH_2)_{15}COOMe$

1, $SOCl_2$, pyridine 2, NaI, acetone 3, NaC≡CH, liquid ammonia 4, NaI, NaCN; KOH; HCl 5, H_2, Lindlar 6, $SOCl_2$; morpholino cyclohex-1-ene; HCl 7, NaOH, H_2O 8, N_2H_4, ethanolamine; KOH; HCl; MeOH, HCl

METHYL OCTADEC-17-ENOATE

1,9-Dichlorononane

To a melted mixture of 1,9-nonanediol (90 g., 0.563 mole), pyridine (78 ml.) and thionyl chloride (22.6 g.), thionyl chloride (244 g.) was added dropwise at such a rate to maintain the temperature of the reaction at 25°. The mixture was then refluxed for 2 hr. and dichlorononane (100.1 g.) was obtained in the usual manner. Distillation gave the dichloride (94.5 g., 85%), b.p. 129-131°/11 mm. n_D^{25} 1.4590 (lit.[15] 86-89°/2 mm. n_D^{25} 1.4586).

1,9-Chloro-iodononane

Dichlorononane (94 g., 0.48 mole) was refluxed together with sodium iodide (72 g., 0.48 mole) in dry acetone (420 ml.) for 4½ hr. with stirring. Extraction with petroleum ether gave a mixture of dichloro, iodochloro, and di-iodononane (129.4 g.) which was distilled to give chloro-iodononane (69.8 g., 50.5%) b.p. 110-113°/0.4 mm.

The dichlorononane obtained (29.5 g.) as the first fraction was recycled to give more chloro-iodononane (22.4 g.) which was redistilled together with the first batch to give pure chloro-iodononane (90.4 g.). n_D^{25} 1.5016 (lit.[15] 123-126°/4mm. n_D^{25} 1.5074).

11-Chloro-undec-1-yne

1.9-Chloro-iodononane (89.5 g., 0.314 mole) in dry ether (50 ml.) was added dropwise over 45 min. to a suspension of sodium acetylide made from sodium (8.5 g., 0.36 mole) and liquid ammonia (700 ml.). The mixture was stirred for 12 hr. and 11-chloro-undec-1-yne (52.8 g., 90.4%) b.p. 74°/0.3 mm. n_D^{25}, 1.4576 then obtained in the usual manner.

Dodec-11-ynoic Acid

11-Chloro-undec-1-yne (52.3 g., 0.28 mole) was heated under reflux for 48 hr. with sodium iodide (44.1g.) and sodium cyanide (44.1 g.) in ethanol (80%, 440 ml.). Potassium hydroxide (151.2 g.) in water (215 ml.) was then added and the mixture refluxed for a further 48 hr. Isolation and distillation of the acidic product gave dodec-11-ynoic acid (43.5 g., 79%) b.p. 132-136°/0.6 mm. (lit.[203] m.p. 43.5-44.5°

An Alternative Preparation of Dodec-11-enoic Acid

11-Bromo-undec-1-ene

Undec-10-en-1-ol (100 g., 0.59 mole) and pyridine (11.8 ml.) were dissolved in dry ether (115 ml.) and the solution cooled to 0°. Phosphorus tribromide (64.9 g., 0.236 mole) was added over ½ hr. with stirring. The mixture was then refluxed for 3 hr. cooled to room temperature, and diluted with water (150 ml.). The organic material was extracted with ether, washed with dilute sodium carbonate, then thoroughly with water and dried. Distillation gave 11-bromo-undec-1-ene (111 g., 82%) b.p. 81-84°/0.5 mm. (lit.[15] 125-127°/12 mm.).

Dodec-11-enoic Acid

The C_{11} bromide (88 g., 0.378 mole) in ether (500 ml.) was added slowly to clean strips of magnesium (9.6 g., 0.4 mole) in ether (50 ml.) and a crystal of iodine. The rate of addition of the bromide was controlled to maintain a gentle reflux. The suspension of the magnesium derivative was refluxed for an hour, cooled to room temperature and poured into cardice (~200 g.) contained in a beaker (2 l.) and stirred. The crude acidic material (52 g.) was distilled to give dodec-11-enoic acid (49.4 g., 63%) b.p. 125-126°/0.3 mm.

Von Rudloff oxidation of the acid showed 3.4% of the Δ^{10} isomer.

Dodec-11-enoic acid (from first preparation of C_{12} acid).

Dodec-11-ynoic acid (40 g.) was partially hydrogenated in the presence of Lindlar's catalyst (22 g.) to dodec-11-enoic acid (39.3 g.). The acid was not distilled at this stage but used directly for the preparation of the acid chloride.;

Dodec-11-enoyl chloride

Dodec-11-enoic Acid (38.5 g.) was converted to the acid chloride with thionyl chloride (46 g.). Distillation under reduced pressure gave dodec-11-enoyl chloride (37.6 g., 89%) b.p. 89-91°/0.6 mm.

2-Dodec-11-enoyl cyclohexanone

Dodec-11-enoyl chloride (37.6 g., 0.174 mole) in dry chloroform (160 ml.) was added over 1½ hr., to an efficiently stirred mixture of morpholino-cyclohex-1-ene (32 g.) and triethylamine (26.8 ml.) in chloroform (226 g.), maintained at 35°. After stirring for a further 2 hr., the orange solution was left until the next day at room temperature. The crude diketone, (55 g.), max. 272.4 mμ, (methanol) was obtained after refluxing the solution with c. hydrochloric acid (52 ml.) and water (260 ml.).

7-Keto-octadec-17-enoic Acid

The crude diketone (52 g.) was refluxed with sodium hydroxide (7.6 g.) in water (154 ml.) for 4 hr., after which the acidified solution was extracted with ether and crude 7-keto-octadec-17-enoic acid (47.5 g.) .

Methyl Octadec-17-enoate

The crude 7-keto-octadecenoic acid (44 g.) was refluxed for an hour with hydrazine hydrate (85%, 33 g.) and potassium hydroxide (7.1 g.) in ethanolamine (170 ml.) to give the hydrazone which was decomposed, as usual, to the mono-ethenoic acid (35 g.) with more potassium hydroxide (30.3 g.) and ethanolamine (170 ml.). The crude C_{18} acid (30 g.) was distilled as its methyl ester through a spinning band column to give octadec-17-enoate (14.8 g.) b.p. 148-150°/1 mm (Found: C, 77.17 ; H, 12.20, $C_{19}H_{35}O_2$ requires C, 76.95; H, 12.26). m.p. of the octadecenoic acid - 55.5-56.5°. (lit.[15] 55.5-56.1° and lit.[97] 55-55.5°).

In another attempt to prepare Δ^{17} octadecenoic acid, the keto group was reduced by treating the corresponding tosyl derivative with sodium borohydride.

The dodec-11-enoic acid prepared from undec-10-en-1-ol as described before had 3.4% of the Δ^{10} isomer. The C_{12} acid was extended to the 7-keto-octadec-17-enoic acid which then had 5.4% of the Δ^{16} isomer.

Hydrazone of 7-Keto-octadec-17-enoic Acid

The keto-acid (3.0 g.) was refluxed for ½ hr. with tosylhydrazine (2.6 g.) and c. sulphuric acid (0.6 ml.) in methanol (150 ml.). The hydrazone was extracted with chloroform and used directly in the next stage.

Methyl Octadec-17-enoate

Sodium borohydride (6 g.) was added over 10 min. to the hydrazone (from keto acid, 3.0 g.) in dry methanol (150 ml.) and the mixture refluxed for 8 hr. The mixture was diluted with water (250 ml.) and extracted with ether. The extract was washed with water, dried and evaporated.

Examination of the isolated product by t.l.c. showed the absence of any keto-acid but indicated at least 3 other compounds including a spot corresponding to octadecenoic acid. The components were separated as their esters by column chromatography using silicic acid. The least polar material was eluted first with petroleum ether (40-60°). On changing the solvent system to ether/petroleum ether (1:9), the C_{18} ester was isolated. Examination of this fraction by t.l.c. showed only a main spot with a trace of the less polar material.

With an Apiezon L column g.l.c., showed one peak with the same retention time as methyl stearate, but showed two peaks on a polar phase. The two peaks corresponded to methyl stearate and octadec-17-enoate in the ratio 58:42 respectively. The unsaturated ester was separated by thin layer chromatography using silica impregnated with silver nitrate.

Von Rudloff oxidation of the sample showed it to be 93.6% pure, the Δ^{16} isomer forming the rest.

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