RECENT DEVELOPMENTS IN THE PREPARATION OF NATURAL AND SYNTHETIC STRAIGHT-CHAIN FATTY ACIDS

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Many aliphatic carboxylic acids have been isolated from natural sources or prepared by synthetic methods. The number of normal saturated acids is relatively small, whereas the number of possible normal unsaturated acids is much greater owing to variation in the number, position, and configuration of the unsaturated centres. Methods of synthesising saturated acids were developed many years ago but the synthesis of unsaturated acids is a more recent development, oleic and linoleic acids being first synthesised only in 1934 and 1950 respectively.

In the last decade many aliphatic acids have been prepared and several, previously unknown, acids have been isolated from natural sources. In this Review the methods of synthesis of normal saturated and unsaturated acids containing not less than six carbon atoms are reviewed and recent contributions to our knowledge of naturally occurring fatty acids are discussed.

Some aspects of this subject are included in the works of Hilditch,[1] Markley,[2] Ralston,[3] and Johnson,[4] and in some more recent reviews.[5]

The Geneva nomenclature ($CO_2H = 1$) is used throughout this Review and systematic names are preferred to trivial names except in a few established cases. Trivial names are used for the following saturated acids, lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), stearic (C_{18}), and behenic (C_{22}), and for the unsaturated acids listed below.

Sorbic	$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$	Hexa-2 : 4-dienoic acid
Oleic *	$CH_3{\cdot}[CH_2]_7CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$	Octadec-9-enoic acid
Stearolic	$CH_3{\cdot}[CH_2]_7{\cdot}C\vdots C{\cdot}[CH_2]_7{\cdot}CO_2H$	Octadec-9-ynoic acid
Linoleic *	$CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$	Octadeca-9 : 12-dienoic acid
Linolenic	$CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$	Octadeca-9 : 12 : 15-trienoic acid

* Elaidic, linelaidic, and brassidic acids are the *trans*-isomers of the naturally occurring *cis*-acids.

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[1] Hilditch, " The Chemical Constitution of Natural Fats ", Chapman and Hall Ltd., London, 1947.

[2] Markley, " Fatty Acids, their Chemistry and Physical Properties ", Interscience Publ., Inc., New York, 1947.

[3] Ralston, " Fatty Acids and their Derivatives ", John Wiley and Sons, Inc., New York, 1948.

[4] Johnson, " Acetylene Compounds ", Vol. II, " Acetylenic Acids ", Edward Arnold and Co., London, 1950.

[5] Lennartz, *Angew. Chem.*, 1947, **59**, *A*, 10; Breusch, *Fortschr. Chem. Forsch.*, 1950, **1**, 567; Seher, *Fette u. Seifen*, 1951, **53**, 692.

Elaeostearic	$CH_3\cdot[CH_2]_3\cdot CH{:}CH\cdot CH{:}CH\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$	Octadeca-9 : 11 : 13-trienoic acid
Ricinoleic	$CH_3\cdot[CH_2]_5\cdot CH(OH)\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$	12-Hydroxyoctadec-9-enoic acid
Arachidonic	$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_3\cdot CO_2H$	Eicosa-5 : 8 : 11 : 14-tetraenoic acid
Erucic *	$CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot[CH_2]_{11}\cdot CO_2H$	Docos-13-enoic acid

* Elaidic, linelaidic, and brassidic acids are the *trans*-isomers of the naturally occurring *cis*-acids.

1. Synthesis of Saturated Fatty Acids

Methods of synthesising saturated acids may be divided into three groups depending on whether the reaction leaves the chain length unchanged, or whether there is chain extension or chain degradation.

Methods involving no Change in Chain Length.—Saturated fatty acids are often prepared from closely related compounds possessing the required carbon chain. Included under this head are reduction of the unsaturated acids and oxidation of alcohols and aldehydes. These are general methods, applicable to a wide range of compounds but limited, for practical purposes, to starting materials either more readily accessible, or available in a purer condition, than is the saturated acid.

Hydrogenation of unsaturated acids. Since it is sometimes possible to prepare unsaturated acids free from lower or higher homologues this method had been used to prepare pure saturated acids, especially undecanoic, stearic, and behenic acids, from one or other of their unsaturated analogues. Catalytic reduction is preferred though chemical methods have been used.

Oxidation of alcohols and aldehydes. Because of the proviso already stated concerning the relative availability of alcohols, aldehydes, and acids this method has been used mainly for the preparation of heptanoic acid (from heptaldehyde obtained by pyrolysis of ricinoleic acid) and the higher members of the series (above C_{25}). There has been much confusion among the higher, naturally occurring alcohols. The alcohols, and consequently the resulting acids also, have often been homologous mixtures, whilst, sometimes, wrong formulæ have been assigned to both alcohol and acid. Piper, Chibnall, and Williams [6] in a summarising paper describe the C_{26}, C_{28}, and C_{30} acids obtained by oxidation of the corresponding alcohols.

Production of fatty acids from hydrocarbons. Attempts to convert hydrocarbons into acids by oxidation or by interaction with carbon monoxide have yielded mixtures of acids used directly for the production of soap or edible fat. These processes are not designed primarily for the production of individual acids though they may become more important in this connection. Useful summaries are given by Markley [7] and in the *Annual Reports on the Progress of Applied Chemistry*.[8]

Methods involving Chain Extension.—These methods may be further

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[6] Piper, Chibnall, and Williams, *Biochem. J.*, 1934, **28**, 2175.

[7] Ref. 2, pp. 540—547.

[8] *Ann. Reports Progr. of Applied Chem.*, 1950, **35**, 239; 1951, **36**, 119.

divided according to the number of carbon atoms added to the starting material.

Reactions resulting in the addition of one carbon atom. Of the standard procedures used for increasing the length of a carbon chain by one unit that involving the reaction sequence given below has been used most extensively :

$$R{\cdot}CO_2H \longrightarrow R{\cdot}CO_2R' \longrightarrow R{\cdot}CH_2{\cdot}OH \longrightarrow R{\cdot}CH_2X \longrightarrow R{\cdot}CH_2{\cdot}CN \longrightarrow R{\cdot}CH_2{\cdot}CO_2H$$

The starting material is generally a naturally occurring acid or (less frequently) alcohol and, since these contain an even number of carbon atoms, the acids so obtained are mainly those containing an odd number of carbon atoms. The starting material must be pure if pure products are to result : indeed the main difficulty in these reactions is the separation of the products from impurities with very similar physical properties. For this reason pure stearic and behenic acid, obtained by the reduction of oleic and erucic acid, are useful starting materials. Many steps are involved but yields are good and pure products are claimed given the above safeguard. Almost every acid in the series between C_{17} and C_{35} has been prepared in this way.[6, 9, 10]

Other methods of increasing chain length by one unit which have been used include the Arndt–Eistert reaction [11] and carboxylation of the Grignard reagent. Isotopically labelled acids have been prepared by the latter method.[12]

Reactions resulting in the addition of two carbon atoms. By using malonic ester it is possible to add two carbon atoms to the appropriate alkyl halide and this method has been used mainly to prepare the higher acids containing an even number of carbon atoms. Stearic and behenic acids are again the most important starting materials. The procedure is described by Bleyberg and Ulrich [13] and by Francis *et al.*,[10, 14, 15] who have prepared most of the acids between C_{20} and C_{38}.

Reactions resulting in the addition of several carbon atoms. Some standard condensation reactions have been successfully applied to the preparation of saturated acids. These methods, being mainly of recent description, have been developed largely for other reasons, such as the preparation of branched-chain acids or of keto-acids, but appropriate modifications lead to the normal saturated acids.

(a) *The use of acetoacetic ester as a coupling unit.* In 1925 Robinson and Robinson [16] described a method of preparing long-chain keto-acids involving

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[9] Levene and Taylor, *J. Biol. Chem.*, 1924, **59,** 905.

[10] Francis, Piper, and Malkin, *Proc. Roy. Soc.*, 1930, *A*, **128,** 214.

[11] Proštenik, *Arkiv Kemi*, 1946, **18,** 1 ; Vandenheuvel and Yates, *Canad. J. Res.*, 1950, **28,** *B*, 556.

[12] Harwood and Ralston, *J. Org. Chem.*, 1947, **12,** 740 ; Dauben, *J. Amer. Chem. Soc.*, 1948, **70,** 1376.

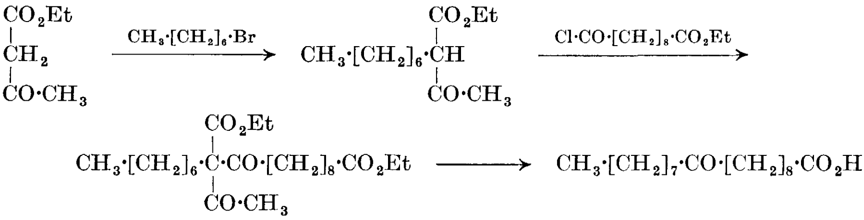
[13] Bleyberg and Ulrich, *Ber.*, 1931, **64,** 2504.

[14] Francis, King, and Willis, *J.*, 1937, 999.

[15] Francis, Collins, and Piper, *Proc. Roy. Soc.*, 1937, *A*, **158,** 691.

[16] G. M. Robinson and R. Robinson, *J.*, 1925, **127,** 175 ; 1926, 2204.

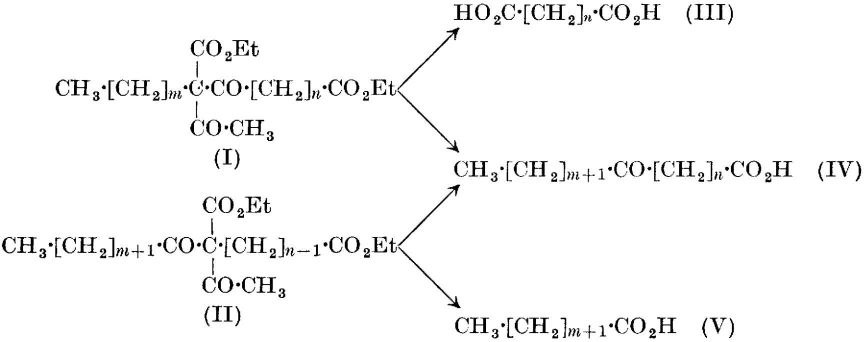
condensation of (i) an alkyl halide and (ii) a carbethoxy-acyl halide with acetoacetic ester. Subsequent stepwise hydrolysis afforded a keto-acid



$$\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{CH_2}\\|\\\mathrm{CO{\cdot}CH_3}\end{array} \xrightarrow{\mathrm{CH_3{\cdot}[CH_2]_6{\cdot}Br}} \mathrm{CH_3{\cdot}[CH_2]_6{\cdot}}\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{CH}\\|\\\mathrm{CO{\cdot}CH_3}\end{array} \xrightarrow{\mathrm{Cl{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2Et}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_6{\cdot}}\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{C}\\|\\\mathrm{CO{\cdot}CH_3}\end{array}\mathrm{{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2Et} \longrightarrow \mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CO{\cdot}[CH_2]_8{\cdot}CO_2H}$$

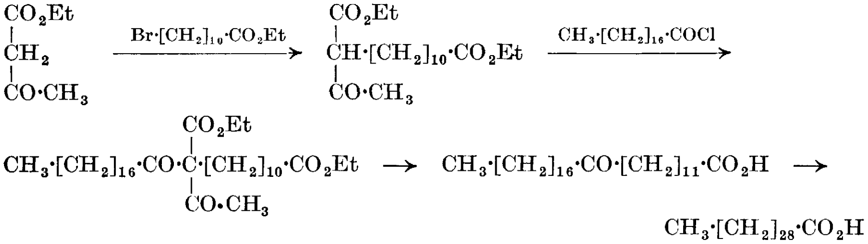
which could be reduced by the Clemmensen procedure. Later one of these authors[17] drew attention to the rather low yields obtained. The main product appears to be a dibasic acid (III), produced by the alternative hydrolysis of the condensation production (I). Other work on the hydrolysis of diketones of the type $\mathrm{R{\cdot}CO{\cdot}CH_2{\cdot}COR'}$ shows that the stronger acid preponderates. The desired keto-acid (IV) may result from either (I) or



$$\underset{\text{(I)}}{\mathrm{CH_3{\cdot}[CH_2]_{\mathit{m}}{\cdot}}\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{C}\\|\\\mathrm{CO{\cdot}CH_3}\end{array}\mathrm{{\cdot}CO{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2Et}} \begin{array}{l}\nearrow\ \mathrm{HO_2C{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2H}\quad\text{(III)}\\ \searrow\ \mathrm{CH_3{\cdot}[CH_2]_{\mathit{m}+1}{\cdot}CO{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2H}\quad\text{(IV)}\end{array}$$

$$\underset{\text{(II)}}{\mathrm{CH_3{\cdot}[CH_2]_{\mathit{m}+1}{\cdot}CO{\cdot}}\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{C}\\|\\\mathrm{CO{\cdot}CH_3}\end{array}\mathrm{{\cdot}[CH_2]_{\mathit{n}-1}{\cdot}CO_2Et}} \begin{array}{l}\nearrow\ \mathrm{CH_3{\cdot}[CH_2]_{\mathit{m}+1}{\cdot}CO{\cdot}[CH_2]_{\mathit{n}}{\cdot}CO_2H}\quad\text{(IV)}\\ \searrow\ \mathrm{CH_3{\cdot}[CH_2]_{\mathit{m}+1}{\cdot}CO_2H}\quad\text{(V)}\end{array}$$

(II), and since (III) is a stronger acid than (V) it was conceived that (II) might give a better yield of the acid (IV). This was confirmed in practice and the improved procedure has been used for the preparation of several



$$\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{CH_2}\\|\\\mathrm{CO{\cdot}CH_3}\end{array} \xrightarrow{\mathrm{Br{\cdot}[CH_2]_{10}{\cdot}CO_2Et}} \begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{CH}\\|\\\mathrm{CO{\cdot}CH_3}\end{array}\mathrm{{\cdot}[CH_2]_{10}{\cdot}CO_2Et} \xrightarrow{\mathrm{CH_3{\cdot}[CH_2]_{16}{\cdot}COCl}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_{16}{\cdot}CO{\cdot}}\begin{array}{c}\mathrm{CO_2Et}\\|\\\mathrm{C}\\|\\\mathrm{CO{\cdot}CH_3}\end{array}\mathrm{{\cdot}[CH_2]_{10}{\cdot}CO_2Et} \longrightarrow \mathrm{CH_3{\cdot}[CH_2]_{16}{\cdot}CO{\cdot}[CH_2]_{11}{\cdot}CO_2H} \longrightarrow \mathrm{CH_3{\cdot}[CH_2]_{28}{\cdot}CO_2H}$$

acids.[14, 18] The method is limited only by the availability of the ω-bromo-esters; the C_{10} and C_{11} compounds were, however, accessible when this work was described, thus permitting the addition of eleven or twelve carbon atoms in one cycle of reactions.

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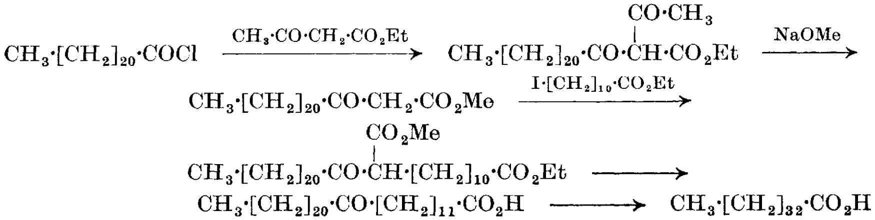
[17] G. M. Robinson, *J.*, 1930, 745.

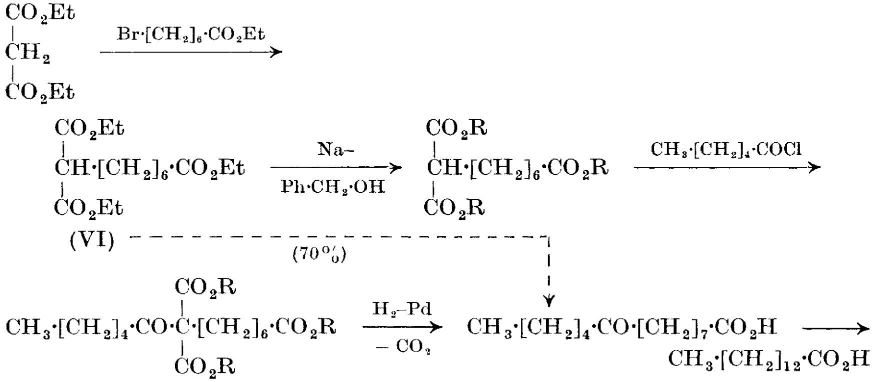
[18] *Idem*, *J.*, 1934, 1543; Ashton, Robinson, and Smith, *J.*, 1936, 283.

Ställberg-Stenhagen, Stenhagen, *et al.* have developed an improved modification of this reaction by which they have synthesised many normal and branched-chain acids. The preparation of tetratriacontanoic acid is illustrative.[19]

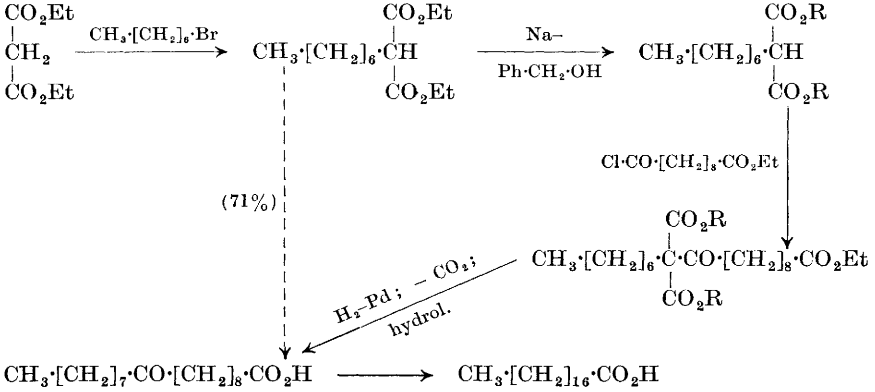


$$CH_3\cdot[CH_2]_{20}\cdot COCl \xrightarrow{CH_3\cdot CO\cdot CH_2\cdot CO_2Et} CH_3\cdot[CH_2]_{20}\cdot CO\cdot\overset{\overset{CO\cdot CH_3}{|}}{C}H\cdot CO_2Et \xrightarrow{NaOMe}$$
$$CH_3\cdot[CH_2]_{20}\cdot CO\cdot CH_2\cdot CO_2Me \xrightarrow{I\cdot[CH_2]_{10}\cdot CO_2Et}$$
$$CH_3\cdot[CH_2]_{20}\cdot CO\cdot\overset{\overset{CO_2Me}{|}}{C}H\cdot[CH_2]_{10}\cdot CO_2Et \longrightarrow$$
$$CH_3\cdot[CH_2]_{20}\cdot CO\cdot[CH_2]_{11}\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_{32}\cdot CO_2H$$

(b) *The use of malonic ester as a coupling unit.* Bowman and his colleagues[20] have recently described methods, similar to those of Robinson, but using malonic ester as the coupling unit. The novelty of the method is in the



$$\begin{matrix}CO_2Et\\|\\CH_2\\|\\CO_2Et\end{matrix} \xrightarrow{Br\cdot[CH_2]_6\cdot CO_2Et}$$
$$\underset{(VI)}{\begin{matrix}CO_2Et\\|\\CH\cdot[CH_2]_6\cdot CO_2Et\\|\\CO_2Et\end{matrix}} \xrightarrow[Ph\cdot CH_2\cdot OH]{Na-} \begin{matrix}CO_2R\\|\\CH\cdot[CH_2]_6\cdot CO_2R\\|\\CO_2R\end{matrix} \xrightarrow{CH_3\cdot[CH_2]_4\cdot COCl}$$
$$(VI) \dashrightarrow^{(70\%)} CH_3\cdot[CH_2]_4\cdot CO\cdot[CH_2]_7\cdot CO_2H$$
$$CH_3\cdot[CH_2]_4\cdot CO\cdot\begin{matrix}CO_2R\\|\\C\\|\\CO_2R\end{matrix}\cdot[CH_2]_6\cdot CO_2R \xrightarrow[-\ CO_2]{H_2-Pd} CH_3\cdot[CH_2]_4\cdot CO\cdot[CH_2]_7\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_{12}\cdot CO_2H$$



$$\begin{matrix}CO_2Et\\|\\CH_2\\|\\CO_2Et\end{matrix} \xrightarrow{CH_3\cdot[CH_2]_6\cdot Br} CH_3\cdot[CH_2]_6\cdot\begin{matrix}CO_2Et\\|\\CH\\|\\CO_2Et\end{matrix} \xrightarrow[Ph\cdot CH_2\cdot OH]{Na-} CH_3\cdot[CH_2]_6\cdot\begin{matrix}CO_2R\\|\\CH\\|\\CO_2R\end{matrix}$$
$$\xrightarrow{Cl\cdot CO\cdot[CH_2]_8\cdot CO_2Et} CH_3\cdot[CH_2]_6\cdot\begin{matrix}CO_2R\\|\\C\\|\\CO_2R\end{matrix}\cdot CO\cdot[CH_2]_8\cdot CO_2Et \xrightarrow[hydrol.]{H_2-Pd;\ -CO_2;}$$
$$CH_3\cdot[CH_2]_6\cdot CH(CO_2Et)_2 \dashrightarrow^{(71\%)} CH_3\cdot[CH_2]_7\cdot CO\cdot[CH_2]_8\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_{16}\cdot CO_2H$$

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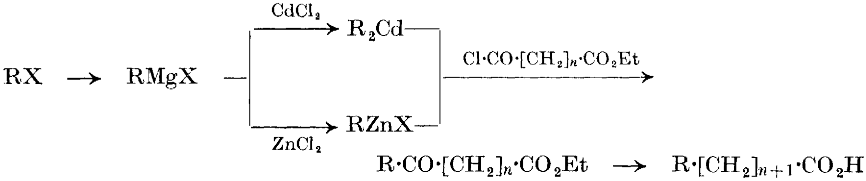
[19] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min., Geol.*, 1945, **19**, *A*, No. 1 (and many later papers by these authors).

[20] Ames, Bowman, and Mason, *J.*, 1950, 174 ; Bowman and Mason, *J.*, 1951, 2748.

use of the benzyl esters, since the benzyl group may be split off by hydrogenation, thus avoiding the hydrolysis by which undesirable by-products are formed. The benzyl esters are prepared from the ethyl esters by trans-esterification. Yields are high and the desired intermediates are readily prepared. The reaction may be carried out in two ways (see reaction chart). In addition to these acids (C_{14} and C_{18}) the C_{23}, C_{39}, and C_{56} acids have been prepared. The preparation of ω-bromoheptanoic acid from tetrahydropyran (60%) is described, also an alternative preparation of triesters of type (VI).

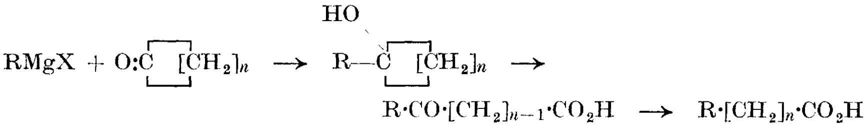
(c) *The use of organo-metallic compounds.* Fatty acids result, *via* the keto-esters, from interaction of a carbethoxy-acyl halide with an organo-metallic compound, generally a zinc or cadmium compound. These methods, which have found extensive use in the preparation of branched-chain compounds,[21] are summarised thus :



$$RX \rightarrow RMgX \begin{cases} \xrightarrow{CdCl_2} R_2Cd \\ \xrightarrow[ZnCl_2]{} RZnX \end{cases} \xrightarrow{Cl\cdot CO\cdot[CH_2]_n\cdot CO_2Et} R\cdot CO\cdot[CH_2]_n\cdot CO_2Et \rightarrow R\cdot[CH_2]_{n+1}\cdot CO_2H$$

The C_{26}—C_{35} straight-chain acids have been prepared in this way.[22]

Interaction of a Grignard compound with an aldehydo-ester affords a hydroxy-ester. This reaction has been used mainly to prepare unsaturated acids (see below), but Fieser *et al.*[23] have indicated how saturated acids result from alicyclic ketones.



$$RMgX + O{:}C\,[CH_2]_n \rightarrow R{-}\overset{HO}{C}\,[CH_2]_n \rightarrow R\cdot CO\cdot[CH_2]_{n-1}\cdot CO_2H \rightarrow R\cdot[CH_2]_n\cdot CO_2H$$

The method was illustrated by the description of the C_{20}, C_{22}, C_{24}, and C_{26} acids and has since been used for the preparation of some *anteiso*-acids.[24]

(d) *Anodic syntheses.* The Kolbe electrolytic synthesis has recently been adapted for the production of saturated fatty acids. A discussion of this method is included in a recent review.[25]

(e) *Other condensations.* Kuhn [26] has reported that acetaldehyde or crotonaldehyde undergoes condensation in presence of piperidine acetate, yielding polyene-aldehydes, $R\cdot[CH{:}CH\cdot]_n\cdot CHO$. These may be reduced to saturated alcohols and then oxidised to the acids, or condensed with malonic acid before hydrogenation.

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[21] Cason, Taylor, and Williams, *J. Org. Chem.*, 1951, **16,** 1187, and earlier papers in this series.

[22] Drake and Melamed, *J. Amer. Chem. Soc.*, 1948, **70,** 364 ; Jones, *ibid.*, 1947, **69,** 2350 ; Schuette, Roth, and Christenson, *Oil and Soap*, 1945, **22,** 107 ; Schuette, Maylott, and Roth, *J. Amer. Oil Chem. Soc.*, 1948, **25,** 64.

[23] Fieser and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1948, **70,** 3352.

[24] Nunn, *J.*, 1951, 1740.

[25] Weedon, *Quart. Reviews*, 1952, **6,** 390.

[26] Kuhn, *J.*, 1938, 605.

A method of extending chain length by six carbon atoms, involving *C*-alkylation of *cyclo*hexane-1 : 3-dione and subsequent hydrolysis and reduction, has recently been reported.[27]

Methods involving Chain Degradation.—There are many ways of degrading saturated or unsaturated acids to lower homologues. Although most of these have been designed for determination of structure, where yields are high and starting materials readily available, they have also been used as preparative methods.

Degradation of saturated acids. An early method of degradation, due to Krafft,[28] involves oxidation of the methyl ketone which results from heating the barium salt of the acid with barium acetate :

$$\mathrm{R{\cdot}CH_2{\cdot}CO_2Ba_{\frac{1}{2}}} \xrightarrow{\mathrm{Ba(OAc)_2}} \mathrm{R{\cdot}CH_2{\cdot}CO{\cdot}CH_3} \longrightarrow \mathrm{R{\cdot}CO_2H}$$

The modification of the Hofmann reaction in which an amide is converted into a nitrile containing one less carbon atom has yielded several acids.[29]

Another method involves decomposition of the α-hydroxy-acid by heat and subsequent oxidation or by direct oxidation : [30]

$$\begin{tikzcd}
& \mathrm{R{\cdot}CHO} \arrow[dr, "\mathrm{Ag_2O}"] & \\
\mathrm{R{\cdot}CH(OH){\cdot}CO_2H} \arrow[ur, "\mathrm{Heat}"] \arrow[rr, "\mathrm{KMnO_4\ or\ Pb(OAc)_4}"'] & & \mathrm{R{\cdot}CO_2H}
\end{tikzcd}$$

Degradation of unsaturated acids. Degradation of unsaturated acids is achieved by alkali fusion or by oxidation.

Unsaturated acids, whether naturally occurring or prepared from saturated acids by bromination and subsequent dehydrobromination, yield the saturated acid with two fewer carbon atoms when fused with potassium hydroxide. When the double bond is not in the αβ-position, migration to this position probably precedes fission. Stearic and erucic acids have long been known to give palmitic [31] and eicosanoic acid [32] respectively by this means. Farmer [33] states that under appropriate conditions oleic acid affords isomeric octadecenoic acids. Hunter and Popjak [34] have described optimum conditions for the degradation of the αβ-unsaturated acid.

Of the many oxidation procedures designed for fission of unsaturated acids the most satisfactory method, particularly from the preparative viewpoint, is oxidation by potassium permanganate in acetone or acetic acid solution.[35, 36]

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[27] Stetter and Dierichs, *Chem. Ber.*, 1952, **85**, 61, 290, 1061.

[28] Krafft, *Ber.*, 1879, **12**, 1664, 1668 ; 1882, **15**, 1687.

[29] Hofmann, *Ber.*, 1884, **17**, 1406 ; Lutz, *Ber.*, 1886, **19**, 1433 ; Wallis and Lane, *Org. Reactions*, **3**, 267.

[30] Levene and West, *J Biol. Chem.*, 1914, **16**, 475 ; Mendel and Coops, *Rec. Trav. chim.*, 1939, **58**, 1133.

[31] Varrentrapp, *Annalen*, 1840, **35**, 196.

[32] Fitz, *Ber.*, 1871, **4**, 442 ; Morgan and Bowen, *J. Soc. Chem. Ind.*, 1924, **43**, 346T.

[33] Farmer, *Trans. Faraday Soc.*, 1942, **38**, 356 ; cf. Egorov, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 975.

[34] Hunter and Popjak, *Biochem. J.*, 1951, **50**, 163.

[35] Armstrong and Hilditch, *J. Soc. Chem. Ind.*, 1925, **44**, 43T.

[36] Begemann, Keppler, and Boekenoogen, *Rec. Trav. chim.*, 1950, **69**, 439.

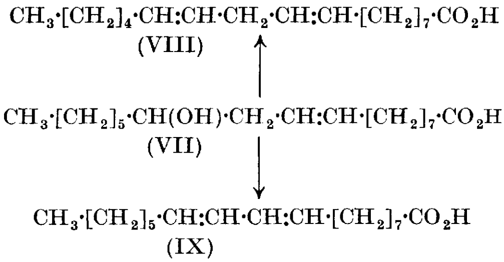
2. Synthesis of Unsaturated Fatty Acids

Unsaturated fatty acids have been prepared by various procedures which fall into two main groups. Included in the first are those methods in which some naturally occurring acid, or other readily accessible and closely related compound, is modified to give an unsaturated acid. The second group contains those methods of condensation by which long-chain unsaturated acids may be synthesised.

Modification of Other Fatty Acids.—This group is conveniently subdivided into three sections depending on whether there is an increase, a decrease, or no change in the degree of unsaturation.

Methods resulting in an increase in the degree of unsaturation. (a) *Dehydration of hydroxy-compounds.* This method has found commercial application in the production of a drying oil from castor oil, which contains a high proportion of ricinoleic acid. For the formation of individual acids this procedure suffers from the fact that dehydration may afford two isomers and from the limited availability of hydroxy-acids.

12-Hydroxyoleic and -stearic acids are the most readily available hydroxy-acids. Dehydration of 12-hydroxystearic acid with a variety of dehydrating agents yields a mixture of 11 : 12- and 12 : 13-unsaturated acids.[36, 37] Dehydration of ricinoleic acid (VII) or its glyceride affords octadecadienoic acids (VIII and IX) or glycerides. Dehydration is effected by heating it with various catalysts, and the more unsaturated product has enhanced drying properties.[38] The claim [39] that the conjugated acid (IX) is the main product has not been upheld.[40] The octadeca-*trans*-9 : *trans*-11-,[41–45] -*cis*-9 : *trans*-11-,[45] and -*cis*-9 : *trans*-12-dienoic acids have been isolated from dehydrated ricinoleic acid. Another acid, isolated by



$$\begin{tikzcd} CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H \ \text{(VIII)} \\ CH_3\cdot[CH_2]_5\cdot CH(OH)\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H \ \text{(VII)} \arrow[u] \arrow[d] \\ CH_3\cdot[CH_2]_5\cdot CH{:}CH\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H \ \text{(IX)} \end{tikzcd}$$

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[37] Fokin, *J. Russ. Phys. Chem. Soc.*, 1914, **46,** 1027 ; Grün and Czerny, *Ber.*, 1926, **59,** 54.

[38] Forbes and Neville, *Ind. Eng. Chem.*, 1940, **32,** 555.

[39] Böeseken and Hoevers, *Rec. Trav. chim.*, 1930, **49,** 1165.

[40] Priest and von Mikusch, *Ind. Eng. Chem.*, 1940, **32,** 1314.

[41] Mangold, *Monatsh.*, 1894, **15,** 307.

[42] Böeseken and Hoevers, *Rec. Trav. chim.*, 1930, **49,** 1161.

[43] Smit, *ibid.*, p. 539.

[44] Nichols, Herb, and Riemenschneider, *J. Amer. Chem. Soc.*, 1951, **73,** 247.

[45] Jackson, Paschke, Tolberg, Boyd, and Wheeler, *J. Amer. Oil Chem. Soc.*, 1952, **29,** 229.

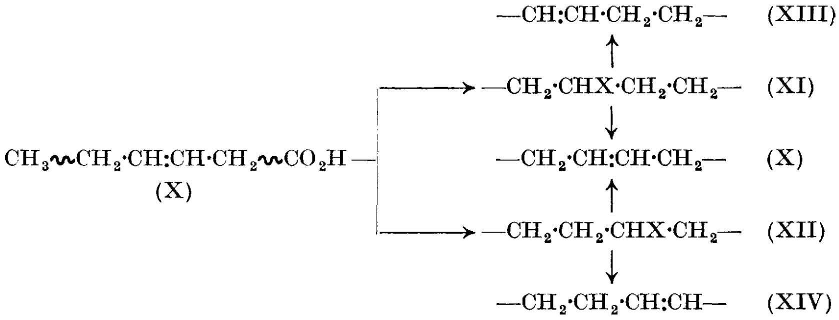
Smit,[43] has been shown to be the *trans*-8 : *trans*-10-isomer.[46] The dehydration reaction is obviously more complex than was at first realised.

(b) *Dehydrohalogenation of halogeno-compounds.* The commonest method of introducing an unsaturated linkage involves dehydrohalogenation of a halogeno-compound. This reaction is generally effected by treatment with alkali or a nitrogenous base (diethylaniline, quinoline, or collidine). Alkali, although used extensively, has the disadvantage that the product may be accompanied by some hydroxy-acid and by isomeric unsaturated acids resulting from double-bond migration. The halogenated acids may be produced in four ways : (i) bromination by phosphorus and bromine, giving the α-bromo-acid, (ii) conversion of some functional group already present (*e.g.*, hydroxyl) into a halogen substituent, (iii) interaction of a double bond with HX or X_2 (X = halogen), and (iv) allylic bromination of unsaturated acids by *N*-bromosuccinimide.

Method (i) has been widely used for the preparation of αβ-unsaturated acids. Optimum yields are claimed for dehydrobromination of the *neo*-pentyl α-bromo-ester with diethylaniline.[34] Method (ii) is limited to the use of ricinoleic and 12-hydroxy-stearic acid and is of little importance.

$$—CH_2{\cdot}CH_2{\cdot}CO_2R \longrightarrow —CH_2{\cdot}CHX{\cdot}CO_2R \longrightarrow —CH{:}CH{\cdot}CO_2R$$

Unsaturated acids yield isomeric acids by hydrohalogenation and subsequent dehydrohalogenation. On a purely random basis such a reaction would lead to three products (XIII, X, and XIV), though, in practice, one isomer may predominate and be isolatable. Factors affecting the product of this reaction include the position of the carboxyl group and other ethylenic linkages, the degree of substitution of the carbon atoms involved, and the experimental conditions. It has been claimed that (XI) and (XIII) are the main products and several octadecenoic acids have been prepared in this way.[47]



$$\begin{tikzcd}[column sep=small] & —CH{:}CH{\cdot}CH_2{\cdot}CH_2— \text{ (XIII)} \\ & —CH_2{\cdot}CHX{\cdot}CH_2{\cdot}CH_2— \text{ (XI)} \arrow[u] \arrow[d] \\ \underset{\text{(X)}}{CH_3{\sim}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\sim}CO_2H} \arrow[ur] \arrow[dr] & —CH_2{\cdot}CH{:}CH{\cdot}CH_2— \text{ (X)} \\ & —CH_2{\cdot}CH_2{\cdot}CHX{\cdot}CH_2— \text{ (XII)} \arrow[u] \arrow[d] \\ & —CH_2{\cdot}CH_2{\cdot}CH{:}CH— \text{ (XIV)} \end{tikzcd}$$

The reaction of *N*-bromosuccinimide with several unsaturated acids or esters has been examined. Schmid and Lehmann[48] brominated methyl

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[46] von Mikusch, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 114.

[47] Eckert and Halla, *Monatsh.*, 1913, **34**, 1815 ; Pigulevskiĭ and Simonova, *J. Gen. Chem., U.S.S.R.*, 1939, **9**, 1928 ; Vanin and Chernoyarova, *ibid.*, 1935, **5**, 1537 ; cf. Arnaud and Posternak, *Compt. rend.*, 1910, **150**, 1525.

[48] Schmid and Lehmann, *Helv. Chim. Acta*, 1950, **33**, 1494.

elaidate and methyl brassidate in the allylic position and, after dehydrobromination, isolated octadeca-9 : 11-dienoic and docosa-13 : 15-dienoic acids. As the properties of the former differ from those of the known octadeca-*trans*-9 : *trans*-11-dienoic acid confirmation of these results is desirable. Methyl undeca-8 : 10-dienoate has been similarly prepared from methyl undec-10-enoate.[49] Allylic bromination of methyl linoleate has also been studied.[50]

Dehydrohalogenation of a saturated dihalogeno-acid has been widely used for the preparation of acetylenic acids from the corresponding ethylene

$$\text{—CH:CH—} \rightarrow \text{—CHX·CHX—} \rightarrow \text{—C⋮C—}$$

compounds *via* the dihalogen acid.[51] The dehydrohalogenating agent is generally potassium hydroxide in aqueous or alcoholic solution though sodamide in liquid ammonia has been used. Johnson [52] states that this method cannot be used to prepare 2-ynoic acids.

Methods resulting in a decrease in the degree of unsaturation. Unsaturated acids may be prepared by partial reduction of more unsaturated compounds which are readily accessible. Partial reduction of polyethenoid acids, however, generally yields a complex mixture of isomers, for, in addition to the fact that different ethylenic bonds may become saturated, *cis-trans*-isomerism and double-bond migration occur simultaneously ; it is not surprising, therefore, that only a few individual compounds have been isolated.

Partial hydrogenation of sorbic acid gives hex-3-enoic acid as the main product, accompanied by appreciable quantities of hex-4-enoic acid.[53] Linoleic acid is reported to give both octadec-9- and -12-enoic acids, whilst linolenic acid yields first diethenoid and then monoethenoid acids : one diethenoid acid (*iso*linoleic) has been isolated.[54] Elaeostearic acid is readily hydrogenated yielding *trans*-octadec-11-enoic acid as the main product.[36, 55] Arachidonic acid is reported to give eicosa-5 : 14- and -8 : 14-dienoic acids (80—90%, 5–10% respectively) when partially hydrogenated.[56] The hydrogenation of methyl parinarate (methyl octadeca-9 : 11 : 13 : 15-tetraenoate) has also been studied.[57]

In contrast to these reactions, which are of little value for preparative purposes, though of considerable interest from other viewpoints, the partial hydrogenation of acetylenic acids is of great synthetic importance.[58] The value of this reaction is enhanced by the fact that the resulting ethylenic acids are essentially *cis* or *trans* depending on whether the reduction is

[49] Haskelburg, *J. Amer. Chem. Soc.*, 1951, **73,** 4035.

[50] Teeter, *J. Amer. Oil Chem. Soc.*, 1948, **25,** 243 ; Sutton and Dutta, *J.*, 1949, 939 ; Bergström and Hansson, *Acta Chem. Scand.*, 1950, **4,** 435.

[51] Ref. 4, pp. 4—12.

[52] Ref. 4, p. 4.

[53] Letch and Linstead, *J.*, 1934, 1994.

[54] Lemon, *Canad. J. Res.*, 1944, **22,** *F*, 191 ; 1949, **27,** *B*, 605 ; Lemon and Cross, *ibid.*, p. 610 ; Rebello and Daubert, *J. Amer. Oil Chem. Soc.*, 1951, **28,** 177, 183.

[55] Hilditch and Pathak, *Proc. Roy. Soc.*, 1949, *A*, **198,** 323 ; Woltemate and Daubert, *J. Amer. Chem. Soc.*, 1950, **72,** 1233.

[56] Mowry, Brode, and Brown, *J. Biol. Chem.*, 1941, **142,** 679.

[57] Riley, *J.*, 1951, 2579.

[58] Ref. 4, pp. 41—46.

effected catalytically or by chemical means.[59] The favoured catalyst is palladium, though platinum and nickel have been used, whilst chemical methods include the use of zinc and acetic acid, metals and alkalis, or reduction of the halogen halide mono-addition product. Many acids have been prepared by these methods from acetylenic precursors and some examples will be given later. Dideutero-oleic acid results from catalytic deuteration of stearolic acid.[60]

Methods involving no change in the degree of unsaturation. (a) *Elaidinisation.* Unsaturated fatty acids can exist in *cis*- and *trans*-forms and since many naturally occurring acids have the *cis*-structure it is possible to convert these into their more stable *trans*-isomers. This change has been most fully studied in the case of oleic acid, which is converted into elaidic acid ; [61] the latter name has given rise to the term elaidinisation for the *cis* ⟶ *trans* change. The process is an equilibrium reaction and both oleic and elaidic acid yield the same isomeric mixture (containing *ca.* 67% of the *trans*-form). Mixtures of similar composition result from other mono-ethenoid acids. The reagents most frequently used include the nitrogen oxides, sulphur, selenium, and iodine and/or ultra-violet light. Elaidinisation is also known to occur under conditions of hydrogenation and during autoxidation [62] and thermal polymerisation.[63]

By using the reagents listed above, various unsaturated acids have been converted into their *trans*-isomers. For non-conjugated polyethenoid acids it is considered that all the ethylenic linkages have been converted into the *trans*-configuration.[64] Acids containing conjugated double bonds isomerise more readily, generally under the influence of light and/or traces of iodine.

trans-Octadec-2-enoic acid has been changed into its *cis*-isomer by a series of chemical reactions,[65] and the interconversion of *cis*- and *trans*-undec-9-enoic acid has been described.[66]

(b) *Double-bond migration.* The double bond(s) present in an unsaturated fatty acid may migrate under certain conditions. Thus it is possible to convert the system (XV), present in many naturally occurring acids,

$$\text{(XV)}\quad \text{—CH:CH·CH}_2\text{·CH:CH—} \longrightarrow \text{—CH:CH·CH:CH·CH}_2\text{—}\quad \text{(XVI)}$$

into the conjugated system (XVI) which is readily identified by its characteristic ultra-violet absorption. This is the basis of a quantitative method of determining the presence of acids containing the system (XV).[67] This migration, which may be accompanied by elaidinisation, is usually

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[59] Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 145 ; Crombie, *Quart. Reviews*, 1952, **6**, 128.

[60] Khan, Deatherage, and Brown, *J. Amer. Oil Chem. Soc.*, 1951, **28**, 27.

[61] Griffiths and Hilditch, *J.*, 1932, 2315.

[62] Knight, Eddy, and Swern, *J. Amer. Oil Chem. Soc.*, 1951, **28**, 188.

[63] Paschke, Jackson, and Wheeler, *Ind. Eng. Chem.*, 1952, **44**, 1113.

[64] Cf. Kass and Burr, *J. Amer. Chem. Soc.*, 1939, **61**, 1062.

[65] Myers, *ibid.*, 1951, **73**, 2100.

[66] Ames and Bowman, *J.*, 1952, 677.

[67] Mitchell, Kraybill, and Zscheile, *Ind. Eng. Chem., Anal.*, 1943, **15**, 1 ; Hilditch, Morton, and Riley, *Analyst*, 1945, **70**, 67.

effected by alkali at high temperatures (up to 200°) though it also occurs under conditions of hydrogenation and autoxidation.

Hex-2- and -3-enoic acid form an equilibrium mixture, produced from either isomer by sodium ethoxide, and containing *ca.* 90% of the 2-enoic acid.[68] Undec-10-ynoic acid isomerises to undec-9-ynoic acid under strongly alkaline conditions, so that the latter is often isolated in attempts to prepare the 10-isomer from 10 : 11-dibromoundecanoic acid. Fusion of oleic acid with potassium hydroxide yields palmitic acid, migration of the double bond to the $\alpha\beta$-position preceding fission.

Moore [69] has reported that prolonged hydrolysis of unsaturated fats leads to isomerisation of linoleic and linolenic acids to conjugated forms. From linseed oil (containing over 60% of linolenic acid) he isolated a solid acid which has been shown to be octadeca-*trans*-10 : *cis*-12 : *trans*-14-trienoic acid.[44, 70] Isomerisation of dehydrated castor oil acids yields a solid mixture from which an individual acid, considered to be octadeca-*trans*-10 : *trans*-12-dienoic acid,[71] can be isolated. In an interesting paper Riemenschneider and his co-workers [44, see also 45] isolated two acids, from alkali-isomerised linoleic acid, which they believe to be the *trans*-10 : *cis*-12- and the *cis*-9 : *trans*-11-isomer. When treated with iodine these acids elaidinise to the known wholly *trans*-isomers. The authors assume that the double bond which does not shift retains its configuration and suggest that when the migrating bond was *trans* the new bond is either *cis* or *trans* whilst if it was *cis* the new bond is predominantly *trans*. Arachidonic acid isomerises to a mixture from which a solid acid with four conjugated double bonds has been isolated.[72]

Other methods of preparing unsaturated acids. Unsaturated acids have also been prepared from more readily accessible compounds by methods of chain extension and degradation. By the nitrile method undec-10-enoic acid has been converted into dodec-11-enoic acid,[73] and linoleic acid, by successive applications of the Arndt–Eistert procedure, has yielded nonadeca-10 : 13-dienoic and eicosa-11 : 14-dienoic acids.[74] Barbier–Wieland degradation of oleic acid affords heptadec-8-enoic and hexadec-7-enoic acids,[75] but erucic acid is reported to give a glycol of the expected C_{21} acid.[76] The preparation of undec-10-enoic acid by pyrolysis of castor oil is now carried out on an industrial scale.[77]

Electrolysis of compounds such as $KO_2C{\cdot}[CH_2]_n{\cdot}CO_2R$ gives, in addition to the main product $RO_2C{\cdot}[CH_2]_{2n}{\cdot}CO_2R$, an unsaturated ester of the type

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[68] Kon, Linstead, and Maclennan, *J.*, 1932, 2454.

[69] Moore, *Biochem. J.*, 1937, **31**, 141.

[70] Kass and Burr, *J. Amer. Chem. Soc.*, 1939, **61**, 3292.

[71] von Mikusch, *ibid.*, 1942, **64**, 1580.

[72] Mowry, Brode, and Brown, *J. Biol. Chem.*, 1941, **142**, 671.

[73] Tomecko and Adams, *J. Amer. Chem. Soc.*, 1927, **49**, 522; Chuit, Boelsing, Hausser, and Malet, *Helv. Chim. Acta*, 1927, **10**, 113.

[74] Karrer and Koenig, *ibid.*, 1943, **26**, 619.

[75] Mitter and Bagchi, *J. Indian Chem. Soc.*, 1941, **18**, 461.

[76] Buu-Hoï and Janicaud, *Bull. Soc. chim.*, 1946, **13**, 147.

[77] Krafft, *Ber.*, 1877, **10**, 2034; Vernon and Ross, *J. Amer. Chem. Soc.*, 1936, **58**, 2430; Barbot, *Ann. Chim.*, 1939, **11**, 519.

$CH_2{:}CH{\cdot}[CH_2]_{n-2}{\cdot}CO_2R$. Several such acids have been prepared in this way.[78] Unsaturated acids with the double bond in this position have also been prepared from the ω-hydroxy-ester by pyrolysis of the palmitoyl ester.[79]

Condensation Reactions.—Several condensation reactions have been utilised in the preparation of unsaturated fatty acids. In some the double bond is formed at the point of condensation ; in others the double bond, or some suitable precursor, is present in one of the reacting components. It is in this section that most advance has been made in recent years.

Malonic acid and malonic ester condensations. The use of malonic ester to extend chain length by two carbon atoms has already been discussed as a means of preparing saturated acids. It has also been applied, with success, to the preparation of several unsaturated acids.

Another method, frequently used, involves condensation of an aldehyde with malonic acid, generally in the presence of pyridine, to give an $\alpha\beta$-unsaturated acid[80] which is believed to have the *trans*-structure.[81] Sorbic

$$CH_3{\cdot}[CH_2]_n{\cdot}CHO + CH_2(CO_2H)_2 \longrightarrow CH_3{\cdot}[CH_2]_n{\cdot}CH{:}C(CO_2H)_2 \longrightarrow CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CO_2H$$

acid[82] and other polyunsaturated acids, intermediates in the synthesis of herculin and pellitorine,[83–85] have also been prepared by this means. When dimethylaniline or triethanolamine replaces pyridine the $\beta\gamma$-acid results.[86]

Condensations involving organo-metallic compounds. The higher unsaturated acids were first synthesised from simpler components by means of the Grignard reaction. In 1934 Noller and Bannerot[87] described the first synthesis of oleic and elaidic acids, the main reaction being condensation of 1 : 2-dibromo-9-chloro-1-methoxynonane (XVII) with octylmagnesium

$$Cl{\cdot}[CH_2]_7{\cdot}CH_2{\cdot}CHO \xrightarrow[\text{(2) MeOH–HBr}]{\text{(1) Br}_2\text{ ;}} \underset{\text{(XVII)}}{Cl{\cdot}[CH_2]_7{\cdot}CHBr{\cdot}CHBr{\cdot}OMe} \xrightarrow{Br{\cdot}Mg{\cdot}[CH_2]_7{\cdot}CH_3}$$

$$\underset{\text{(XVIII)}}{Cl{\cdot}[CH_2]_7{\cdot}CHBr{\cdot}CH(OMe){\cdot}[CH_2]_7{\cdot}CH_3} \xrightarrow[\text{(3) Hydrol.}]{\text{(1) Zn ; (2) NaCN ;}} HO_2C{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CH_3$$

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[78] Crum Brown and Walker, *Annalen*, 1893, **274**, 41 ; Walker and Lumsden, *J.*, 1901, **79**, 1197 ; Carmichael, *J.*, 1922, **121**, 2545 ; Fairweather, *Proc. Roy. Soc. Edinburgh*, 1926, **46**, 71.

[79] Baudart, *Bull. Soc. chim.*, 1946, **13**, 85.

[80] Bachman, *J. Amer. Chem. Soc.*, 1933, **55**, 4279 ; Tulus, *Rev. Fac. Sci. Univ. Istanbul*, 1944, **9**, *A*, 105.

[81] Refs. quoted by Crombie, *J.*, 1952, 2999.

[82] Allen and van Allan, *Org. Synth.*, 1944, **24**, 92.

[83] Crombie, *Chem. and Ind.*, 1952, 1034.

[84] Jacobsen, *J. Amer. Chem. Soc.*, 1950, **72**, 1489.

[85] Crombie, *J.*, 1952, 2997.

[86] Boxer and Linstead, *J.*, 1931, 740 ; Howton and Davies, *J. Org. Chem.*, 1951, **16**, 1405.

[87] Noller and Bannerot, *J. Amer. Chem. Soc.*, 1934, **56**, 1563.

bromide, yielding 8-bromo-1-chloro-9-methoxyheptadecane (XVIII). Removal of the 8 : 9-substituents by treatment with zinc gave a double bond in this position, and the chloride was converted into the acid *via* the nitrile. The final product was a mixture of elaidic and oleic acids. Even this is not a complete synthesis since the chlorononanal was obtained from butyl oleate.

Noller and Girvin [88] later attempted a similar synthesis of linoleic acid by the annexed scheme. The product, obtained in poor yield, gave no tetrabromostearic acid on bromination, though a little tetrahydroxystearic acid was isolated after oxidation, indicating the presence of some linoleic acid.

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}MgBr + CH_2{:}CH{\cdot}CHO} \longrightarrow$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH(OH){\cdot}CH{:}CH_2} \xrightarrow{\mathrm{PBr_3}} \mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CHBr{\cdot}CH{:}CH_2} \rightleftharpoons$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2Br} \xrightarrow[\mathrm{Mg{-}Cl{\cdot}[CH_2]_7{\cdot}CHBr{\cdot}CHBr{\cdot}OMe}]{}$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH(OMe){\cdot}CHBr{\cdot}[CH_2]_7{\cdot}Cl} \xrightarrow[\text{(3) Hydrol.}]{\text{(1) Zn ; (2) NaCN ;}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H}$$

Baudart has also prepared (i) oleic and elaidic acids [89] and (ii) linelaidic acid [90] by a slight modification of this process. The starting material (XIX) for the linelaidic acid preparation was obtained from glutaraldehyde, and the final product yielded a little tetrabromostearic acid identical with that obtained from linelaidic acid.

$$\underset{\text{(XIX)}}{\mathrm{Br{\cdot}CH(OEt){\cdot}CHBr{\cdot}CH_2{\cdot}CHBr{\cdot}CHBr{\cdot}OEt}} \xrightarrow[\text{(2) }\mathrm{BrMg{\cdot}[CH_2]_6{\cdot}OMe}]{\text{(1) }\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}MgBr}\text{ ;}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH(OEt){\cdot}CHBr{\cdot}CH_2{\cdot}CHBr{\cdot}CH(OEt){\cdot}[CH_2]_6{\cdot}OMe} \xrightarrow[\text{(3) HBr ; (4) Zn}]{\text{(1) Zn ; (2) }\mathrm{Br_2}\text{ ;}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_6{\cdot}Br} \xrightarrow[\text{(2) }\mathrm{CH_2(CO_2Et)_2}\text{, etc.}]{\text{(1) NaI ;}}$$

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H}$$

Elaidic and vaccenic (*trans*-octadec-11-enoic acid) acids have recently been prepared by another modification [91] (shown below) in which the double bond is already present in one of the starting materials. The products were contaminated with their *cis*-isomers and with a vinylpalmitic acid resulting from reaction of the Grignard complex with (XX). An improvement of this method has recently been published.[92]

Delaby *et al.*[93] have used the Grignard reagent to prepare several unsaturated acids. Interaction of an alkylmagnesium halide with acraldehyde gave a vinyl secondary alcohol (XXI) which on bromination affords the

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[88] Noller and Girvin, *J. Amer. Chem. Soc.*, 1937, **59**, 606.

[89] Baudart, *Compt. rend.*, 1943, **217**, 399.

[90] *Idem, Bull. Soc. chim.*, 1944, **11**, 336.

[91] Gensler, Behrmann, and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 1071.

[92] Gensler and Thomas, *ibid.*, 1952, **74**, 3942.

[93] Delaby and Guillot-Allègre, *Bull. Soc. chim.*, 1933, **53**, 301 ; Delaby and Lecomte, *ibid.*, 1937, **4**, 738, 749, 1007, 1016.

$$\underset{(n\,=\,7\text{ or }9)}{CH_2{:}CH{\cdot}CH_2{\cdot}[CH_2]_n{\cdot}CO_2Me} \xrightarrow{C_2H_4(CO)_2NBr} \underset{(XX)}{CH_2{:}CH{\cdot}CHBr{\cdot}[CH_2]_n{\cdot}CO_2Me} \rightleftharpoons$$

$$Br{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_n{\cdot}CO_2Me \xrightarrow[(m\,=\,6\text{ or }4)]{CH_3{\cdot}[CH_2]_m{\cdot}MgBr} CH_3{\cdot}[CH_2]_m{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_n{\cdot}CO_2Me$$

compound (XXII). This yields an unsaturated acid *via* the alcohol (Δ^2) or the nitrile (Δ^3). Acids of the C_6—C_9 series have been so prepared.

$$\begin{tikzcd}
CH_3{\cdot}[CH_2]_n{\cdot}MgX + CH_2{:}CH{\cdot}CHO \arrow[r] & CH_3{\cdot}[CH_2]_n{\cdot}CH(OH){\cdot}CH{:}CH_2 \ \text{(XXI)} \arrow[d, "PBr_3"'] \\
\underset{\text{(XXII)}}{CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CH_2Br} \arrow[r, phantom, "\rightleftharpoons"] \arrow[d, "NaOAc"] \arrow[dd, bend right, "CuCN"'] & CH_3{\cdot}[CH_2]_n{\cdot}CHBr{\cdot}CH{:}CH_2 \\
CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OAc \arrow[r, "\text{Hydrol.;}", "\text{oxidn.}"'] & CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CO_2H \\
CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN \arrow[r, "\text{Hydrol.}"'] & CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H
\end{tikzcd}$$

The organo-cadmium compounds have been little used for preparation of unsaturated acids though the preparation of octadec-17-enoic acid by this means has been reported.[94] The important reaction is between diundec-10-enylcadmium and 6-carbethoxyhexanoyl chloride.

$$Cd([CH_2]_9{\cdot}CH{:}CH_2)_2 + 2Cl{\cdot}CO{\cdot}[CH_2]_5{\cdot}CO_2Et \longrightarrow 2CH_2{:}CH{\cdot}[CH_2]_9{\cdot}CO{\cdot}[CH_2]_5{\cdot}CO_2Et$$

Condensation of acetylenic compounds. The preparation of unsaturated acids *via* acetylenic precursors provides a versatile method which has been widely and successfully exploited in recent years. There is, however, one well-known reaction of acetylenic compounds which has been used for a longer period. It provides a convenient route to the $\alpha\beta$-acetylenic acids and hence to the $\alpha\beta$-ethylenic acids. Acids of this type are readily obtained by reaction of the sodio-derivative or Grignard complex of an ethynyl compound with carbon dioxide, ethyl carbonate, or ethyl chloroformate. Most of the acids of this type in the range C_6—C_{12} have been so prepared [95] and also some polyunsaturated acids.[85, 96]

$$CH_3{\cdot}[CH_2]_n{\cdot}C{\vdots}CH \longrightarrow \underset{(M\,=\,Na\text{ or }MgX)}{CH_3{\cdot}[CH_2]_n{\cdot}C{\vdots}CM} \longrightarrow \underset{(R\,=\,H\text{ or }Et)}{CH_3{\cdot}[CH_2]_n{\cdot}C{\vdots}C{\cdot}CO_2R}$$

In 1928 behenolic acid was obtained by condensing a sodium acetylide

$$CH_3{\cdot}[CH_2]_7{\cdot}C{\vdots}CNa + Br{\cdot}[CH_2]_{11}{\cdot}CO_2Me \longrightarrow CH_3{\cdot}[CH_2]_7{\cdot}C{\vdots}C{\cdot}[CH_2]_{11}{\cdot}CO_2H$$

with an ω-bromo-ester.[97] Ten years later tetradec-5-ynoic acid was prepared by the condensation of dec-1-yne with 3-chloropropyl toluene-*p*-

$$CH_3{\cdot}[CH_2]_7{\cdot}C{\vdots}CH + C_6H_4Me{\cdot}SO_2{\cdot}[CH_2]_3{\cdot}Cl \longrightarrow CH_3{\cdot}[CH_2]_7{\cdot}C{\vdots}C{\cdot}[CH_2]_3{\cdot}Cl \longrightarrow CH_3{\cdot}[CH_2]_7{\cdot}C{\vdots}C{\cdot}[CH_2]_3{\cdot}CO_2H$$

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[94] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.

[95] Moureu and Delange, *Bull. Soc. chim.*, 1903, **29**, 648; Zoss and Hennion, *J. Amer. Chem. Soc.*, 1941, **63**, 1151.

[96] Raphael and Sondheimer, *J.*, 1950, 115, 120.

[97] Bhattacharya, Saletore, and Simonsen, *J.*, 1928, 2678.

sulphinite in the presence of sodamide, the condensation product being subsequently converted into the acid *via* the nitrile.[98]

Another ten years elapsed before the general usefulness of this reaction was demonstrated by Strong and his co-workers,[99] who showed that ethynyl compounds (XXIII) interact, as their sodium derivatives or Grignard complexes, with $\alpha\omega$-dihalogeno-compounds (XXIV). The resulting acetylenic compound (XXV) is readily converted into an acid, partial catalytic hydrogenation of which affords the *cis*-ethylenic acid (XXVI). This is of

$$\underset{\text{(XXIII)}}{CH_3\cdot[CH_2]_m\cdot C{\vdots}CH} + \underset{\text{(XXIV)}}{I\cdot[CH_2]_n\cdot Cl} \longrightarrow$$

$$\underset{\text{(XXV)}}{CH_3\cdot[CH_2]_m\cdot C{\vdots}C\cdot[CH_2]_n\cdot Cl} \longrightarrow \underset{\text{(XXVI)}}{CH_3\cdot[CH_2]_m\cdot CH{:}CH\cdot[CH_2]_n\cdot CO_2H}$$

particular importance since it permits the synthesis of the naturally occurring *cis*-acids. These methods have been used by others [94, 100] for a wide range of unsaturated fatty acids.

Similar reactions have been applied to the synthesis of the diethenoid linoleic acid,[101] which was achieved independently by three sets of workers. The methods used are similar, though not identical, and only the first description, due to Raphael and Sondheimer, is shown in the accompanying

$$\left.\begin{array}{l} CH_3\cdot[CH_2]_4\cdot C{\vdots}C\cdot CH_2\cdot OH \xrightarrow{CH_3\cdot SO_2Cl} CH_3\cdot[CH_2]_4\cdot C{\vdots}C\cdot CH_2\cdot O\cdot SO_2\cdot CH_3 \\ Cl\cdot[CH_2]_6\cdot Cl \xrightarrow{(1)\ NaI;\ (2)\ CH{\vdots}CNa} HC{\vdots}C\cdot[CH_2]_6\cdot Cl \end{array}\right\} \xrightarrow{EtMgBr}$$

$$CH_3\cdot[CH_2]_4\cdot C{\vdots}C\cdot CH_2\cdot C{\vdots}C\cdot[CH_2]_6\cdot Cl \xrightarrow[(3)\ H_2\text{–}Pd]{(1)\ NaI;\ (2)\ CH_2(CO_2Et)_2,\ etc.}$$

$$CH_3\cdot[CH_2]_4\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$$

reaction sequence. The product gave tetrabromostearic acid (63%), indicating the presence of natural linoleic acid.

Attempts to synthesise the insecticides herculin and pellitorine have led to the preparation of dodeca-2 : 8-dienoic and deca-2 : 6-dienoic acids as intermediates. Various stereoisomers have been obtained by methods based mainly on the use of acetylenic compounds [85, 96, 102] and this work, which provides a good example of the flexibility of these methods, has led to a revised formula for pellitorine [83] and to doubt concerning the structure of herculin.

Sörensen and his collaborators [103] have prepared some highly unsaturated

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[98] Johnson, Schwartz, and Jacobs, *J. Amer. Chem. Soc.*, 1938, **60**, 1882.

[99] Ahmad and Strong, *ibid.*, 1948, **70**, 1699 ; Ahmad, Bumpus, and Strong, *ibid.*, p. 3391 ; Taylor and Strong, *ibid.*, 1950, **72**, 4263.

[100] Lumb and Davies, *J.*, 1952, 5032 ; Fusari, Greenlee, and Brown, *J. Amer. Oil Chem. Soc.*, 1951, **28**, 416 ; Newman and Wotiz, *J. Amer. Chem. Soc.*, 1949, **71**, 1292.

[101] Raphael and Sondheimer, *J.*, 1950, 2100 ; Gensler and Thomas, *J. Amer. Chem. Soc.*, 1951, **73**, 4601 ; Walborsky, Davies, and Howton, *ibid.*, p. 2590.

[102] *Idem, J.*, 1951, 2693 ; Crombie, *J.*, 1952, 4338.

[103] Bruun, Haug, and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 850 ; Bruun, Christensen, Haug, Stene, and Sörensen, *ibid.*, 1951, **5**, 1244 ; Christensen and Sörensen, *ibid.*, 1952, **6**, 602 ; Baalsrud, Holme, Nestvold, Pliva, Sörensen, and Sörensen, *ibid.*, p. 883 ; Christensen and Sörensen, *ibid.*, p. 893.

derivatives of methyl decanoate by oxidative coupling, in attempts to confirm the structures of compounds isolated from the essential oils of several species of *Compositae* (see p. 194). The method is illustrated by the preparation of methyl deca-*trans*-2-ene-4 : 6 : 8-triynoate (XXVII). Other related compounds have been similarly prepared, and the method has been used by Black and Weedon [104] for octadec-17-ene-9 : 11-diynoic acid (XXVIII).

$$CH_3{\cdot}C{\vdots}C{\cdot}C{\vdots}CH + HC{\vdots}C{\cdot}CH{:}CH{\cdot}CO_2Me \longrightarrow CH_3{\cdot}C{\vdots}C{\cdot}C{\vdots}C{\cdot}C{\vdots}C{\cdot}CH{:}CH{\cdot}CO_2Me$$

(XXVII)

$$CH_2{:}CH{\cdot}[CH_2]_4{\cdot}C{\vdots}C{\cdot}C{\vdots}C{\cdot}[CH_2]_7{\cdot}CO_2H$$

(XXVIII)

Condensations yielding acyloins or alkoxy-ketones. Another method of preparing unsaturated acids involves the use of acyloins or alkoxy-ketones as intermediates. The former may be prepared by Ruzicka's acyloin synthesis [105] or, alternatively, both may be prepared by Bowman's ketone synthesis.[106] In either case the intermediate is readily converted into an unsaturated compound *via* the dibromide, thus :

$$\begin{tikzcd}
\text{—}CH(OH){\cdot}CO\text{—} \arrow[d] & & \\
\left.\begin{array}{l}\text{—}CH(OH){\cdot}CH(OH)\text{—}\\ \text{—}CH(OMe){\cdot}CH(OH)\text{—}\end{array}\right] \arrow[r] & \text{—}CHBr{\cdot}CHBr\text{—} \arrow[r] & \text{—}CH{:}CH\text{—} \\
\text{—}CH(OMe){\cdot}CO\text{—} \arrow[u] & &
\end{tikzcd}$$

An advantage of the acyloin method is that the $\alpha\beta$-glycol may be separated into *threo*- and *erythro*-forms which subsequently afford the *trans*- and the *cis*-unsaturated acid respectively. In general, excellent results are obtained but in some cases the alkoxy-ketone procedure is preferable. Ames and Bowman [107] have compared the two methods.

Baudart,[108] using Ruzicka's acyloin synthesis, prepared the *cis*- and the *trans*-forms of octadec-9-enoic and hexadec-9-enoic acid thus :

$$CH_3{\cdot}[CH_2]_n{\cdot}CO_2Et + EtO_2C{\cdot}[CH_2]_7{\cdot}OEt \xrightarrow{Na}$$

$(n = 5 \text{ or } 7)$

$$CH_3{\cdot}[CH_2]_n{\cdot}CO{\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}OEt \xrightarrow{Ni\text{–}H_2}$$

$$CH_3{\cdot}[CH_2]_n{\cdot}CH(OH){\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}OEt \xrightarrow[\text{(2) Zn}]{\text{(1) HBr–AcOH ;}}$$

(Two isomers
separated)

$$CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}Br \xrightarrow[\text{(2) hydrol.}]{\text{(1) KCN ;}}$$

$$CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$$

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[104] Black and Weedon, *Chem. and Ind.*, 1953, 40.

[105] Ruzicka, Plattner, and Widmer, *Helv. Chim. Acta*, 1942, **25**, 604.

[106] Bowman, *J.*, 1950, 325.

[107] Ames and Bowman, *J.*, 1951, 1079.

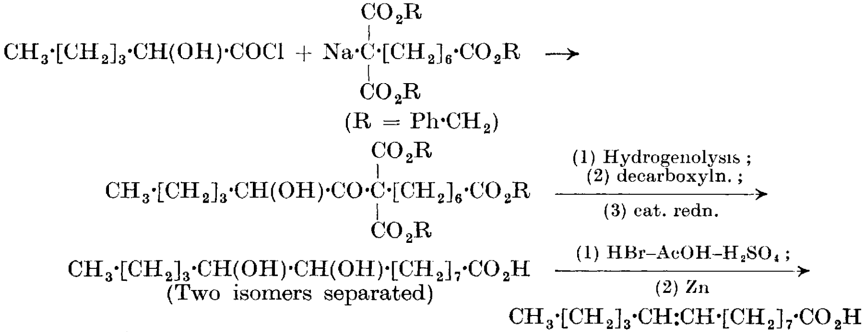
[108] Baudart, *Bull. Soc. chim.*, 1946, **13**, 87.

In the preparation of hendec-6-enoic acid (XXIX) the ethoxy-ester was replaced by an ω-unsaturated ester, subsequent oxidation of which gave the desired acid.

$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CO_2Et + EtO_2C{\cdot}[CH_2]_3{\cdot}CH{:}CH_2} \longrightarrow$$
$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CO{\cdot}CH(OH){\cdot}[CH_2]_3{\cdot}CH{:}CH_2} \xrightarrow{\mathrm{Al(OPr^i)_3}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH(OH){\cdot}CH(OH){\cdot}[CH_2]_3{\cdot}CH{:}CH_2} \xrightarrow[\text{(3) oxidn.}]{\text{(1) Ac}_2\text{O ; (2) O}_3\text{ ;}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH(OAc){\cdot}CH(OAc){\cdot}[CH_2]_3{\cdot}CO_2H} \xrightarrow[\text{(2) HBr ; (3) NaI–Zn}]{\text{(1) Hydrol. ;}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}[CH_2]_3{\cdot}CO_2H}$$
(XXIX)

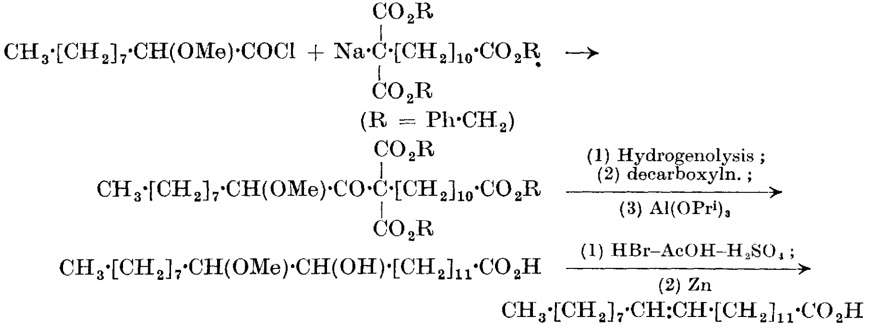
Bowman and his collaborators [107, 109] have prepared several unsaturated acids, in addition to certain branched-chain compounds.[110] In each case pure *cis-* and *trans-*isomers were obtained. The details of this procedure have already been discussed and two examples only are given in the annexed schemes.

Acyloin.



$$\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CH(OH){\cdot}COCl + Na{\cdot}}\overset{\mathrm{CO_2R}}{\underset{\mathrm{CO_2R}}{\mathrm{C}}}\mathrm{{\cdot}[CH_2]_6{\cdot}CO_2R} \longrightarrow$$
$$\mathrm{(R = Ph{\cdot}CH_2)}$$
$$\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CH(OH){\cdot}CO{\cdot}}\overset{\mathrm{CO_2R}}{\underset{\mathrm{CO_2R}}{\mathrm{C}}}\mathrm{{\cdot}[CH_2]_6{\cdot}CO_2R} \xrightarrow[\text{(3) cat. redn.}]{\text{(1) Hydrogenolysis ; (2) decarboxyln. ;}}$$
$$\underset{\text{(Two isomers separated)}}{\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CH(OH){\cdot}CH(OH){\cdot}[CH_2]_7{\cdot}CO_2H}} \xrightarrow[\text{(2) Zn}]{\text{(1) HBr–AcOH–H}_2\text{SO}_4\text{ ;}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H}$$

Alkoxy-ketone.



$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH(OMe){\cdot}COCl + Na{\cdot}}\overset{\mathrm{CO_2R}}{\underset{\mathrm{CO_2R}}{\mathrm{C}}}\mathrm{{\cdot}[CH_2]_{10}{\cdot}CO_2R} \longrightarrow$$
$$\mathrm{(R = Ph{\cdot}CH_2)}$$
$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH(OMe){\cdot}CO{\cdot}}\overset{\mathrm{CO_2R}}{\underset{\mathrm{CO_2R}}{\mathrm{C}}}\mathrm{{\cdot}[CH_2]_{10}{\cdot}CO_2R} \xrightarrow[\text{(3) Al(OPr}^{\text{i}}\text{)}_3]{\text{(1) Hydrogenolysis ; (2) decarboxyln. ;}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH(OMe){\cdot}CH(OH){\cdot}[CH_2]_{11}{\cdot}CO_2H} \xrightarrow[\text{(2) Zn}]{\text{(1) HBr–AcOH–H}_2\text{SO}_4\text{ ;}}$$
$$\mathrm{CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_{11}{\cdot}CO_2H}$$

Other methods. The Robinson procedure (p. 177), or one of its modifications, has been used for preparation of a few unsaturated acids.[17, 111]

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[109] Bowman, *J.*, 1950, 177 ; Boughton, Bowman, and Ames, *J.*, 1952, 671.

[110] Ames and Bowman, *J.*, 1951, 1087.

[111] Kapp and Knoll, *J. Amer. Chem. Soc.*, 1943, **65**, 2062 ; Stenhagen, *Arkiv Kemi*, 1949, **1**, 99.

3. Recent Contributions to our Knowledge of Naturally Occurring Fatty Acids

The remainder of this Review will be concerned with (i) methods of isolation of pure acids from natural sources and (ii) a brief account of acids which have only recently been reported or the structure of which has been adequately described only in recent years.

The Isolation of Fatty Acids from Natural Sources.—Partly because of the plentiful occurrence of several fatty acids and partly because of the difficulties, only now being overcome, of synthesising many of these compounds, much effort has been expended in attempts to isolate pure acids from natural sources. The difficulty of isolating pure acids from mixtures of closely related acids is well known to workers in this field. The improvement of older methods and the development of new techniques, however, make it increasingly possible to achieve this separation. The procedures most used in the past were distillation (generally of the methyl esters), and crystallisation of the acids or their metallic salts, whilst the polyunsaturated acids have generally been isolated as polybromides, the acids being subsequently recovered by debromination. It is well to remember that whilst distillation may separate acids of different chain length it does not give much enrichment of acids having the same number of carbon atoms but of varying unsaturation ; that normal methods of crystallisation can only be applied to solid acids ; that crystallisation of salts (*e.g.*, lead salts from alcohol, or lithium salts from acetone) is of more value for preparation of concentrates than for isolation of pure compounds ; and that, whilst it is possible to prepare a pure polybromide, doubt has been expressed concerning the homogeneity of the debrominated acid.[112] The main recent advance in this field has been the isolation of unsaturated acids by physical means only. The more recent technique of forming urea complexes has already been used to prepare concentrates of single acids,[113–115] but it is too early to say how extensively this method will be used in the future.

Brown and his colleagues have been mainly responsible for demonstrating the value of low-temperature crystallisation for the isolation of fatty acids. By this technique it is possible to crystallise compounds that are liquid at room temperature. The isolation, from suitable natural sources, of oleic (purity $>$ 99·6%), linoleic (93·5%), linolenic (88%), arachidonic (95%), and ricinoleic acid (95·6%) has been described.[116] Improvements in the separation of linoleic (97—100%) [117] and ricinoleic acid (99%) [118] have since been reported. The method is clearly of value for preparation of

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[112] Matthews, Brode, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 1064 ; Frankel and Brown, *ibid.*, 1943, **65**, 415.

[113] Ligthelm, Schwartz, and von Holdt, *J.*, 1952, 1088.

[114] Nunn, *J.*, 1952, 313.

[115] Swern and Parker, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 431.

[116] Cf. Brown, *Chem. Reviews*, 1941, **29**, 333.

[117] Frankel, Stoneburner, and Brown, *J. Amer. Chem. Soc.*, 1943, **65**, 259.

[118] Hawke, *J.S. African Chem. Inst.*, 1949, **2**, 1.

mono- and di-ethenoid acids in high purity but of less value for more unsaturated acids.

It is not surprising that the methods of chromatography, so widely used in other branches of chemistry, have also been applied with success to the problem now under consideration. Riemenschneider *et al.* separated the methyl esters on a column of silicic acid in an atmosphere of nitrogen or carbon dioxide. The preparation of methyl linoleate (100% pure) and methyl linolenate (100%) has been described.[119] By a combination of this method with distillation and low-temperature crystallisation methyl arachidonate of high purity,[120] and concentrates of methyl eicosapentaenoate and docosapentaenoate, have been isolated from lipids of fresh beef suprarenal glands.[121] This technique, coupled with those previously used, makes it possible to prepare unsaturated acids in a high state of purity even when they were originally present in very small amounts. The methods are such that degradative or other undesirable changes are reduced to the minimum.

Fatty Acids of Recent Description.—The acids now to be described are either major component acids of fats not previously investigated, acids present in small quantities but not previously reported in fats already examined, or aliphatic acids of non-fatty origin.

Matricaria and related acids. Sörensen and his co-workers [103, 122] have isolated a number of highly unsaturated derivatives of methyl decanoate from the essential oils of several species of *Compositæ.* Structures are based largely on spectroscopic evidence and on the isolation of methyl decanoate after quantitative hydrogenation. The following have been described :

Matricaria ester	$CH_3\cdot CH{:}CH\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH{:}CH\cdot CO_2Me$ (*cis*-2 : *cis*-8 and *cis*-2 : *trans*-8)
Composit-cumuleen I	$CH_3\cdot[CH_2]_4\cdot CH{:}C{:}C{:}CH\cdot CO_2Me$
Dehydromatricaria ester	$CH_3\cdot C{\vdots}C\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH{:}CH\cdot CO_2Me$ (not the *trans*-2 isomer)
or	$CH_3\cdot CH{:}CH\cdot C{\vdots}C\cdot C{\vdots}C\cdot C{\vdots}C\cdot CO_2Me$
Dihydromatricaria ester	$CH_3\cdot CH{:}CH\cdot C{\vdots}C\cdot C{\vdots}C\cdot[CH_2]_2\cdot CO_2Me$ (*cis*-8)
Lachnophyllum ester	$CH_3\cdot[CH_2]_2\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH{:}CH\cdot CO_2Me$ (probably *cis*-2)

Deca-2 : 4-*dienoic acid.* The composition of Stillingia oil indicated by early analyses * did not conform with the superior drying properties of this oil, which are now believed to be due to the presence (*ca.* 5%) of deca-2 : 4-dienoic acid.[123] This is the first polyethenoic acid containing less than

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[119] Riemenschneider, Herb, and Nichols, *J. Amer. Oil Chem. Soc.*, 1949, **26**, 371 ; see, also, Hilditch, Patel, and Riley, *Analyst*, 1951, **76**, 81.

[120] Herb, Riemenschneider, and Donaldson, *J. Amer. Oil Chem. Soc.*, 1951, **28**, 55.

[121] Herb, Witnauer, and Riemenschneider, *ibid.*, p. 505 ; cf. White and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 4269.

[122] Sörensen and Stene, *Annalen*, 1941, **549**, 80 ; Holman and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 416 ; Sörensen and Stavholt, *ibid.*, pp. 1080, 1567, 1575.

[123] Crossley and Hilditch, *J.*, 1949, 3353 ; Devine, *J. Sci. Food Agric.*, 1950, **1**, 88 ; Crossley and Hilditch, *ibid.*, p. 292.

* Where references are not given to early work details are to be found in Hilditch (ref. 1) or in the references quoted for the more recent work.

sixteen carbon atoms which has been isolated from a fat. A tentative report [124] of the occurrence of dodeca-2 : 4-dienoic acid needs to be confirmed. The relation between deca-2 : 4-dienoic acid and pellitorine has been noted.[83]

Mycomycin. The antibiotic mycomycin is a highly unsaturated derivative (XXX) of tridecanoic acid. The compound is optically active by reason of the allene group and is readily isomerised to *iso*mycomycin (XXXI).[125]

$$\text{(XXX)}\quad CH{\vdots}C\cdot C{\vdots}C\cdot CH{:}C{:}CH\cdot CH{:}CH\cdot CH{:}CH\cdot CH_2\cdot CO_2H$$

$$\text{(XXXI)}\quad CH_3\cdot C{\vdots}C\cdot C{\vdots}C\cdot C{\vdots}C\cdot CH{:}CH\cdot CH{:}CH\cdot CH_2\cdot CO_2H$$

Hexa-7 : 10 : 13-*trienoic acid.* This acid occurs among rape-leaf glycerides.[126] A concentrate was prepared by distillation and low-temperature crystallisation. Its constitution was derived from a study of the hydrogenation and oxidation products. Alkali isomerisation produced triene conjugation analogous to that observed with linolenic acid.

Octadec-11-*enoic acid.* Recent work suggests that the individuality of vaccenic acid (*trans*-octadec-11-enoic acid) from land-animal fats is again in question. *trans*-Octadec-11-enoic acid has been synthesised and compared with natural vaccenic acid. Although the infra-red spectra were essentially identical, their *X*-ray diffraction patterns differed significantly,[127] and it is suggested that the natural acid may contain isomers. Hilditch and his collaborators have concluded, from a study of oxidation products, that the *trans*-octadecenoic acid present in animal fats is a mixture of the Δ^{10}- and Δ^{11}-isomer.[128] More recently beef fat has been shown to contain both elaidic and vaccenic acid, which are considered to result from oxidative changes.[129]

cis-Octadec-11-enoic acid, not previously reported from natural sources, has now been isolated from the lipids of horse brain [130] and of *Lactobacillus arabinosus*.[131]

Octadecadienoic acid. The question of whether all samples of octadecadienoic acid of natural origin are identical with the widely occurring linoleic acid is still a matter for discussion, but no other isomer has been isolated directly from a natural fat. Spectroscopic corroboration of the reported occurrence of free octadeca-9 : 11-dienoic acid [132] is desirable.

Acetylenic acids with eighteen carbon atoms. Xymenynic acid, which has been obtained from three species of the *Ximenia* genus,[113] contains one ethylenic and one acetylenic linkage and has the structure (XXXII) or (XXXIII). The former is preferred on the basis of ozonolysis experiments.

[124] Hanks and Potts, *J. Amer. Oil Chem. Soc.*, 1951, **28**, 292.

[125] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870, 2245, 3838 ; 1953, **75**, 1372.

[126] Heyes and Shorland, *Biochem. J.*, 1951, **49**, 503 ; *Nature*, 1945, **156**, 269.

[127] Bumpus, Taylor, and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 2116.

[128] Gupta, Hilditch, Paul, and Shrivastava, *J.*, 1950, 3484.

[129] Swern, Knight, and Eddy, *J. Amer. Oil Chem. Soc.*, 1952, **29**, 44.

[130] Morton and Todd, *Biochem. J.*, 1950, **47**, 327.

[131] Hofmann, Lucas, and Sax, *J. Biol. Chem.*, 1952, **195**, 473.

[132] Kartha and Menon, *Proc. Indian Acad. Sci.*, 1943, **17**, *A*, 11.

A recent report[104] indicates that erythrogenic (isanic) acid obtained

$CH_3\cdot[CH_2]_5\cdot CH{:}CH\cdot C{\vdots}C\cdot[CH_2]_7\cdot CO_2H$ (XXXII)

$CH_3\cdot[CH_2]_5\cdot C{\vdots}C\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$ (XXXIII)

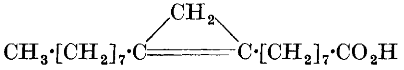
from the seed oil of *Onguekoa Gore* (Engler) is probably identical with synthetic octadec-17-ene-9 : 11-diynoic acid (XXVIII).

Hydroxy-acids containing eighteen carbon atoms. An isomer of ricinoleic acid, 9-hydroxyoctadec-12-enoic acid, has been shown to occur in the seed oils of three *Strophanthus* species.[133] Hydroxy-acids are also reported in *Onguekoa Gore* (Engler) seed oil,[134] in *Mallotus philippinensis* seed oil,[135] in *Rhus trichocarpa* wax,[136] and in the mother-liquors from the crystallisation of santonin.[137]

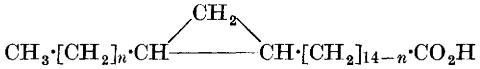
The free fatty acids of human-hair fat. The unsaturated acids in human-hair fat appear to have their ethylenic linkages in unusual positions. Hexadec-6-enoic acid has been isolated and the presence of tetradec-5-enoic, penta-, hepta-, and octa-dec-6-enoic, hepta- and octa-dec-8-enoic, oleic, and possibly octadeca-6 : 9-dienoic acid were indicated by oxidative techniques.[138]

Acids containing a cyclo*propane or* cyclo*propene ring.* Two acids have recently been described which contain these cyclic systems. Sterculic acid, obtained from the seed oil of *Sterculia foetida* and some other *S.* species, is a C_{19} acid with the remarkable structure (XXXIV).[114] On hydrogenation one mol. of hydrogen is absorbed to give a saturated compound, which reacts with a second mol. of hydrogen to give a mixture of acids, probably consisting of nonadecanoic acid and 9- and 10-methyloctadecanoic acids. Oxidation gives azelaic and nonanoic acids as main products.

(XXXIV)



(XXXV)



The fatty acids of *Lactobacillus arabinosus* contain, *inter alia*, lactobacillic acid[131] which has the structure (XXXV). Nonadecanoic acid has been isolated after hydrogenation ; methyloctadecanoic acids are probably also present. The suggestion[139] that $n = 5$ is not proved.

*Eicos-*11*-enoic and docosa-*13 : 16*-dienoic acids.* Eicos-11-enoic acid, previously reported only in a seed wax, and, possibly in some fish oils, is

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[133] Gunstone, *J.*, 1952, 1274 ; *J. Sci. Food Agric.*, 1952, **3,** 185 ; 1953, **4,** 129.

[134] Riley, *J.*, 1951, 1346 ; Kaufmann, Baltes, and Herminghaus, *Fette u. Seifen*, 1951, **53,** 537.

[135] Gupta, Sharma, and Aggarwal, *J. Sci. Ind. Res.* (*India*), 1952, **11,** 463 ; Calderwoode and Gunstone, *Chem. and Ind.*, 1953, 436 ; *cf.* Puntambekar, *Proc. Indian Acad. Sci.*, 1952, **35,** *A*, 57.

[136] Tsukamoto, *J. Pharm. Soc. Japan*, 1942, **62,** 375.

[137] Kariyone, Fukui, Kiguchi, Ishimasi, and Miki, *ibid.*, 1948, **68,** 269, 271, 272.

[138] Weitkamp, Smiljanic, and Rothman, *J. Amer. Chem. Soc.*, 1947, **69,** 1936.

[139] Kosower, *Science*, 1951, **113,** 604.

now known to be present in certain *Cruciferae* seed fats [140, 141] and in cod liver oil.[142] A docosadienoic acid (almost certainly $\Delta^{13:16}$) was also isolated from rape oil.[141] Small quantities of eicos-11-enoic and eicosadienoic acids are reported in certain land-animal fats.[143]

Acids of marine origin. Eicos-12-enoic,[144] eicosa-11 : 14-dienoic, and eicosa-8 : 11 : 14-trienoic acids [145] have been reported. Matsuda [146] has studied the highly unsaturated acids of bonito oil. The structures of several acids are discussed but the results must be accepted with reserve in view of the known difficulties of working with these compounds. Bergman and Swift [147] in an examination of sponge lipids have described the hitherto unknown hexacosa-17 : 24-dienoic acid along with an octacosenoic acid and octacosatrienoic acid, the detailed structures of which are not reported.

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[141] Baliga and Hilditch, *J.*, 1949, S 91.

[142] Hopkins, Chisholm, and Harris, *Canad. J. Res.*, 1949, **27,** *B*, 35.

[143] de la Mare and Shorland, *Analyst*, 1944, **69,** 337 ; *Nature*, 1945, **155,** 48 ; *Biochem. J.*, 1945, **39,** 246.

[144] Hata and Kunisaki, *J. Chem. Soc. Japan*, 1942, **63,** 1585.

[145] Baudart, *Bull. Soc. chim.*, 1944, **11,** 174.

[146] Matsuda, *J. Soc. Chem. Ind. Japan*, 1942, **45,** 3, 4, 6, 8, 49, 134, 158.

[147] Bergmann and Swift, *J. Org. Chem.*, 1951, **16,** 1206.