REACTIONS OF THE HYDROCARBON CHAIN OF FATTY ACIDS

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I. Introduction

Long-chain normal aliphatic carboxylic acids constitute the major components of fats and oils in plant and animal tissue. These "fatty acids" are tremendously important in the fields of nutrition, medical science, and industrial technology. For over one hundred and fifty years the chemistry of the fatty acids has been studied. Numerous scientific and technical publications have been issued including articles, reference books, and treatises. Although most attention probably has been devoted to the chemistry of the carboxyl group, reactions of the hydrocarbon chain have received a good share. Much of this chemistry and especially older work has been recorded in the several reference books on fatty acid chemistry (211, 317, 327, 422). Also, reviews have appeared which usually have dealt with some specific aspect of the chemistry of the hydrocarbon chain of fatty acids. None, however, is available

which integrates the existing knowledge in terms of systematic organic chemistry. Such is the purpose of this review.

To a very large extent the chemical reactions of the hydrocarbon chains of fatty acids are the reactions of saturated and unsaturated normal aliphatic hydrocarbons. The physical characteristics of fatty acids and the presence of the terminal polar group exert a profound influence upon the behavior of these substances toward many reagents. Frequently, it is necessary to employ special techniques in order to effect reactions which proceed readily with substances of lower molecular weight or substances with different solubility characteristics. Also, the separation and identification of the reaction products may present unusual difficulty because of the predominantly hydrocarbon nature of the molecule. There is considerable justification for the attitude which prevails among some workers in the field of fatty acid chemistry that theirs is a discipline which operates outside the rules of classical organic chemistry.

One common source of error found in the literature on fatty acids and one which may seem to have been belabored in this article has its origin in the formation of eutectic or minimum-melting mixtures. This tendency is very common among fatty acids and their derivatives, probably because of structural similarity which leads to mutual solubility. Eutectic formation must always be assumed in mixtures of fatty acids or their derivatives unless evidence to the contrary is available. It is impossible to separate a eutectic or a minimum-melting mixture into both pure components by any process of equilibrium crystallization (553). Those who do not realize this may be misled regarding the purity of a product; a eutectic mixture may be mistaken for a pure compound. All of this is complicated by the fact that fatty acids always occur as mixtures of homologs and the isolation and purification of a single substance are laborious. Yet it is difficult to obtain clear-cut experimental results when using impure materials. Because of these complications there is an especial need for painstaking, sophisticated experimentation in the field of fatty acid chemistry. It is hoped that in the following pages this need will be convincingly demonstrated.

In those instances in which disagreement with conclusions stated in the literature has been expressed, reasons for disagreement have been presented in considerable detail. Physical constants of specific compounds are included only when they will be useful for purposes of comparison.

II. SCOPE OF THE REVIEW

For the most part this review covers the chemical literature since 1945. In some sections earlier work has been included, but this is not generally the case.

Chemical Abstracts was searched through Volume 52; coverage of later literature was less complete, especially of more inaccessible foreign journals. The literature on the chemistry of the hydrocarbon chains of fatty acids is very large, and it has been necessary to be very selective even at the risk of making serious omissions. Searching was limited to the most prevalent fatty acids, their esters (other carboxyl derivatives were not searched), and carbon-chain derivatives containing eight or more carbon atoms with the expectation that all important chemical reactions investigated during the period covered would be discovered. Branched-chain acids were not included. The patent literature is a less reliable source of scientific information; therefore only those patents are cited which seem to have special significance or which contain information not available elsewhere.

The subject matter of this review is arranged systematically under five major classes of reactions: replacement, addition, elimination, isomerization, and cleavage. A short section on autoxidation is also included. Only those reactions are included which involve bonds directly attached to carbon atoms of the hydrocarbon chain. The chemistry of substituent groups, unless a chain-carbon bond is involved, is considered outside the scope of the article.

III. NOMENCLATURE

The nomenclature used is that currently being employed by *Chemical Abstracts*. For convenience some common trivial names of acids or esters are used; all carbon-chain derivatives are named systematically. Table 1 gives the trivial names for acids which are used and their systematic equivalents.

TABLE 1

Trivial name	Systematic name
Caprylic acid.........	Octanoic acid
Capric acid..........	Decanoic acid
Lauric acid..........	Dodecanoic acid
Myristic acid........	Tetradecanoic acid
Palmitic acid........	Hexadecanoic acid
Stearic acid.........	Octadecanoic acid
Oleic acid...........	*cis*-9-Octadecenoic acid
Elaidic acid.........	*trans*-9-Octadecenoic acid
Linoleic acid........	*cis*-9-*cis*-12-Octadecadienoic acid
Linolenic acid.......	*cis*-9-*cis*-12-*cis*-15-Octadecatrienoic acid
α-Eleostearic acid....	*cis*-9-*trans*-11-*trans*-13-Octadecatrienoic acid
β-Eleostearic acid....	*trans*-9-*trans*-11-*trans*-13-Octadecatrienoic acid
Stearolic acid.......	9-Octadecynoic acid
Ricinoleic acid.......	D(+)-12-Hydroxy-*cis*-9-octadecenoic acid

Two-dimensional structural formulas are employed and these conventions are used for geometrical isomers:

cis   trans   erythro   threo
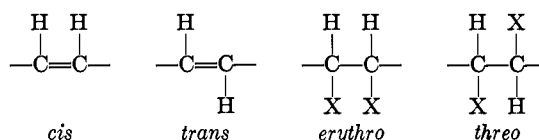
Mixtures of positional isomers, such as are obtained by random addition to double bonds, are named by showing one of the positions parenthetically, e.g., 9(10)-bromoöctadecanoic acid.

Almost without exception asymmetric carbon atoms represent a racemic mixture, since the resolution of racemates seldom has been attempted.

IV. Replacement Reactions

Replacement reactions will include all reactions in which one substituent directly attached to one of the carbon atoms of the hydrocarbon chain of a fatty acid is replaced by another. Allylic substitution in an unsaturated fatty acid is considered a replacement reaction as is the substitution of a hydrogen atom on an unsaturated carbon; opening of an oxirane ring is not. The latter is discussed in the section on addition reactions.

A. SUBSTITUTION OF HYDROGEN

1. Substitution of Hydrogen by Halogen

Treatment of saturated fatty acids with chlorine or bromine and without the use of other reagents results in the introduction of one or more halogen atoms. Some lack of consistency will be noted in the results of the several investigations described below. Halogenation only in the 2-position by the direct chlorination of ethyl stearate evidently was not successful, since the product of the reaction was not identical with ethyl 2-chloroöctadecanoate produced by other means (209). Polychlorination occurred yielding a chlorinated ester which was fractionally distilled without decomposition. A dichlorohexadecanoic acid has been prepared by the chlorination of palmitic acid at 70° (564). Evidence obtained by dehydrohalogenation and oxidative cleavage indicated that halogenation had occurred in all positions. Methyl palmitate plus chlorine at 40–59° yielded a dichloro ester; palmitic acid plus chlorine yielded products which closely correspond in chlorine content to the dichloro and tetrachloro acids (565). Introduction of amounts of chlorine greater than the weight of the original fatty acid have been reported (309). Results based upon a study of the properties of synthetic 2-, 3-, 4-, and 5-chloro acids indicated that the addition of 1 mole of chlorine to a fatty acid chloride produced 50 per cent of the 4- and 5-chloro acids and 25 per cent each of the 2- and 3-chloro derivatives (207). The mixed chloro acids could not be separated by fractional distillation. Chlorination or bromination of keto acids [12-oxoöctadecanoic, 9(10)-oxoöctadecanoic, 13(14)-oxodocosanoic] in carbon tetrachloride at low temperatures (<75°) is said to be selective, yielding dihalides with substitution adjacent to the carbonyl but without substitution at the 2-position (357).

Direct fluorination of a carbon tetrachloride solution of palmitic acid at 12° resulted in a halogenated acid containing 21 per cent fluorine and 12 per cent chlorine (174). Complete substitution of hydrogen with fluorine has been accomplished through the electrolysis of solutions of the fatty acids or their anhydrides in anhydrous hydrogen fluoride, thus producing the perfluoro acid fluoride (145, 266). Perfluoro acids up to a carbon chain length of fourteen have been produced by this process (through hydrolysis of the acid fluoride). As compared to the original acids, the perfluoro compounds are characterized by relatively low boiling points and low solubilities. Perfluoro acids of high purity were not described. 18,18,18-Trifluoroöctadecanoic acid has been synthesized (186), as has a series of ω-fluoro fatty acids (394, 396).

Various reagents have been employed for the introduction of halogen atoms (chlorine or bromine) into the saturated fatty acid molecule. Most of these reagents are selective in their action and provide a means for introducing the halogen preferentially into the 2-position of the acid molecule. Most commonly used is the procedure originally described by Hell and co-workers (225, 226, 227) for the bromination of aliphatic acids. This procedure was also used by LeSueur in his studies of fatty acid derivatives (315, 316). The acid, when treated with bromine and red phosphorus, is converted into the 2-bromo acid bromide, which is usually hydrolyzed immediately to the corresponding 2-bromo acid (119, 332, 352, 468, 524) or it may be converted to an ester by treatment with an alcohol (62).

$$R(CH_2)_nCH_2COOH \xrightarrow{Br_2, P} R(CH_2)_nCHBrCOBr \xrightarrow{H_2O} R(CH_2)_nCHBrCOOH$$
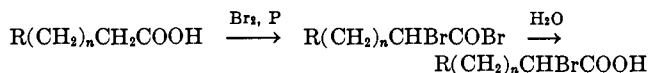
Published values for the melting points of a series of 2-bromo acids are given in Table 2. It is obvious that the value for the C_{14} compound is much too low.

TABLE 2

Acid	Melting point, °C.	References
C_{12}	30.5	316
C_{14}	31	227
C_{15}	42.5	316
C_{16}	51.5–52	225, 316
	52.3–52.5 (corr.)	524
C_{17}	52.5	315
C_{18}	60–61	226, 315

A similar procedure for 2-chlorination has been reported (436, 437). The bromination has been carried out in thionyl chloride to yield the 2-bromo acid chloride (524).

A modification of the bromination procedure employed bromine plus catalytic amounts of phosphorus trichloride and led directly to the 2-bromo acid (68, 123, 542). 2-Bromination through the use of potassium
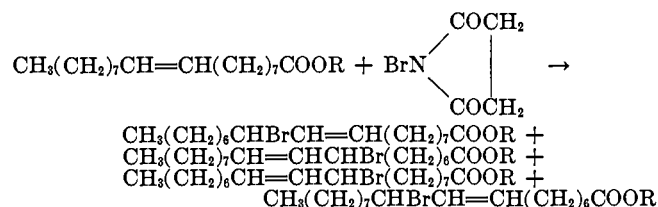
bromide in concentrated sulfuric acid and 2-iodination through the use of iodine in nitrosulfonic acid (a mixture of fuming nitric acid, nitric acid, and sulfur dioxide) have been reported (571).

Chlorination of saturated fatty acids with poly-chloroalkanes ($CHCl_3$, CCl_4, $C_2H_4Cl_2$, etc.) or sulfuryl chloride plus benzoyl peroxide appears to proceed in a random manner, although the position of substitution was not established (475). With the chlorinated solvents 0.07 to 1.06 chlorine atoms per chain were introduced using 0.75 to 4.4 moles of chlorine per mole of peroxide. With sulfuryl chloride 0.83 to 1.4 chlorine atoms per chain were introduced using a chlorine–peroxide ratio of 88:140. Chlorination in the 2-position of methyl laurate was reported when N-chlorosuccinimide and benzoyl peroxide were used in carbon tetrachloride (102). A fraction corresponding in chlorine content to the dichloro ester was also isolated. 2-Chloro acids of various chain lengths (C_6 to C_{18}) have been synthesized through chlorination of the appropriate alkylmalonic acid with sulfuryl chloride followed by decarboxylation (207).

$$RCH(COOH)_2 \xrightarrow{SO_2Cl_2} RCCl(COOH)_2 \xrightarrow{-CO_2} RCHClCOOH$$

Processes for the chlorination of fatty acids dissolved in solvents both with (439, 440) and without (176) promotion by radiation have been reported. Halogenation in the presence of elements of Group V, VI, or VII or their compounds when carried out at elevated temperatures and under ultraviolet irradiation is said to result in either mono- or polyhalogenation, depending upon the wave length of the light used (512).

Allylic halogenation was first applied by Ziegler and co-workers (602) to ethyl 10-undecenoate and methyl oleate, using N-bromosuccinimide as the halogenating reagent. This reaction is accompanied by allylic rearrangement. Thus, as an example, an oleate should yield a mixture of bromoöctadecenoates:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOR + BrN\begin{array}{c} COCH_2 \\ | \\ COCH_2 \end{array} \rightarrow$$

$$CH_3(CH_2)_6CHBrCH{=}CH(CH_2)_7COOR +$$
$$CH_3(CH_2)_7CH{=}CHCHBr(CH_2)_6COOR +$$
$$CH_3(CH_2)_6CH{=}CHCHBr(CH_2)_7COOR +$$
$$CH_3(CH_2)_7CHBrCH{=}CH(CH_2)_6COOR$$

The relative proportions of these products have not been established. Other reports of allylic halogenation, using N-bromosuccinimide (216, 355, 383, 477, 521, 543) or tert-butyl hypochlorite (52, 544, 549) with various unsaturated fatty acids or mixtures thereof, have not included definite characterization of the products. This work has been directed largely toward increasing the unsaturation of the fatty acid molecule through halogenation followed by dehydrohalogenation (see pages 132 and 133). One such report presents

evidence which is said to show that monobromination occurs in the allylic position farthest from the carboxyl group (356). The evidence, which is not unequivocal, will be discussed in the section on dehydrohalogenation (see page 133). The reaction is accelerated by ultraviolet light (56). Allylic bromination with N-bromosuccinimide is now generally recognized as a free-radical reaction (338).

Products of the bromination of methyl 10-undecenoate with N-bromosuccinimide have been described (223) and characterized through reaction with a Grignard reagent (189) (see page 106). Apparently the bromination yielded approximately two parts of 9-bromo-10-undecenoate and one part of 11-bromo-9-undecenoate. Bromination of 6-octadecenoic acid with N-bromosuccinimide yielded a monobromoöctadecenoic acid which has been identified as the 8-bromo acid (125). The evidence for this identification is not conclusive (see the discussion of dehydrohalogenation on page 133), and it is probable that the monobromoöctadecenoic acid is a mixture of 5- and 8-bromo-6-octadecenoic acids.

2. Substitution of Hydrogen by Sulfur

Introduction of the sulfo group into the 2-position of saturated fatty acids has been accomplished through treatment with sulfur trioxide in tetrachloroethylene or carbon tetrachloride (192, 516, 584, 585). Yields in excess of 80 per cent were obtained. Evidence that sulfonation occurs exclusively in the 2-position has been presented (586). Chlorosulfonic acid also has been employed for the sulfonation of saturated fatty acids (64). The reaction of lauroyl chloride with chlorine and thionyl chloride under actinic light followed by hydrolysis and oxidation (of the sulfino group) is said to yield sulfonated lauric acid (417). The position of substitution was not indicated.

3. Substitution of Hydrogen by Nitrogen

Introduction of nitro groups into the aliphatic chain of higher fatty acids, esters, and nitriles by reaction in the liquid phase with N_2O_4 has been described (27). Presumably substitution is random; no pure compounds were described. Nitric acid vapor also has been employed for the nitration of fatty acids (438).

4. Substitution of Hydrogen by Carbon

The acetoacetic ester condensation has been applied to fatty acid esters, leading to the formation of 2-acyl esters. Various basic condensing agents were employed,

$$2RCH_2COOC_2H_5 \rightarrow RCH_2COCHRCOOC_2H_5$$
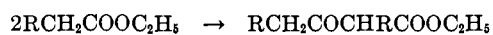
including sodium alkoxides (94, 182), Grignard reagents (mesitylmagnesium bromide) (504), diisopropyl-aminomagnesium bromide (178), and sodium hydride (124, 218). Saponification of the keto ester is accom-

panied by decarboxylation with formation of the symmetrical higher aliphatic ketone.

Condensation of fatty acid esters with diethyl oxalate in the presence of sodium ethoxide led to the formation of a 3-ethoxycarbonyl-2-oxo acid (39). Decarboxylation of this product yielded the 2-oxo acid.

$$RCH_2COOC_2H_5 + (COOC_2H_5)_2 \xrightarrow[\text{(2) }H_2SO_4]{\text{(1) }NaOC_2H_5}$$

$$\underset{\overset{|}{COOC_2H_5}}{RCHCOCOOH} \xrightarrow[CH_3COOH]{H_2SO_4} RCH_2COCOOH$$

This procedure has been applied to a series of saturated acids.

Oxidative coupling to 10-undecynoic acid has been employed for the preparation of 10,12-docosadiynedioic acid and methyl 22-hydroxy-10,12-docosadiynoate (119).

$$2HC{\equiv}C(CH_2)_8COOH \xrightarrow{(O)}$$
$$HOOC(CH_2)_8C{\equiv}C—C{\equiv}C(CH_2)_8COOH$$

$$HO(CH_2)_9C{\equiv}CH + HC{\equiv}C(CH_2)_8COOCH_3 \xrightarrow{(O)}$$
$$HO(CH_2)_9C{\equiv}C—C{\equiv}C(CH_2)_8COOCH_3$$

B. SUBSTITUTION OF HALOGEN

1. Substitution of Halogen by Hydrogen

Reduction of halo acids is sometimes used as a means for obtaining the parent fatty acid for purposes of preparation or characterization. Thus, methyl 9,10,-18-triiodoöctadecanoate and methyl 10,16-diiodohexadecanoate were reduced with zinc and hydrochloric acid to methyl stearate and methyl palmitate, respectively (342), and 12-iodoöctadecanoic acid was reduced by zinc and acetic acid to stearic acid (481).

2. Substitution of Halogen by Halogen

Iodine is frequently introduced into the fatty acid molecule by interaction of the corresponding bromide with sodium or potassium iodide. 2-Iodohexadecanoic and 2-iodoöctadecanoic acids have been prepared in this manner (352, 524) as well as 11-iodoundecanoic acid (513). Esters of 11-fluoroundecanoic and 12-fluorododecanoic acids have been produced by treatment of the corresponding bromo esters with silver fluoride (98). A variety of ω-fluoro acids and esters were prepared from the bromo compounds by means of either potassium fluoride or silver fluoride (395).

3. Substitution of Halogen by Oxygen

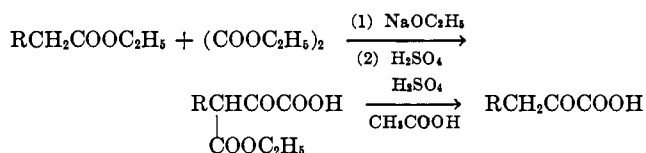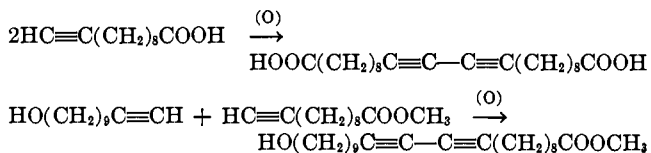Halogens are readily replaced by hydroxyl, acyloxy, alkoxy, or aryloxy groups through treatment with an appropriate base under proper conditions. Thus, alkali (followed by acidification) converted methyl 2-chlorododecanoate to 2-hydroxydodecanoic acid (102), 2-bromoöctadecanoic acid to the corresponding 2-hydroxy

compound (209), 2-bromodocosanoic acid to 2-hydroxydocosanoic acid, and 13(14)-bromodocosanoic acid to the 13(14)-hydroxy acid (119). 9(10)-Chloro-10(9)-hydroxyoctadecanoic acid was converted to 9,10-dihydroxyoctadecanoic acid by sodium bicarbonate at 150° (364). A stronger base, sodium carbonate, even at lower temperatures results in dehydrohalogenation (see page 133). Substitution of hydroxyl for halogen may also be accomplished by introduction of the acetoxy group by means of sodium or potassium acetate in glacial acetic acid followed by saponification, e.g., with 2-chloroöctadecanoic acid (207) and 21-bromoheneicosanoic acid (89). This procedure is effective for substitution at all but the 3-position of the fatty acid chain. 3-Chloro esters upon treatment with sodium acetate in glacial acetic acid yielded only the unsaturated ester; no evidence of substitution was observed (207). 2(3)-Acetoxy-3(2)-bromoöctadecanoic acid was converted to 2,3-dihydroxyoctadecanoic acid by treatment with silver acetate in acetic acid followed by saponification and acidification (353). Hydroxylation was effected through the cyclization (lactone formation) of terminally substituted halo acids. Yields ranging from 56 per cent (C_9) to 97 per cent (C_{17}) were obtained from the bromo acids by heating with potassium carbonate in methyl ethyl ketone (248). Kinetic studies of the cyclization of the potassium salts of 11-bromoundecanoic acid and 15-bromopentadecanoic acid have indicated that the ionization of bromine is the rate-determining step (141). The yield is at a minimum near the eleven-carbon chain length.

The reaction of 30 per cent ethanolic potassium hydroxide with 2-bromo acids yielded a mixture of 2-hydroxy, 2-ethoxy, and 2-unsaturated acids. Thus, 2-bromohexadecanoic acid yielded 21–25 per cent 2-hydroxyhexadecanoic, 68–74 per cent 2-ethoxyhexadecanoic, and 3.7–7.4 per cent 2-hexadecenoic acids (33); 2-bromodocosanoic acid yielded 71–81 per cent 2-ethoxydocosanoic, 4.6–5.5 per cent 2-docosenoic, and 2-hydroxydocosanoic (presumably about 15 per cent) acids (34). With 6 per cent ethanolic potassium hydroxide 2-bromohexadecanoic acid yielded 93 per cent 2-hydroxyhexadecanoic acid, whereas the 2-iodo compound yielded 57 per cent 2-hexadecenoic acid with some 2-hydroxyhexadecanoic acid as a by-product (524).

A variety of alkoxy and aryloxy groups has been introduced into the fatty acid hydrocarbon chain by interaction of a halo acid with the appropriate sodium alkoxide or aryloxide. Examples are given in Table 3.
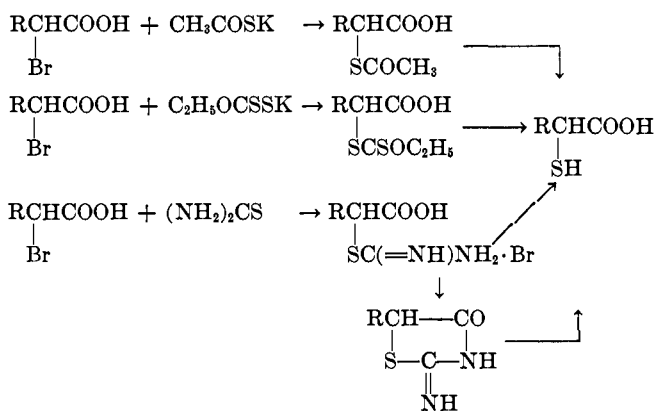
4. Substitution of Halogen by Sulfur

Substitution of sulfur for halogen is accomplished by means of a number of reagents, selection of which depends upon the specific sulfur-containing group to be introduced. It is reported that mercapto groups

TABLE 3

Alkoxy (aryloxy) Acids

Halo acid (ester)	Alkoxy (aryloxy) acid	References
2-Bromodecanoic	2-Phenoxydecanoic	253
	2-o-Methylphenoxydecanoic	253
	2-o-Methoxyphenoxydecanoic	253
11-Bromoundecanoic	11-Methoxyundecanoic	469
	11-Biphenylyloxyundecanoic	397
	11-Phenoxyundecanoic	397, 431
2-Bromotetradecanoic	2-Butoxytetradecanoic	209
2-Bromohexadecanoate	2-(2-Hydroxyethoxy)hexadecanoate	208
	2-Methoxyhexadecanoate	508
2-Bromoöctadecanoate	2-(2,3-Dihydroxypropoxy)octadec-anoate	208
11-Chloroundecanoate	11-(p-Methoxycarbonylphenoxy)-undecanoate	254

may be substituted for bromine atoms by treatment of the bromo acid with sodium sulfide plus sulfur followed by catalytic hydrogenation, e.g., 10,11-dibromo-undecanoic acid was thus converted to 10,11-dimercap-toundecanoic acid (310). 2-Bromoöctadecanoic acid was converted to the 2-mercapto acid with potassium hydrosulfide (332). When treated with sodium sulfide plus sulfur 11-bromoundecanoic acid yielded 11,-11'-dithiodiundecanoic acid (446), which was then oxidized with nitric acid to 11-sulfoundecanoic acid. With excess potassium sulfide 2-bromoöctadecanoic acid yielded 2,2'-dithiodioctadecanoic acid (332). Usually, however, mercapto groups are introduced by means of a salt of thiolacetic acid or of a salt of ethyl xanthate, or through interaction with thiourea. In each instance hydrolysis of the intermediate acetylthio, xanthate, pseudothiouronium compound, or pseudo-thiohydantoin is required to produce the mercapto group according to one of the reactions:

RCHCOOH + CH₃COSK → RCHCOOH
| |
Br   SCOCH₃

RCHCOOH + C₂H₅OCSSK → RCHCOOH
| | → RCHCOOH
Br   SCSOC₂H₅ |
                                                 SH

RCHCOOH + (NH₂)₂CS → RCHCOOH
| |
Br   SC(=NH)NH₂·Br
                              ↓
                     RCH——CO
                        | |
                        S—C—NH
                           ‖
                           NH

Specifically, 6,8-dimercaptoöctanoic acid (434) and 10,11-dimercaptoundecanoic acid (398) have been prepared from thiolacetic acid; 2-mercaptododecanoic, -tetradecanoic, -hexadecanoic, and -octadecanoic acids from potassium ethyl xanthate (306); and 11-mercapto-undecanoic (69, 583), 2-mercaptohexadecanoic (586), and 2-mercaptoöctadecanoic acids (164) from thiourea and the pseudothiouronium bromide or the pseudo-thiohydantoin.

Various other sulfur-containing derivatives of fatty acids have been reported and are listed in Table 4, together with the halo acid from which they were derived and the reagent which was employed in their preparation.

5. Substitution of Halogen by Nitrogen

Amino or substituted amino groups may be introduced into the hydrocarbon chain of fatty acids by substitution for halogen. 2-Amino fatty acids of various chain lengths have been produced by treatment of the 2-bromo acid with aqueous ammonia (152, 163, 388, 542), alcoholic ammonia (68, 388), or anhydrous ammonia (46). 10-Aminodecanoic (496) and 11-aminoundecanoic (494) acids were prepared by interaction of the corresponding bromo acids with aqueous ammonia and 10-aminoundecanoic acid by means of anhydrous ammonia (11). 9-Chlorononanoic and 11-chloroundecanoic acids were converted to the corresponding amino acids with aqueous ammonia (368). 11-Amino-10-hydroxyundecanoic acid was obtained by the reaction of 11-chloro- (329) or 11-bromo-10-hydroxyundecanoic acid (109) with ammonium hydroxide. The actual identification of the amino acid was based upon the assumed homogeneity of the halogen compounds. 2-Amino groups also have been introduced through treatment of a 2-bromo ester with sodium azide, and then catalytic hydrogenation of the 2-azido group (246).

A variety of substituted amino fatty acids have been produced through the reaction of a halo (usually bromo) acid with an amine (Table 5).

6. Substitution of Halogen by Carbon

Various condensation or coupling reactions have been used with halo acids or esters in order to produce specific structural modifications in the fatty acid molecule. Condensation of acetoacetic ester with 11-iodoundecanoic acid followed by saponification of the resulting dicarboxylic acid ester and decarboxylation produced 12-oxotetradecanoic acid (517).

I(CH₂)₁₀COOC₂H₅ + CH₃COCH₂COOC₂H₅ $\xrightarrow{\text{NaOC}_2\text{H}_5}$

C₂H₅OOCCH(COCH₃)(CH₂)₁₀COOC₂H₅ $\xrightarrow[\text{(2) decarboxylation}]{\text{(1)   KOH}}$

CH₃CO(CH₂)₁₁COOH
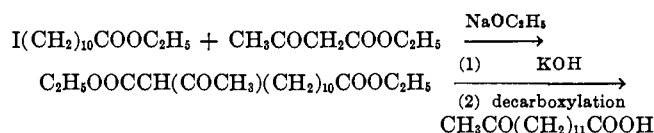
The malonic ester condensation with 2-bromo esters followed by saponification and decarboxylation has been employed to produce a series of dicarboxylic acids (62).

RCHBrCOOC₂H₅ + NaCH(COOC₂H₅)₂ →

RCH(COOC₂H₅)CH(COOC₂H₅)₂ $\xrightarrow[\text{(2) decarboxylation}]{\text{(1)   KOH}}$

RCH(COOH)CH₂COOH

R = C₄, C₈, C₉, C₁₀, C₁₂
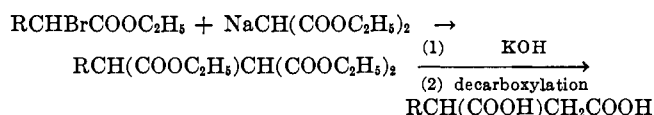
Comparison of yields of tridecanedioic acid obtained

TABLE 4

Preparation of Sulfur-Containing Fatty Acid Derivatives

Halo acid	Reagent	Product	References
6,8-Dichloroöctanoic acid	C₆H₅SNa	C₆H₅SCH₂CH₂CH(CH₂)₄COOH $\vert$ SC₆H₅	434
6,8-Dibromoöctanoic acid	C₆H₅SNa	C₆H₅SCH₂CH₂CH(CH₂)₄COOH $\vert$ SC₆H₅	434
Ethyl 6,8-dibromoöctanoate	CH₃COSK	CH₃COSCH₂CH₂CH(CH₂)₄COOC₂H₅ $\vert$ SCOCH₃	354
10-Bromodecanoic acid	HSC₂H₄NH₂	NH₂C₂H₄S(CH₂)₉COOH	111
11-Bromoundecanoic acid	HSC₂H₄NH₂	NH₂C₂H₄S(CH₂)₁₀COOH	110, 111
	KSCN^a	NCS(CH₂)₁₀COOH	69
	KSCSOC₂H₅	C₂H₅OCSS(CH₂)₁₀COOH	69
	C₁₂H₂₅SNa	C₁₂H₂₅S(CH₂)₁₀COOH	69
2-Bromoöctadecanoic acid	(NH₂)₂CS	C₁₆H₃₃CH——CO $\vert\quad\vert$ SC(=NH)NH	381, 523
	C₆H₅Na	C₁₆H₃₃CH(SC₆H₅)COOH	464
	Na₂CS₃	[C₁₆H₃₃CH(COOH)S]₂CS	581
	NH₂CS₂NH₄	[C₁₆H₃₃CH(COOH)S]₂CO	582
11-Amino-10-chloroundecanoic acid	Na₂CS₂O	H₂C——CH(CH₂)₈COOH^b N$\diagdown$S $\diagdown$C$\diagup$ CSH	329

a The corresponding selenium derivative is also reported (69). *b* Assignment structure based on proposed structure of halo acid (see page 131).

TABLE 5

Substituted Amino Acids Prepared from Halo Acids

Amino acid	Reference
CH₃NH(CH₂)₁₀COOH	10
(C₂H₅)₂N(CH₂)₁₀COOH	146
CH₃(CH₂)₅CH(NHC₆H₁₁)COOR	257
HOC₂H₄NH(CH₂)₁₆COOH	12
CH₃(CH₂)₁₅CH(NHCH₂CH₂OH)COOH	209
[—CH₂NH(CH₂)₁₆COOCH₃]₂	63
(CH₂)ₙ[NH(CH₂)₁₀COOH]₂ (n = 4, 6, 7, 8)	539
[—SC₂H₄NH(CH₂)₁₀COOH]₂	111
CH₃(CH₂)₁₅CH(NHC₆H₄CH-o)COOH	587
CH₂=CHCH₂NH(CH₂)₁₀COOH	112
CH₂=CH(CH₂)NH(CH₂)₁₀COOH	108

through the condensation of malonic ester with 11-bromoundecanoic acid or its ester has shown that a good yield (87 per cent) can be obtained with the acid, providing that an excess of the sodium derivative of the malonate (3:1) is used (418). It was postulated that one mole of sodium is used to form the sodium soap. However, a much lower yield (39 per cent) was obtained when the soap was used in place of the acid.

Coupling of methyl 8-iodoöctanoate with 8-bromoöctanoyl chloride by means of a copper–zinc alloy and then saponification led to the formation of 16-bromo-9-oxohexadecanoic acid (248).
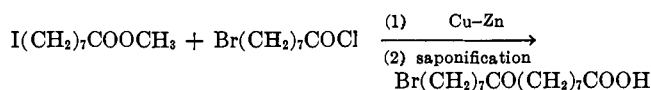
$$I(CH_2)_7COOCH_3 + Br(CH_2)_7COCl \xrightarrow[\text{(2) saponification}]{\text{(1)} \quad Cu-Zn} Br(CH_2)_7CO(CH_2)_7COOH$$

In the same manner were prepared 16-bromo-12-oxo-hexadecanoic acid and 13-bromo-5-oxotridecanoic acid. The mixture of 9-bromo-10-undecenoate and 11-bromo-9-undecenoate obtained by the bromination of methyl 11-undecenoate with N-bromosuccinimide, when treated with heptylmagnesium bromide, yielded (after saponification) a mixture of cis- and trans-9-octadecenoic

acids plus 9-heptyl-11-undecenoic acid (189). The relative proportion of these products was interpreted as an indication of the ratio of the original bromo esters (see page 103). The separations were made by crystallization and could not have been quantitative.

$$BrCH_2CH=CH(CH_2)_7COOCH_3 \xrightarrow[\text{(2) saponification}]{\text{(1)} \ CH_3(CH_2)_6MgBr} CH_3(CH_2)_7CH=CH(CH_2)_7COOH$$

$$CH_2=CHCHBr(CH_2)_7COOCH_3 \xrightarrow[\text{(2) saponification}]{\text{(1)} \ CH_3(CH_2)_6MgBr} CH_3(CH_2)_6CH(CH=CH_2)(CH_2)_7COOH$$
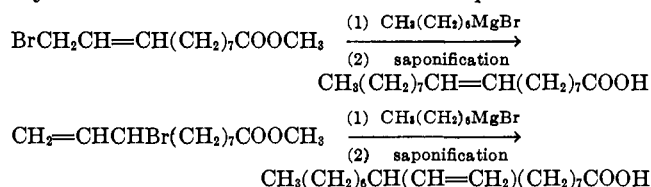
Ethyl 11-cyanoundecanoate was produced from the 11-bromo ester by reaction with potassium cyanide (229). This process provides a route for the synthesis of dodecanedioic acid. In the same way 2-bromodocosanoic acid was converted to the 2-cyano acid (119). 12-(2,6-Dimethylpyrimidinyl)-dodecanoic acid has been prepared from 11-bromoundecanoate and 2,6-dimethyl-pyrimidinylmethyllithium (229). Coupling of ethyl 2-bromoöctanoate through treatment with sodium diethyl phosphite has been reported (117).

$$C_6H_{13}CHBrCOOC_2H_5 + NaPO(OC_2H_5)_2 \rightarrow \\ (C_6H_{13}CHCOOC_2H_5)_2$$
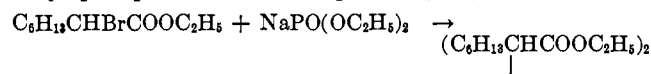
7. Substitution of Halogen by Phosphorus

A series of the vinyl esters of 2-bromo acids has been converted to the corresponding 2-(diethylphosphono) esters by the reaction with triethyl phosphite (470),

$$RCHBrCOOC_2H_5 + (C_2H_5O)_3P \rightarrow RCH[PO_3(C_2H_5)_2]COOC_2H_5$$

and by the same general reaction a variety of 2-(dialkyl-phosphono) esters have been prepared (3). Also, 11-(dialkylphosphono)undecanoates have been prepared from 11-bromoundecanoate by means of trialkyl phosphite (471) or sodium dibutyl phosphite (116).

TABLE 6

Halogenation of Hydroxy (or Alkoxy) Acids (or Esters)

Hydroxy acid or ester	Reagent	Product	References
$HO(CH_2)_{10}COOH$	PCl_5	$Cl(CH_2)_{10}COOH$	1
$CH_3CHOH(CH_2)_8COOH$		$CH_3CHCl(CH_2)_8COOH$	1
$HO(CH_2)_{17}COOH$	$SOCl_2$	$Cl(CH_3)_{17}COOH$	214
$ClCH_2CH_2CHOH(CH_2)_4COOC_2H_5$		$ClCH_2CH_2CHCl(CH_2)_4COOC_2H_5$	434
$CH_3(CH_2)_5CHOHCH_2CH=CH(CH_2)_7COOCH_3$ (*cis* and *trans*)		$CH_3(CH_2)_5CHClCH_2CH=CH(CH_2)_7COOCH_3$ (*cis* and *trans*)	203
$CH_3(CH_2)_5CHOHCH_2C\equiv C(CH_2)_7COOCH_3$		$CH_3(CH_2)_5CHClCH_2C\equiv C(CH_2)_7COOCH_3$	203
$NH_2CH_2CHOH(CH_2)_8COOH\cdot HCl$		$NH_2CH_2CHCl(CH_2)_8COOH\cdot HCl$	329
$CH_3(CH_2)_5CHOHCH_2CH=CH(CH_2)_7COOCH_3$	$POCl_3$	$CH_3(CH_2)_5CHClCH_2CH=CH(CH_2)_7COOCH_3$	134
$CH_3(CH_2)_6CHOHCHOH(CH_2)_7COOH$ (*erythro* and *threo*)	HBr, CH_3COOH, and H_2SO_4	$CH_3(CH_2)_6CHBrCHBr(CH_2)_7COOH$ (*erythro* and *threo*)	20
$CH_3(CH_2)_7CHOHCHOH(CH_2)_7COOH$ (*erythro*)		$CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOH$ (*threo*)	20, 58
$CH_3(CH_2)_4CHOHCHOH(CH_2)_{10}COOH$ (*threo*)		$CH_3(CH_2)_4CHBrCHBr(CH_2)_{10}COOH$ (*erythro*)	65
$CH_3(CH_2)_7CH(OCH_3)CHOH(CH_2)_7COOCH_3$		$CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOCH_3$	20
$CH_3(CH_2)_7CHOHCHOH(CH_2)_{11}COOH$ (*erythro* and *threo*)		$CH_3(CH_2)_7CHBrCHBr(CH_2)_{11}COOH$ (*erythro* and *threo*)	84
$CH_3O(CH_2)_{20}COOH$		$Br(CH_2)_{20}COOH$	89
$CH_3(CH_2)_7CH(OCH_3)CHOH(CH_2)_7COOC_2H_5$	HBr and CH_3COOH	$CH_3(CH_2)_7CHBrCHOH(CH_2)_7COOC_2H_5$	20
$CH_3(CH_2)_7CH(OCH_3)CHOH(CH_2)_{11}COOH$	HBr	$CH_3(CH_2)_7CHBrCHBr(CH_2)_{11}COOH$	87
$HO(CH_2)_{21}COOH$		$Br(CH_2)_{21}COOH$	148
$CH_3(CH_2)_7CHOHCHOH(CH_2)_7COOH$ (*threo*)	Br_2	$CH_3(CH_2)_7CHBrCHBr(CH_2)_7COOH$ (*erythro*)	84
$CH_3(CH_2)_5CHOH(CH_2)_{10}COOH$	I_2 and red P	$CH_3(CH_2)_5CHBr(CH_2)_{10}COOH$	481

C. SUBSTITUTION OF OXYGEN

1. Substitution of Oxygen by Hydrogen

The direct reduction of hydroxyl or alkoxy groups on the fatty acid chain is not a common reaction; Wolff-Kishner reduction of keto acids frequently is employed. However, the reduction of 9-oxo-10-methoxyoctadecanoic acid (an acyloin ether) with sodium in ethanol is reported to yield 9-hydroxyoctadecanoic acid, m.p. 75.5° (21). With zinc and hydrochloric acid 10-hydroxyoctadecanoic acid, m.p. 81–82°, was obtained. The melting points of these hydroxy acids and of the keto acids produced therefrom are in reasonable accord with the structures as stated (*cf.* 127). Reduction of the 9-oxo-10-methoxyoctadecanoic acid with hydrazine hydrate plus sodium hydroxide yielded a mixture containing 75 per cent octadecenoic acids (oleic and elaidic) and octadecanoic acid. 14-Methoxy-13-oxodocosanoic acid with sodium and ethanol yielded 13-hydroxydocosanoic acid, m.p. 86–87°; with zinc amalgam and hydrochloric acid, 14-hydroxydocosanoic acid, m.p. 90°, is obtained (87) (see page 129). The melting point of a mixture of the two products was 78–82°. Reduction of simple keto acids with hydrazine and sodium or potassium hydroxide (Wolff-Kishner) yields the corresponding saturated acid. This process has been applied to 5-oxohexadecanoic acid (138), to 9-oxotetradecanoic, 10-oxoöctadecanoic, and 10-oxotricosanoic acids (22), to the 7-, 8-, 9-, 10-, and 12-carbon 5-keto acids (514), to 18-oxononatricosanoic and 18-oxoheptacosanoic acids (88), and to 12-phenyl-10-oxododecanoic acid (497). 9(10)-Oxoöctadecanoic acid was converted to octadecanoic acid via the semicarbazone and sodium ethoxide (131).

2. Substitution of Oxygen by Halogen

The substitution of hydroxyl by halogen frequently has been employed in studies of the chemistry of fatty acids. Classical methods are usually employed; recent examples of some of these are listed in Table 6, which shows the halogenating agent and the hydroxy (or alkoxy) acid or ester.

A study of the chemistry of 2,3-dihydroxyoctadecanoic acid (352) deserves more detailed comment. *threo*-2,3-Dihydroxyoctadecanoic acid (I), m.p. 126°, when treated with hydrogen bromide in acetic anhydride as solvent, yielded an acetoxybromo acid (IV) which melted at 57° after recrystallization. *erythro*-2,3-Dihydroxyoctadecanoic acid (II), m.p. 107°, after similar treatment yielded a crude product which was separated by crystallization into two fractions (VI, m.p. 49°, and V, m.p. 84.5–85°). The fraction (VI) melting at 49° was refluxed with methanol in the presence of a small amount of sulfuric acid, and the resulting product (presumably bromohydroxyoctadecanoic acid) was debrominated by catalytic hydrogenolysis (353). The resulting material was identified as 3-hydroxyoctadecanoic acid (VII). The same hydroxy acid was obtained from the acetoxybromoöctadecanoic acid (IV) melting at 57°. Therefore, it was concluded that the substances melting at 49° and 57° are 3-acetoxy-2-bromoöctadecanoic acids and, on the basis of the methods of synthesis, that the former has the *threo* configuration and the latter the *erythro*. An essentially similar procedure when applied to the acetoxybromoöctadecanoic acid (V) melting at 84.5–85° yielded 2-hydroxyoctadecanoic acid (VIII), thus indicating that this acetoxybromo acid is *threo*-2-acetoxy-3-bromoöctadecanoic acid.

Theoretically two *erythro-* (III and IV) and two *threo*-acetoxybromoöctadecanoic acids (V and VI) are produced from both *threo-* and *erythro*-2,3-dihydroxyoctadecanoic acids by the reaction described above. It is probable that in each instance the pairs of *erythro* and *threo* compounds will form eutectic or minimum-melting mixtures, the composition of which is dependent to a large extent on the relative melting points of the individual components. If minimum-melting mixtures are formed, it would not be possible to separate both pure components by fractional crystallization; whether either can be isolated depends upon how close to a one-to-one ratio the composition of the minimum-melting mixture lies.

In the investigation under discussion it appears that it was possible to isolate one of the components of the *erythro*-acetoxybromoöctadecanoic acid pair, namely, the 3-acetoxy-2-bromo-isomer (IV), m.p. 57°. The actual yield (less than 42 per cent) of the compound which was isolated is in accord with this possibility; the remaining material must have consisted of a mixture of the 2,3- and 3,2-isomers (III and IV). The *threo*-acetoxybromoöctadecanoic acid pair was separated into two components melting at 49° and 84.5°. Only 7 per cent of the latter, the less-soluble component, was isolated; it probably is pure *threo*-2-acetoxy-3-bromoöctadecanoic acid (V). The component melting at 49° must be a mixture of the two *threo* positional isomers (V and VI) of unknown composition. Apparently the debromination process by which the acetoxybromo acids were converted to hydroxyoctadecanoic acids yielded a mixture from which 3-hydroxyoctadecanoic acid (VII) could be crystallized in a reasonably pure state. Here again the

actual yield of this component (less than 43 per cent) does not conflict with the possibility that substantial amounts of 2-hydroxyoctadecanoic acid were also present. It is not unlikely that an inseparable pair of compounds such as the mixture of acetoxybromo acids, m.p. 49°, could be converted to a mixture of hydroxy acids from which one component could be isolated by crystallization. The scheme shown is proposed to explain the above-described observations.

3. Substitution of Oxygen by Nitrogen

Reductive amination of keto acids offers a route for the preparation of amino acids. Conversion by this method of 2-oxononanoic and 2-oxononadecanoic acids to the corresponding amino acids has been reported (169).

D. SUBSTITUTION OF NITROGEN

2-Aminoöctanoic acid was converted to the 2-hydroxy acid by nitrous acid (46). Hydrogenation of the semicarbazone of 6-oxoöctadecanoic acid in the presence of water is said to yield 6-hydroxyoctadecanoic acid (83).

V. ADDITION REACTIONS

This section on addition reactions will include addition to double bonds and to carbonyl compounds plus reactions which open the oxirane ring. Additions to double bonds constitute the largest portion of the section and in fact have received more attention than any other single class of reactions of the hydrocarbon chain of fatty acids.
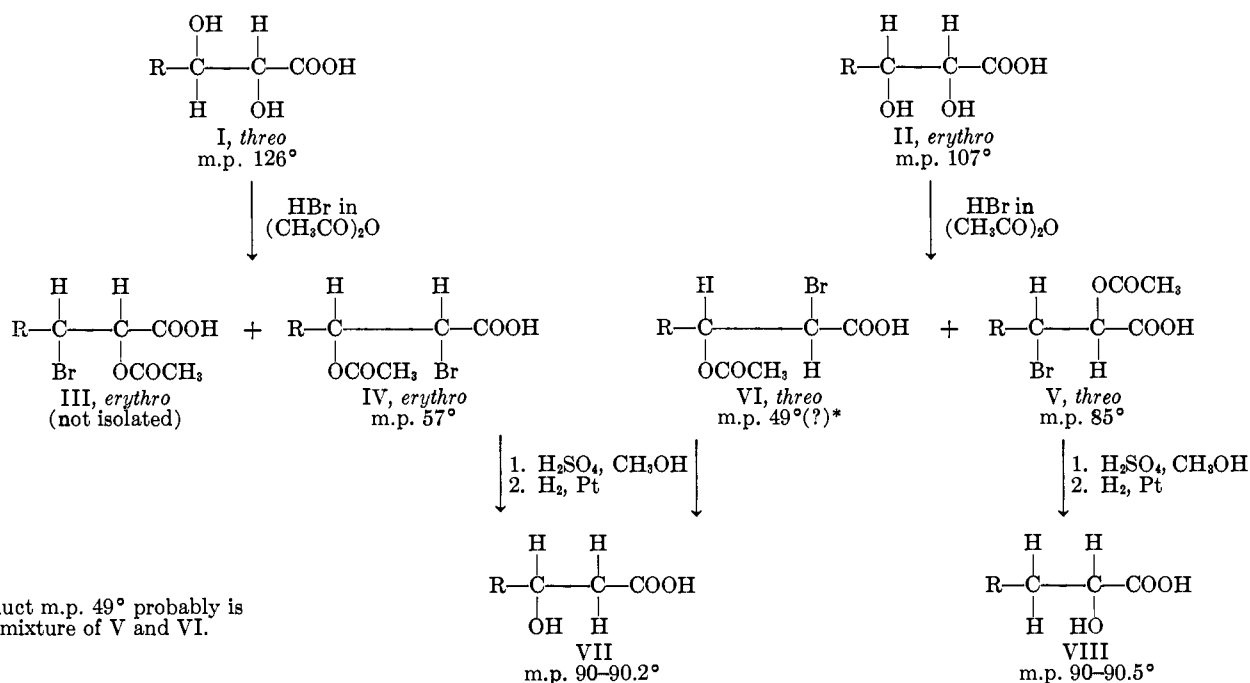
* Product m.p. 49° probably is a mixture of V and VI.

A. ADDITION TO DOUBLE BONDS

1. Addition of Hydrogen

Addition of hydrogen to the olefinic bonds of higher aliphatic acyl radicals in triglyceride fats and oils is one of the more important commercial processing procedures. Considerable attention therefore has been devoted to studies of catalytic hydrogenation, the procedure usually employed. These studies have involved the use of pure unsaturated acids or esters as well as mixtures of pure materials and also of naturally occurring mixtures such as are found in oils and fats. To a large extent these investigations have been concerned with relative rates of reaction. Also the phenomenon of isomerization (geometrical and positional) during hydrogenation has received much attention. For the purposes of this review hydrogenation and isomerization will be discussed separately.

Periodically, reviews have appeared which serve to bring up to date the state of knowledge as of the time of writing. A more recent discussion of the hydrogenation of glyceride oils pertains not only to the organic chemistry of the process but also to catalysts and operating variables (160). The present writing will avoid, insofar as it is possible, restatement of information which has been reviewed adequately elsewhere. An attempt will be made, however, to examine critically in the light of present-day knowledge some of the generally accepted opinions concerning the addition of hydrogen to unsaturated fatty acids. A fair amount of work has been devoted to studies of the kinetics of hydrogenation with a view toward elucidating the mechanism of the reaction. Considering the fact that the mechanism of the hydrogenation of ethylene is not understood (151), it is questionable whether studies of systems as complicated as those involving fatty acids or mixtures of fatty acids are likely to be very fruitful. However, such studies do result in useful although empirical information.

The following discussion of the addition of hydrogen will relate to monoölefinic and polyolefinic acids in that order. No general discussion of catalysts will be included, although catalysts will sometimes be specified in connection with work under discussion.

(a) Addition of Hydrogen to Monoölefinic Acids

Studies of the hydrogenation of oleic acid or its esters (nickel or platinum as catalyst) have resulted in general agreement that first-order kinetics are observed when the reaction is conducted under conditions (temperature below 125°) which do not produce isomerization or dehydrogenation (199, 375, 498, 518, 519, 538, 566). Initially zero-order kinetics may prevail and have been attributed to a rate of hydrogen diffusion

lower than the rate of reaction (566). At higher temperatures the reaction becomes more complex, a result, at least in part, of positional and geometrical isomerization. Values for the activation energy for the hydrogenation of oleic acid have been variously estimated at 7 to 11 kcal./mole and the heat of reaction at 35 to 37 kcal./mole.

The rate of hydrogenation of oleic acid as compared with that of methyl oleate apparently depends upon the catalyst and conditions. With nickel on kieselguhr at 180°, oleic acid is hydrogenated at two to three times the rate of the methyl ester (558). With other esters the relative difference is even greater. With Raney nickel at lower temperatures (80–140°) the rate constant for methyl oleate is greater than that for oleic acid (484).

A number of workers have compared the rates of hydrogenation of cis and trans isomers (326, 403, 415, 416) and most agree that the cis isomer is hydrogenated more rapidly. It is reported, however, that the relative rates are dependent upon the amount of catalyst used (136).

There is growing acceptance of the belief that ease of hydrogenation in a series of alkenoic acids increases as the double bond is removed farther from the carboxyl group (161). This belief is based upon relatively little experimental evidence. Comparison of the rate of hydrogenation with platinum as catalyst of four octadecenoic acids, 2-, 3-, cis-6-, and cis-9-(oleic), has shown a significantly greater rate of hydrogen uptake for the 2- and 3- isomers as compared with the 6- or 9-isomers (402). The difference between the rates for the 6- and 9-isomers is small and probably does not exceed the experimental error. More recently the four hexenoic acids were compared using both colloidal platinum and rhodium on polyvinyl alcohol as catalysts (147). With platinum the rates of hydrogen uptake were in the order 2-, 3-, 4-, 5- (hexenoic acid); with rhodium 3-, 2-, 4-, 5-isomers. These acids and the 2- and 3-octadecenoic acids were synthesized and therefore consisted of the equilibrium mixture of cis and trans isomers (with the exception of 5-hexenoic acid). The relative proportions of the geometrical isomers in each of the positional isomers are not known and therefore the significance of observed differences in rates of hydrogenation must be questioned. The terminally unsaturated acid, 5-hexenoic acid, would be expected to be hydrogenated more readily than the other isomers. Also, it is questionable whether it is reasonable to extrapolate observations made with six-carbon acids to include the higher members of the series. Confirmation of the work with the eighteen-carbon series, and preferably with additional members of the series and all of the same geometrical configuration, should be obtained before the belief is accepted that relative proximity to the carboxyl group (excluding the 2- and 3-positions

and the terminal positions) has an influence on the rate of hydrogenation.

Comparisons of the rates of hydrogenation of alkenoic acids of a range of molecular weights have produced evidence that the rate decreases as the molecular weight increases (35, 147). These comparisons were made on acids of unknown or undisclosed geometrical configuration, and the results should therefore be accepted only tentatively. It is reasonable, however, to expect that a larger molecule would tend to orient less readily upon the catalyst surface and therefore would undergo hydrogenation at a slower rate.

Hydrogenation of substituted alkenoic acids is primarily of concern in the conversion of ricinoleic to 12-hydroxyoctadecanoic acid. This conversion, or the conversion of the ester, can be effected with platinum as the catalyst (206), with nickel at 150–160° and a hydrogen pressure of 200 p.s.i. (215), with Raney nickel in ethanol at room temperature and 40 p.s.i. (507), or with 1 per cent palladium on charcoal modified with silver and bismuth at 100° and 45 p.s.i. (600). Higher temperatures result in hydrogenolysis with loss of hydroxyl. 4-Oxo-2-alkenoic acids containing eleven, twelve, and thirteen carbon atoms have been hydrogenated, using platinum as catalyst, to yield the corresponding 4-oxoalkanoic acids (275).

Hydrogenation of oleic acid has also been accomplished by hydrogen transfer with cyclohexene as the hydrogen donor and palladium as the catalyst (90, 319).

Exposure of methyl oleate to tritium results in tritiation of the double bond with little or no substitution of tritium for hydrogen (258). The actual amount of saturation of the double bond is extremely small but was demonstrated through a combination of chromatographic and radiotracer techniques. Addition of hydrogen to the same extent is not detectable.

Various other reagents and techniques have been used for the reduction of monoölefinic acids. Oleic acid is over 90 per cent reduced by hydrazine (1:5 ratio) after 8 hr. at 60° (41, 106). Similar results were obtained with elaidic and ricinoleic acids. Electrolytic reduction of oleic acid has been reported (24), as have polarographic studies of mixtures of oleic and other unsaturated acids (328). Electrolytic reduction in another form has been accomplished by diffusion of hydrogen atoms generated electrolytically through membranes (septa) of iron, palladium, or platinum (560). Side reactions are said to occur. The reduction of oleic acid has been effected by means of a zinc–nickel couple (158), and reduction of 4-oxoalkenoic acids to yield the 4-oxoalkanoic acid has been accomplished by means of zinc and hydrochloric acid (275).

(b) Addition of Hydrogen to Polyolefinic Acids

Investigations of the hydrogenation of polyolefinic

acids have largely been concerned with selectivity and relative rates of reaction among various mono- and polyolefinic acids. Evidence for preferential reactivity according to the position of the double bond in the molecule also has been reported. The validity of conclusions which have resulted from work in the above-mentioned fields is completely dependent upon the validity of the analytical procedures employed. Therefore, in discussing this work considerable emphasis will be placed on a critical evaluation of the analytical procedures.

In the field of fatty acid chemistry selective hydrogenation refers to the process whereby in a mixture of mono- and polyolefinic acids (or esters) the latter are completely converted to monoölefin before any saturated acid is formed. Complete selectivity is, of course, impossible, but the degree of selectivity can be controlled within wide limits by proper selection of the conditions of hydrogenation and the catalyst. Much work has been done on selectivity and from time to time reviews of the subject have appeared (45, 160, 230, 231). In general, high selectivity is achieved at higher temperatures (180° and above) and lower pressures (15 p.s.i. or below); low selectivity is obtained at lower temperatures (120° and below) and higher pressures (60 p.s.i. and above). These are generalizations, and other factors such as the degree of dispersion of the catalyst and the hydrogen and the activity of the catalyst are important. Selectivity is observed under conditions of relative unavailability of hydrogen such that differences in the reactivity of the various fatty acids becomes most pronounced. Selective hydrogenation followed by crystallization has been recommended as a procedure for preparing relatively pure (95 per cent) oleic acid from tallow fatty acids (527, 536). Conflicting reports have appeared regarding selectivity during the hydrogenation of sodium linoleate (222, 480).

Reactivities of unsaturated fatty acids have been variously estimated (44, 45, 232, 433). Under selective conditions the relative values for oleic, linoleic, linolenic, and eleostearic acids of 1:20:40:80 are representative. Nonselective conditions are said to reduce the relative reactivity of the polyolefinic acids but without a change in the order of reactivities (45). These conclusions are based upon results obtained from the analysis of partially hydrogenated oils or mixtures of pure esters of the several unsaturated acids. The analyses depend upon a combination of chemical and spectral methods which are not necessarily of equal accuracy and precision. Also, hydrogenation is accompanied by positional and geometrical isomerization which produces new unsaturated fatty acids which may obscure the analytical results. The values quoted, however, appear to be reasonable approximations of the relative reactivities of the several acids.

It has been shown that the relative rates of reaction for oleic and linoleic acids are not influenced by the age of the catalyst (568). The influence of temperature upon selectivity has been attributed to isomerization (conjugation) at higher temperatures (318) and to impeded sorption-desorption at lower temperatures (79). Colloidal nickel does not show temperature dependency as a result of extremely effective contact between the oil and the catalyst.

A recent study of the kinetics of the hydrogenation of oleic and linoleic acids employed sesame oil with nickel on kieselguhr as the catalyst, temperatures ranging from 125 to 200°, and hydrogen at atmospheric pressure. Oil samples were analyzed by a paper chromatographic method which showed directly the molar composition of the oil (375). Plots of $\ln k$ vs. $1/T$ show the activation energy per double bond to be the same in oleic and linoleic acids (10 kcal./mole). Differences in rates of hydrogenation must, therefore, be due to differences in "frequency factors" which can be explained on the basis of the greater tendency for sorption of the dienoic acid on the catalyst. This greater sorbability has been attributed to the active —CH₂— in the linoleic acid (230).

Throughout the recent literature pertaining to the hydrogenation of polyolefinic acids there is a frequently stated belief that double bonds farther from the carboxyl group are more reactive. No sound theoretical basis for this phenomenon has been advanced. Examination of the experimental evidence upon which the belief is based reveals only very tenuous proof which can be discounted readily.

One of the earlier investigations purporting to show the preferential reactivity of the double bond at the 12-position in linoleic acid describes the half-saturation of the acid by hydrogen transfer, using tetralin or decalin as the hydrogen source and palladium on barium sulfate as the catalyst (522). The resulting product was oxidized with alkaline potassium permanganate in acetone and from the reaction mixture were isolated by crystallization "dioxystearic" acid, m.p. 130°, pelargonic acid (as the zinc salt, m.p. 131°), and azelaic acid, m.p. 105°. The azelaic acid was identified by mixed melting point, but no information is given on the amounts of the three substances which were isolated.

If the addition of hydrogen to linoleic acid proceeded in a random manner, equal amounts of 9- and 12-octadecenoic acid would have been produced. Oxidative cleavage would result in an equimolar mixture of azelaic and dodecanedioic acids. It is known that binary mixtures of dibasic acids in the nine- to twelve-carbon range form eutectics (242). Although data are not available for the nine- and twelve-carbon dibasic acid system, it can be predicted on the basis of melting points that the eutectic would lie at about 30 weight per cent (26

mole per cent) of the dodecanedioic acid. It would be theoretically possible to isolate by crystallization only the azelaic acid from an equimolar mixture of azelaic and dodecanedioic acids. Therefore, without quantitative information, the result reported above does not constitute evidence for the preferential reduction of the 12-position of linoleic acid; nor can the isolation of "dioxystearic" (presumably 9,10-dihydroxystearic) and pelargonic acids be considered significant without quantitative data.

In a more recent study of isomerization during the hydrogenation of linoleic acid (18) a very different result was obtained. This work included the hydrogenation of linoleic acid at 120° and 180° at 5 p.s.i. with 0.5 per cent reduced nickel formate as catalyst and the hydrogenation of methyl linolenate at 220° and atmospheric pressure with 0.5 per cent nickel and poor dispersion of hydrogen. Samples were withdrawn periodically and analyzed by standard methods; positional isomers were estimated by oxidative cleavage with ozone and partition chromatography of the resulting mono- and dibasic acids. Results with the two linoleic acid hydrogenations indicated that approximately one-third more 9-monoene than 12-monoene was formed during the hydrogenation, whereas with the methyl linoleate under more "selective" conditions the two positional isomers were produced in equal amounts. These results indicate that under the conditions used with the acid itself the 12-position is hydrogenated more rapidly than the 9. Unfortunately, in the acid hydrogenation experiments the 9-monoene was calculated by difference; in the ester experiments the 9-monoene was determined directly. Therefore, the possibility remains that in the former experiments the higher 9-monoene values are the result of accumulated errors. Differences between the reactivity of the 9- and 12-double bonds of linoleic acid still must be regarded as lacking conclusive proof.

Still later work on the hydrogenation of methyl linoleate showed an even distribution pattern of double bonds after partial hydrogenation with the maximum at the 10-position (133). The position of this maximum, however, appeared to depend upon the conditions of hydrogenation. These findings deserve more study.

A study of the hydrogenation of methyl cis-10-cis-12-octadecadienoate has been reported (16). The reaction was carried out in ethyl acetate as solvent with Raney nickel catalyst at room temperature and atmospheric pressure. Positional isomers were estimated in the same manner as described above. Equal amounts of 10-, 11-, and 12-monoenes were formed, indicating that the addition of one molecule of hydrogen occurs with equal ease at the 10-position and the 12-position and by 1,4-addition to produce the 11-monoene. A similar conclusion was reached in a study of the hydrogenation of alkali-conjugated sodium lino-

leate (480); 1,2-, 3,4-, and 1,4-addition appear to take place with equal ease.

Conflicting conclusions have been reached regarding the course of the hydrogenation of linolenic acid. Earlier work describes the hydrogenation of linolenic acid at 180°, using a supporting nickel catalyst (574). The product of partial hydrogenation was subjected to ozonolysis, and the resulting dibasic acids were separated by crystallization from water. Since it is not possible to separate mixtures of dibasic acids quantitatively because of eutectic formation (242), the conclusions (preferential hydrogenation at the 12-position) drawn from this work have little significance. However, later work on the hydrogenation of linseed oil (313) led to the same conclusion. In this case analysis of the partially hydrogenated oil was accomplished through a combination of iodine value, spectral methods for linolenic and linoleic acids, and separation of the lead salts of the saturated acids. It was demonstrated that disappearance of conjugatable diene occurred much more rapidly than could be accounted for on the basis of a random reaction of the total unsaturation. Presumably the 12-position was hydrogenated preferentially leading to dienoic acid (9, 15), which is not conjugated by heating with alkali. It is not unreasonable to expect such a result, since the 12-double bond in linolenic acid is between two active methylene groups. If, as has been suggested earlier (230), the active methylene group participates in the catalyst sorption process, two such groups adjacent to a double bond might lead to a greater activity of that bond.

Other early work with methyl linolenate reports a study of the stepwise reduction of the ester using tetralin as hydrogen donor and palladium on barium sulfate as catalyst (249). Products of one third and two thirds reduction were analyzed by oxidative cleavage and separation of the mono- and dibasic acids. Only those cleavage products that would result from linoleic acid (caproic, malonic, azelaic) and oleic acid (pelargonic, azelaic) are reported. No quantitative values are given. If these results are accepted, hydrogenation occurs first at the 15-position and then at the 12. However, the experimental procedures are subject to the same criticisms which were presented in connection with the similar study of the reduction of linoleic acid and the conclusions are of very doubtful validity.

Three other investigations of the hydrogenation of linolenic acid (561, 562, 563) have led to the conclusion that the order of the reactivity of the double bonds is 15 > 9 > 12. This conclusion is based upon oxidative cleavage of the products and separation of dibasic acids by procedures which are subject to question. One must conclude that the relative reactivities of the double bonds in linoleic acid have yet to be established definitely. However, there is no reason to expect those at the 9- and the 15-positions to differ.

Evidence gained from the hydrogenation of methyl β-eleostearate, using ethyl acetate as solvent and Raney nickel as catalyst at room temperature and atmospheric pressure, has led to the conclusion that reaction occurs predominantly by 1,6-addition to the conjugated triene (598). This conclusion is based in part on the isolation of 11-octadecenoic acid from the partially hydrogenated ester. Other later work (19), in which positional isomers produced during hydrogenation were estimated by ozonolysis and partition chromatography of the resulting mono- and dibasic acids, did not confirm the earlier result. Addition of the first mole of hydrogen apparently occurred in all possible positions and addition of the second mole led to equimolar amounts of the 9-, 10-, 11-, 12-, and 13-octadecenoates.

As with the oleate, exposure of methyl linoleate to tritium gas leads to saturation of the double bond without substitution of hydrogen (258). Tritiated octadecenoates were produced but no tritiated methyl stearate was detected, probably because the amount produced was below that which could be detected by the chromatographic techniques employed. Oxidative cleavage of the mixture of tritiated 9- and 12-octadecenoates followed by partition chromatography of the mixture of mono- and dibasic acids (a two-step procedure was used) yielded tritiated pelargonic and dodecanedioic acids in a molar ratio of 1.4:1.0. This result suggests that the 12-double bond is somewhat more reactive than the 9. This conclusion should be accepted with reservations, since the procedure used for estimating positional isomers quantitatively has not been proved to be infallible. There is no theoretical reason for expecting any significant difference in the reactivity of the two positions.

Reduction of linoleic and eleostearic acids with hydrazine hydrate has been reported (42). A 5:1 ratio of reagent was used at 50° for 8 hr. to effect a 90 per cent reduction in the iodine value of linoleic acid. Reduction of linolenic acid with hydrazine yielded a mixture of mono-, di-, and trienes; no *trans* double bonds were detected (479a).

2. Addition of Halogens

Addition of halogens and especially bromine and iodine to the double bonds of unsaturated fatty acids has been widely applied in connection with their analysis, separation, purification, and identification. Products of the halogenation of unsaturated fatty acids are also commonly used as intermediates in the synthesis of other substituted fatty acids or of unsaturated acids. Addition of halogens to double bonds is *trans*, and therefore a *cis* double bond yields a *threo* dihalide and a *trans* double bond an *erythro* dihalide.

(a) Addition of Fluorine

Direct addition of fluorine to oleic and elaidic acids has been accomplished in carbon tetrachloride solution at 15° (75). The difluorostearic acids melted at 81° (threo) and 84–85° (erythro), respectively. From a second sample of oleic acid was obtained a product, m.p. 95°, whose content of carbon, hydrogen, and fluorine corresponds to difluorostearic acid, but whose relationship to the other substances was not established.

(b) Addition of Chlorine

A limited amount of work on the addition of chlorine to unsaturated fatty acids has been reported. Oleic acid when treated in carbon tetrachloride solution with anhydrous chlorine yielded a dichlorostearic acid which failed to crystallize. Elaidic acid treated in a similar manner yielded a product melting at 47.5° (290). Addition of chlorine to methyl oleate in chloroform at −20° in the dark yielded methyl 9,10-dichlorostearate, m.p. 10–11° (324). At temperatures above −10° evolution of hydrogen chloride occurred, indicating that substitution of hydrogen was occurring. The ratio between substitution and addition is decreased by decreased concentrations of oleic acid or chlorine and also by the presence of various metal catalysts or oxygen (575). Under the conditions described above (−20° in the dark) ethyl linoleate yielded the tetrachloro ester, m.p. 76.0–76.4°. The tetrachloroöctadecanoic acid derived therefrom melts at 126.2–126.6°. No mention is made of a low-melting tetrachloro compound corresponding to the low-melting tetrabromo acid (see page 113). The kinetics of the chlorination of oleic acid have been studied; the rate is proportional to the concentration of the reactants and the activation energy is 2000 cal./gram-mole (459). Other unsaturated fatty acids (or esters) which have been chlorinated include methyl 10-undecenoate (265) and the cis- and trans-6-octadecenic acids (118). Methyl oleate when treated with sulfuryl chloride is reported to yield, after saponification, 9,10-dichlorostearic acid (86).
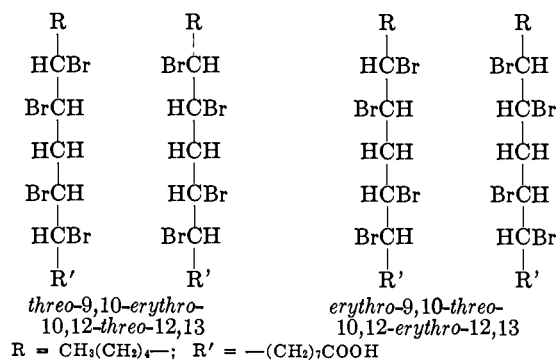
(c) Addition of Bromine

Bromination of the 9-octadecenoic acids yields the isomeric 9,10-dibromostearic acids (235). The dibromo acid (threo) obtained from oleic acid melts at 28.5–29°, whereas that from elaidic acid (erythro) melts at 29–30° (mixed melting point 20°). In later work the melting points of 27–28° for the threo acid and 29.5–30° for the erythro acid are reported (369). The threo form is difficult to crystallize; the erythro form crystallizes readily. Bromination of oleic acid incidental to other work includes kinetic studies (see below) and the preparation of stearolic acid (7, 283, 287).

Bromination of the α-unsaturated acids containing nine- through fourteen-carbon atoms yielded dibro-

mides which were used in characterizing this series of unsaturated acids (559). Configurations of the acids were not specified. The bromination of cis-6-octadecenoic acid yielded threo-6,7-dibromoöctadecanoic acid, m.p. 37–38° (25, 278); trans-2-octadecenoic acid yielded erythro-2,3-dibromoöctadecanoic acid, m.p. 71°; the cis acid yielded the threo dibromide, m.p. 57° (352). The bromination of 10-undecenoic acid (501), of 8,11-dibromoöctadecenoic acid (216), and of esters of ricinoleic acid (134, 203) has been described as a step in the preparation of other substances.

Addition of bromine to the more highly unsaturated fatty acids and especially to linoleic and linolenic acids has been widely employed as a means for separating and characterizing these acids. Quantitative analytical methods based upon the weights of tetrabromo- or hexabromoöctadecanoic acids (tetrabromide and hexabromide number) were at one time employed (97, 511, 590). The empirical nature of this method has been demonstrated (264, 589); it has been supplanted by spectrophotometric methods.

A 9,10,12,13-tetrabromoöctadecanoic acid obtained by the bromination of natural linoleic acid has been reported variously as melting from 114° to 115.8° (47, 59, 61, 244, 335, 340, 380, 503). It also is obtained from synthetic linoleic acid (191, 430). A yield of not more than 50 per cent of this solid tetrabromo acid is obtained even from purified (debromination of the 115° tetrabromo acid) linoleic acid. The remaining product consists of a liquid tetrabromo acid. Although this observation originally led to some question regarding the homogeneity of linoleic acid, it was recognized by some authors that bromination of linoleic acid should lead to two pairs of optically active enantiomorphs (333, 441, 458) which are diastereoisomers. Assuming trans addition to the double bonds of linoleic acid, these pairs of enantiomorphs can be represented as


```
        R              R               R              R
        |              |               |              |
      HCBr           BrCH            HCBr           BrCH
        |              |               |              |
      BrCH           HCBr            BrCH           HCBr
        |              |               |              |
       HCH            HCH             HCH            HCH
        |              |               |              |
      BrCH           HCBr            HCBr           BrCH
        |              |               |              |
      HCBr           BrCH            BrCH           HCBr
        |              |               |              |
        R'             R'              R'             R'
   threo-9,10-erythro-        erythro-9,10-threo-
    10,12-threo-12,13          10,12-erythro-12,13
   R = CH₃(CH₂)₄—;  R' = —(CH₂)₇COOH
```

Presumably one of these pairs of optical isomers is the high-melting form and one the liquid form of 9,10,12,13-tetrabromoöctadecanoic acid. The liquid tetrabromo acid also probably contains impurities resulting from side reactions (formation of hydrogen bromide and then addition) which occur during the bromination of

linoleic acid (305). Further evidence that bromination of linoleic acid or its methyl esters yields two diastereoisomers lies in their chromatographic separation on alumina (243). One peak corresponds to that obtained with purified tetrabromoöctadecanoic acid (m.p. 115°). The other peak is assumed to correspond to the low-melting diastereoisomer. Methyl stearate, methyl threo-9,10-dibromoöctadecanoate, and methyl threo-9,10-erythro-10,12-threo-12,13-tetrabromoöctadecanoate also were resolved. Chromatographic separation of the three corresponding fatty acids has been reported (269).

Preferential addition of one mole of bromine to the 12-double bond of linoleic acid has been reported (339). The selectivity of the 12-position is attributed to an inductive effect originating with the carboxyl group. It is difficult to accept the suggestion that an inductive effect is transmitted through a seven-carbon methylene chain, and especially an effect sufficiently strong to induce addition of bromine *only* at the double bond of the pentadiene system farthest removed from the carboxyl group. Examination of the experimental details discloses that although a quantitative yield of crude dibromoöctadecenoic acid was obtained, this material was twice distilled. The efficiency of the distillation equipment and the yield of "pure" product were not indicated. A sample of the purified dibromo acid was oxidatively cleaved with potassium permanganate in acetone and, after debromination and hydrogenation of the monobasic acid fraction, nonanedioic and nonanoic acids were isolated. This was interpreted as proof that all of the unsaturation was in the 9,10-position. Although the nonanedioic acid appeared to be of fairly high purity, as judged by melting point (104.5–105.5°) and was recovered in 60 per cent yield, the results are not sufficiently quantitative to support beyond question the conclusion regarding complete selectivity. Others have found permanganate in acetone to be an unsatisfactory method for the quantitative cleavage of double bonds (51), since degradation occurs. It appears safe to conclude that the bromination product did contain a substantial proportion of 12,13-dibromo-9-octadecenoic acid.

Linoleic and linolenic acids from beef tallow yield solid tetrabromo and hexabromo acids identical with those derived from acids from vegetable oils (297).

As with linoleic acid, the bromination of linolenic acid produces both solid and liquid products (349, 509). The melting point of the solid 9,10,12,13,15,16-hexabromoöctadecanoic acid usually is reported to be in the range of 181–182°. This hexabromo acid is also obtained from synthetic linolenic acid (376, 377). The opportunity for formation of mixtures of optical isomers has been recognized (334).

Stepwise addition of halogens to eleostearic acid

has been claimed. With carbon tetrachloride as solvent, in the light, three halogen molecules were added; with carbon tetrachloride as solvent, in the light, three halogen molecules were added; with carbon tetrachloride in the dark two were added. In methanol, bromine plus sodium bromide plus iodine resulted in the addition of one halogen (268). α-Eleostearic acid plus bromine in ligroin at 25° resulted in a dibromide, m.p. 85°; in glacial acetic acid at 5–10° a tetrabromide, m.p. 115°, was formed (374).

Bromination of stearolic acid yielded 9,10-dibromo-9-octadecenoic acid (287). The kinetics of the addition of bromine to acetylenic and ethylenic acids have been compared (449). The ratio of the bromination rates of oleic and stearolic acids is 50,000 to 1 and of undecenoic and undecynoic acids is 9000 to 1. The lower reactivity of the acetylenic acids is attributed to the more tightly bound π electrons. The addition of bromine to derivatives of 6-octadecynoic acid has been reported (25).

(d) Addition of Iodine

Addition of iodine (ICl, IBr) to unsaturated fatty acids or their derivatives has been directed principally toward the estimation of the extent of unsaturation (iodine value) (82). Addition products are not isolated; the amount of addition is estimated through titration of unreacted halogen with thiosulfate. Hübl first applied this method, using a 95 per cent ethanol solution of iodine and mercuric chloride as catalyst. Later Wijs modified the reagent, using iodine monochloride in glacial acetic acid, and obtained slightly higher values. Hanus introduced iodine monobromide as the halogenating reagent. This reagent yields slightly lower values than iodine monochloride as a result, it is believed, of incomplete saturation of double bonds. Rapid addition of these halogenating reagents is accomplished through the use of mercuric acetate catalyst.

Quantitative addition of the above-mentioned reagents does not occur with conjugated systems (including α-unsaturation) (474). Methods using large excesses of reagent have been recommended.

Kinetic studies of the addition of iodine monochloride to eleostearic acid led to the conclusion that two bimolecular reactions occur, one involving ICl and the other involving I_2 (liberated in the first reaction) (578). In polar solvents the addition of iodine to monoenoic acids is first order. In nonpolar solvents the reaction is of a higher order (448).

Relatively few specific iodine-containing saturated fatty acids derived from unsaturated acids and iodine or iodine halides have been described. Several are to be found in the earlier literature. Among these are iodo-bromoöctadecanoic from linoleic acid plus IBr (233, 234), and iodobromodocosanoic from cis-13-docosenoic acid plus IBr (234).

3. Addition of Hydrogen Halides

Addition of hydrogen halides to unsaturated fatty acids has not been studied extensively. With one exception (hydrogen bromide plus 10-undecenoic acid) the products have not been well characterized in terms of individual compounds.

(a) Addition of Hydrogen Fluoride

When treated with hydrogen fluoride in carbon tetrachloride, using mercurous chloride as catalyst, ethyl oleate yielded the 9(10)-fluorostearate which upon hydrolysis yielded the acid (396). Upon reaction with the same reagent 5-decynenitrile is said to yield a mixture of 5,5- and 6,6-difluorodecanenitriles, which upon hydrolysis produced the mixed difluorodecanoic acids (370). The high stability of the compounds is given as the reason for believing that CF_2 groups are present.

(b) Addition of Hydrogen Chloride

An early report of the addition of hydrogen chloride to either oleic acid or elaidic acid (dissolved in glacial acetic acid) described a chloroöctadecanoic acid, m.p. 38° (410). More recently, by a similar process (7 hr. at 140–150°), chloroöctadecanoic acid, m.p. 39–41°, was obtained (570). Addition of the chlorine at the 10-position is implied in this work. Also 7-chloroöctadecanoic acid, m.p. 38–39°, is said to result from the addition of hydrogen chloride to cis-6-octadecenoic acid. These conclusions relative to selective addition would bear further investigation. Addition of hydrogen chloride to 10-undecenoic acid results exclusively in 10-chloroundecanoic acid, m.p. 32–33°, in the presence or in the absence of peroxide (1). This conclusion was reached through comparison of the products with binary mixtures of 10- and 11-chloroundecanoic acids prepared by other means (see Table 6) (11-chloroundecanoic acid, m.p. 40.5°; eutectic, m.p. about 23°).

(c) Addition of Hydrogen Bromide

Addition of hydrogen bromide to 9- and 10-undecenoic acids has been studied extensively by Smith and co-workers in connection with an investigation of the peroxide effect. A review of this work is available (491). In the absence of oxygen 10-bromoundecanoic acid is formed, whereas in the presence of oxygen the 11-bromo acid is obtained. Various solvents either allow or impede the effect of the oxygen catalyst. In the absence of solvent the acid itself, like the lower acids, impedes the peroxide effect. No peroxide effect is observed with 9-undecenoic acid; equal amounts of 9- and 10-bromoundecanoic acids are obtained (492). Addition of hydrogen bromide to 10-undecenoic acid has been described in connection with the introduction of amino, thiol, and methoxy groups (10, 11, 469,

494, 583). Modifications of the process have been patented (493, 495). 6-Oxo-7-octenoic acid plus hydrogen bromide yields 8-bromo-6-oxoöctanoic acid (434). Addition of hydrogen bromide to 11-dodecenoic acid in the presence of perbenzoic acid yielded a mixture of approximately 83 per cent 12-bromododecanoic acid and 12 per cent of the 11-bromo compound (463). Oleic acid plus hydrogen bromide under a variety of conditions yielded an equimolar mixture of the 9- and 10-bromo acids (262). 13-Docosenoic acid plus hydrogen bromide yielded 13(14)-bromodocosanoic acid (119). Addition of hydrogen bromide to 12-oxo-cis-9-octadecenoic acid or to the trans isomer yielded apparently only 10-bromo-12-oxoöctadecanoic acid (153, 294).

(d) Addition of Hydrogen Iodide

Addition of hydrogen iodide to 10-undecenoic acid is not susceptible to the peroxide effect; only the 10-iodo acid was produced (1). Oleic acid with hydrogen iodide is said to yield a mixture of the two positional isomers, although these compounds have not been characterized (31).

4. Addition of Hypohalous Acids

The addition of hypobromous acid to 10-undecenoic acid is reported to yield exclusively 11-bromo-10-hydroxyundecanoic acid (109). Apparently, only one product was obtained and identification was made on the basis of infrared absorption data. The product was not subjected to a rigorous examination with respect to homogeneity.

Studies of the addition of hypohalous acids to the 9-octadecenoic (oleic and elaidic) acids have been reported in connection with work on the chemistry of 9,10-epoxy, and 9,10-dihydroxyoctadecanoic acids (40, 290, 360, 525). Assuming trans addition to the ethenoic acids, each will lead to a mixture of halohydroxyoctadecanoic acids which consists of two pairs of enantiomorphs which are positional isomers. Figure 1 depicts these and other structural relationships; each formula represents a racemic mixture, with the exception of those for the unsaturated acids. Addition of hypohalous acids to cis- and trans-6-octadecenoic acids follows the same pattern (158b). Addition of hypochlorous acid has been proposed as a method for the estimation of unsaturation in fats (122, 350).

Table 7 lists melting points which have been reported for 9(10)-halo-10(9)-hydroxyoctadecanoic acids. These melting points represent products which have been purified by crystallization. Presumably some fractionation of the original mixture has occurred, but the exact identity of the component(s) isolated was not established.

The addition of hypochlorous acid to 12-hydroxy-trans-9-octadecenoic acid has been reported, but the
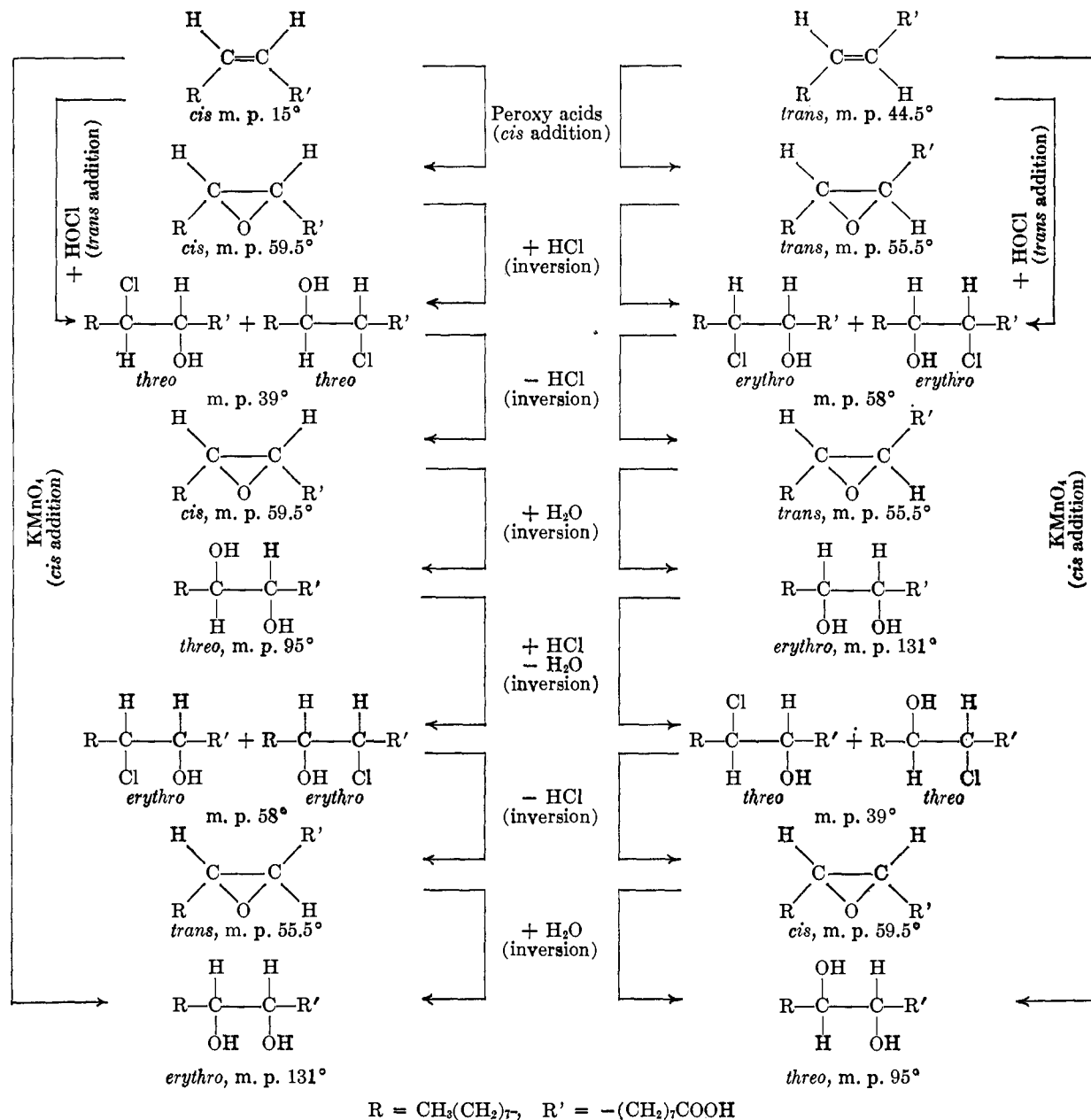
Fig. 1.—Configurational relationships of epoxy, chlorohydroxy, and dihydroxy octadecanoic acids derived from oleic and elaidic acids.

TABLE 7

Melting Points of 9(10)-Halo-10(9)-hydroxyoctadecanoic Acids in °C.

Config-uration	ClOH	Reference	BrOH	Reference	IOH	Reference
threo	39	525	Oil	290	Oil	290
	38–41	290				
erythro	58	40, 525	70–71	290	64.5–65.5	290
	52–57	290				
	73.5	290				
	(pure)[a]					

[a] Recrystallized from mixed halohydroxy acid and assumed to be a pure isomer.

hydroxy chlorohydrins were not purified or characterized (291).

A number of 9(10)-alkoxy-10(9)-chloroöctadecanoates have been produced by the reaction of unsaturated fatty acid esters (oleic, elaidic, linoleic, cis-13-docosenoic) with alkyl hypochlorites (185, 457, 547). The methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, and pentyl derivatives were included. All were oils and none was purified or characterized, although analytical data were reported. The alkoxychloro esters were used as intermediates in the preparation of ketoöctadecanoic acids.

5. Addition of Oxygen

The following discussion of the addition of oxygen or oxygen-containing radicals to unsaturated fatty

acids will pertain primarily to reactions which produce a carbon–oxygen bond (hydroxy, acyloxy, epoxy, or oxo). Introduction of the acyloxy group is considered as one route to a hydroxy acid and will not be set apart in this treatment. Insofar as it is possible, the order monohydroxylation, dihydroxylation, and epoxidation of double bonds will be followed.

(a) Monohydroxylation (Hydration)

Monohydroxylation or hydration of olefinic fatty acids is accomplished through treatment with concentrated sulfuric acid (200, 343, 453) or with formic acid containing catalytic amounts (1 per cent) of perchloric acid (298, 299, 451). The combination of formic and perchloric acids appears to be the reagent of choice. The reaction proceeds through the addition of sulfuric or formic acids to form the sulfate or formate ester, which must be hydrolyzed to obtain the hydroxy acid.

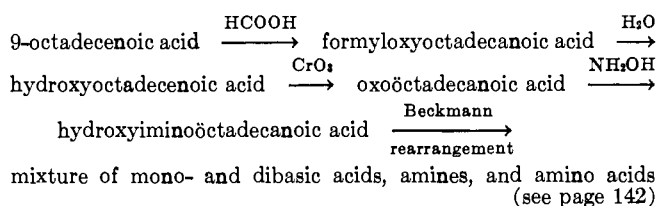The addition of formic acid to 9-octadecenoic acid would be expected to proceed in a random manner to produce a mixture of the 9- and 10-formyloxyoctadecanoic acids. That this apparently is the case has been demonstrated through the following sequence of reactions (451):

9-octadecenoic acid $\xrightarrow{\text{HCOOH}}$ formyloxyoctadecanoic acid $\xrightarrow{\text{H}_2\text{O}}$ hydroxyoctadecenoic acid $\xrightarrow{\text{CrO}_3}$ oxoöctadecanoic acid $\xrightarrow{\text{NH}_2\text{OH}}$ hydroxyiminoöctadecanoic acid $\xrightarrow[\text{rearrangement}]{\text{Beckmann}}$

mixture of mono- and dibasic acids, amines, and amino acids
(see page 142)

Chromatographic analysis of the mixture of dibasic acids resulting from the Beckmann rearrangement disclosed a one-to-one molar ratio of nonanedioic and decanedioic acids. Earlier work describes the isolation by crystallization from crude hydroxyoctadecanoic acid, prepared in the manner just described, of a substance with the m.p. 81.5–82.5° which was believed to be pure 10-hydroxyoctadecanoic acid (298). The identification was confirmed by comparison with an "authentic" sample produced by the hydrogenation of 9,10-epoxyoctadecanoic acid (325). However, it has been shown subsequently that 9- and 10-hydroxyoctadecanoic acids form a one-to-one molecular compound melting at 82.6° (127). Unquestionably the substance melting at 81.5–82.5° is this molecular compound (cf. 127, footnote 33).

Very recently a report of the formoxylation of cis-6-octadecenoic acid (410a) disclosed a result quite different from that described above. The formoxylation was carried out in almost the identical manner, and the product was subjected to the same sequence of reactions culminating in the Beckmann rearrangement. Chromatography of the resulting dibasic acids showed

that addition had occurred at the 5-, 6-, 7-, and 8-carbon atoms in the relative proportions given: 11.2, 35.6, 34.0, and 19.2, respectively. After a longer reaction time some addition at the 8- and 9-positions also was indicated. These results were attributed to migration of a carbonium ion produced through interaction of the olefin with perchloric acid. The difference in the behavior of the 6- and 9-octadecenoic acids was ascribed to the relative difference in the proximity of the carboxyl group. These results perhaps are analogous to the differences in the behavior of 6- and 10-oxo-octadecanoic acids upon fusion with alkali (see page 138).

Refluxing of the above hydroxyoctadecanoic acid, m.p. 81.5–82.5°, for 1 hr. in the formic acid–perchloric acid reagent and then saponification and acidification yielded a product, m.p. 75.5–77°, which was believed to be an "equilibrium mixture" of positional isomers (298). Evidence of group migration during the sulfation of 9-octadecenoic acid has been obtained through the oxidation of the resulting hydroxyoctadecanoic acids (476). The oxidation was carried out by prolonged boiling (8 hr.) with concentrated nitric acid, using ammonium vanadate as catalyst. From the resulting mixture of mono- and dibasic acids was isolated a fraction which consisted of dibasic acids containing fourteen to sixteen carbon atoms. This must have resulted from group migration. The possibility that this migration might have occurred principally during the oxidation process was not mentioned.

In addition to the hydroxylation of oleic acid similar treatment of elaidic, linoleic, and 10-undecenoic acids has been reported (299). A mixture of monohydroxy-octadecenoic and dihydroxyoctadecanoic acids was obtained from linoleic acid.

(b) Dihydroxylation

Dihydroxylation of the double bond of unsaturated fatty acids has been accomplished through the use of a number of oxidizing agents. The configuration (threo, erythro) of a specific vicinal dihydroxy acid is dependent upon the geometrical configuration of the unsaturated fatty acid from which it is derived (cis, trans) and the reagent employed to introduce the hydroxyl groups. Cis addition, which produces an erythro-dihydroxy compound from a cis and a threo from a trans double bond, results from the use of alkaline permanganate (14, 36, 65, 100, 128, 238, 239, 322, 352, 353, 525, 557, 592), manganate (445), osmium tetroxide (43, 267), or wet silver benzoate–iodine complex (423, 595) or wet silver acetate–iodine complex (158a, 213, 424) (Prevost reaction). Trans addition, which produces threo from cis and erythro from trans double bonds, is brought about by organic peroxy acids in acid solution (53, 65, 85, 100, 125, 158a, 179, 239, 245, 277, 322, 529, 577, 594), anhydrous silver acetate– or benzoate–

iodine complex (213, 423, 424, 595), or ammonium persulfate (361, 362).

Cis hydroxylation by MnO_4^- or OsO_4 is attributed to the formation of a cyclic diester which hydrolyzes simultaneously with no inversion (128).

$$\underset{C}{\overset{C}{\|}} + MnO_4^- \rightarrow \underset{C-O}{\overset{C-O}{\diagup}} \underset{O}{\overset{O^-}{Mn}} \xrightarrow{H_2O} \underset{C-OH}{\overset{C-OH}{}}$$
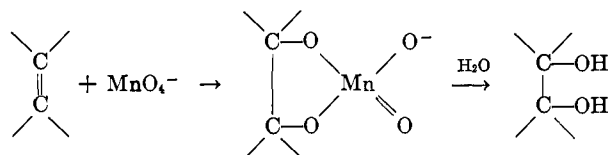
Through the use of ^{18}O-labeled potassium permanganate it has been demonstrated that the oxygen in the hydroxyl groups comes from the permanganate (592). The actual configuration of the two 9,10-dihydroxyocta-decanoic acids has been deduced from their ability to form urea adducts (537). Th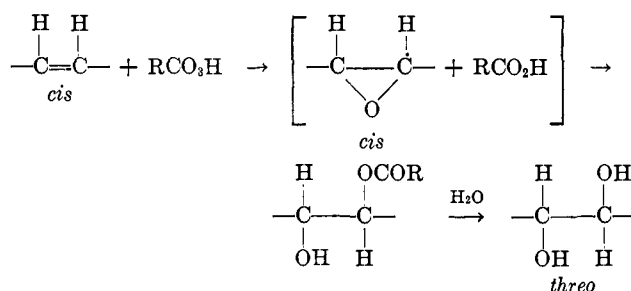e low-melting (95°) *threo* form readily forms the adduct; the high-melting (131°) *erythro* form does not. This is explained on the basis that *cis* addition results in a dihydroxy compound with opposite orientation of the hydroxyl groups and therefore with a larger molecular cross section. By definition *threo* compounds result from *trans* addition to a *cis* or *cis* addition to a *trans* ethylenic compound, whereas *erythro* isomers are products of *cis* addition to a *cis* or *trans* addition to a *trans* ethylenic compound (65). The three-dimensional relationship deduced from the relative ease of formation of the urea adducts should not be confused with the two-dimensional representation of the *erythro* and *threo* forms which is used here. The higher melting point is attributed to chain-to-chain hydrogen bonding of the hydroxyl groups in the *erythro* form which is not possible in the *threo*. These postulates assume the normal zigzag structure of the fatty acid hydrocarbon chain in the solid state. The *threo* configuration of the form which melts at 95° has been proved by synthesis from a molecule known to have the *threo* configuration (190), and the configuration of both the *threo* and *erythro* forms has been confirmed by an examination of their rotatory power (337).

Under proper conditions of pH (9.0–9.5) and concentration it is possible to convert oleic acid to 9(10)-hydroxy-10(9)-oxoöctadecanoic acid (128, 387) to the extent of 65–75 per cent. This was assumed to be the result of hydrolysis of only one of the ester linkages in the intermediate cyclic ester and then oxidation of the hydroxyl group. Elaidic acid did not undergo this reaction as readily, for reasons which are not understood. 11-Hydroxy-10-oxoundecanoic acid was produced from 10-undecenoic acid by treatment for 1 min. with permanganate–periodate (311). Further treatment with periodate yielded 1 mole of formaldehyde, indicating that the 10-hydroxy-11-oxo compound was not produced.

With neutral potassium permanganate both *cis*- and

trans-6-octadecenoic acids yielded 6(7)-hydroxy-7(6)-oxoöctadecanoic acid, m.p. 67–70° (158a). This mixture was separated into its components by conversion to the semicarbazone and extraction of the latter, followed by crystallization of the extracted material and the residue. The former yielded 7-hydroxy-6-oxoöctadecanoic acid, m.p. 77.5–78.5°, and the latter yielded the 6-hydroxy-7-oxo acid, m.p. 74.5–75°. The mixed melting point of the two isomers was 68–70°. Their identity was established by oxidative cleavage (see page 141).

Dihydroxylation by means of peroxy acids is believed to proceed through the epoxide, which then reacts with acid present to open the ring and form the acyloxy-hydroxy compound (529). Hydrolysis of the latter leads to the dihydroxy compound. Inversion occurs during the ring-opening step (537).

$$\underset{cis}{\overset{H\ H}{\underset{|}{\overset{|}{-C}}=\overset{|}{C}-}} + RCO_3H \rightarrow \left[\underset{cis}{\underset{O}{\overset{H\ \ \ \ H}{\underset{|}{\overset{|}{-C}}\underset{\diagdown\diagup}{\overset{|}{C}-}}}} + RCO_2H \right] \rightarrow$$

$$\underset{OH\ H}{\overset{H\ \ OCOR}{\underset{|}{\overset{|}{-C}}\underset{|}{\overset{|}{C}-}}} \xrightarrow{H_2O} \underset{\underset{threo}{OH\ H}}{\overset{H\ \ OH}{\underset{|}{\overset{|}{-C}}\underset{|}{\overset{|}{C}-}}}$$

An unusual instance of ketol formation resulted from the oxidation of 12-oxo-*trans*-9-octadecenoic acid by either *tert*-butyl peroxide with osmium tetroxide as catalyst or alkaline permanganate (372). The product was 9,12-dioxo-10-hydroxyoctadecanoic acid. Similar oxidation of 12-oxo-*cis*-9-octadecenoic acid afforded very little of this product but yielded, principally, *erythro*-9,10-dihydroxy-12-oxoöctadecanoic acid. A mechanism was proposed which explained these effects as resulting from the proximity in the *trans* isomer of the 9-hydrogen and the 12-carbonyl, which enables the latter to act as an internal base and to participate in the further oxidation of the 9-hydroxyl group.

The silver benzoate–iodine or silver acetate–iodine complex is capable of effecting either *cis* or *trans* addition, depending upon whether the reaction is carried out under anhydrous conditions or in the presence of water (213, 423, 424, 595). Thus, *cis*-9-octadecenoic was converted to the low-melting (94°) *threo*-9,10-dihydroxyoctadecanoic acid by the silver benzoate–iodine complex under anhydrous conditions. If water is present, the high-melting (130°) *erythro*-dihydroxy acid is obtained (423). It was postulated that the wet reaction involves a cyclic oxonium intermediate (271).

In Table 8 are listed literature values for the melting points of both forms of a number of vicinal dihydroxy-octadecanoic acids. Each substance represents a pair of enantiomorphs. With one or two exceptions the values for each pair of enantiomorphs are in good agreement. In contrast to members of the series in which substi-

TABLE 8

Vicinal Dihydroxyoctadecanoic Acids

| OH positions	Melting point of erythro form, °C	References	Melting point of threo form, °C	References
2,3	107	353	126	353
6,7	121–121.5	179	114–115	125
	121.5–122	576	115–116	158a
	122	158a	119	322
	124	322		
7,8	130.5–131	179	94–94.5	179
	132–133	245	95–96	245
8,9	118–119	179, 245	94–94.3	179
	127–128	53	96–97	245
9,10	129–131	245	93–94	245
	130–130.5	529	93.5–93.8	277
	130–131	445, 592	94	529
	131	53, 525	95	53, 525
	132	557		
10,11	120–121	245	98–99.5	245
11,12	119–120	245	93–94	14, 100
	127–128	14	94.5–96	245
	127.5–128	179		
	129	85		
	128–129	100		
12,13	117–118	65	96–97	65
	119–120	245	98.5–97 (sic)	245

tution is farther removed from the carboxyl group, the relative order of the melting points of *erythro*- and *threo*-2,3-dihydroxyoctadecanoic acids is reversed. The *threo* acid is the higher melting, a result no doubt of the proximity of the carboxyl group, although the explanation for this in terms of spatial relationships has not been proposed. The relative melting points of the two forms of 6,7-dihydroxyoctadecanoic acid deserve comment. The values for the *erythro* form are within the range of other members of the series (excluding 2,3); the melting point of the *threo* form appears to be much too high. When crystallized from a melt the *threo*-6,7-dihydroxyoctadecanoic acid remelted at about 96° (322). The two forms were attributed to polymorphism, a conclusion which was supported by X-ray diffraction patterns of the two forms.

Various vicinal dihydroxy acids have been reported. In many instances the configuration of the unsaturated acid was not known and therefore the configuration of the dihydroxy compound can not be established. Following are unsaturated acids (or esters) which have been converted to dihydroxy compounds by one of the reagents discussed: 2-alkenoic acids containing nine, ten, eleven, twelve, and fourteen carbon atoms (92), 2-octenoic, 2-tridecenoic (91), 2-nonoenoic, 2-undecenoic (155), 6-undecenoic (15), 10-undecenoic, 12-hydroxy-*cis*-9-octadecenoic (529), *cis*-9-hexadecenoic (85), 9-hydroxy-12-octadecenoic (210), 11-eicosenoic (238, 239, 240), 13-docosenoic (423, 424), 12-oxo-*cis*-9-octadecenoic, 12-oxo-*trans*-10-octadecenoic, 9,12-dioxo-*trans*-10-octadecenoic (372). Partial dihydroxylation of methyl linoleate with hydrogen peroxide in acetic acid yielded a dihydroxyoctadecenoate which upon hydrogenation and oxidative cleavage

with permanganate produced hexanoic and decanedioic acids (26). This evidence was said to indicate preferential addition at the 9,10-position. However, the method of cleavage (potassium permanganate in acetone) and of separating the mixture of mono- and dibasic acids (extraction and crystallization) leaves doubt as to the validity of this conclusion. Hydroxylation and subsequent chromatography of the mixture of saturated and dihydroxy acids has been proposed as an analytical method for the estimation of the composition of mixtures of saturated and unsaturated acids (57).

Dihydroxy acids are among the products of the oxidation of oleic (293) and *trans*-13-docosenoic (487) acids by air. With the former both *erythro*- and *threo*-9,10-dihydroxyoctadecanoic acids were isolated.

Theoretically, eight diastereoisomers of 9,10,12,13-tetrahydroxyoctadecanoic acid can exist, each comprising a pair of enantiomorphs. These racemates can be represented as

R = CH₃(CH₂)₄—; R′ = —(CH₂)₇COOH
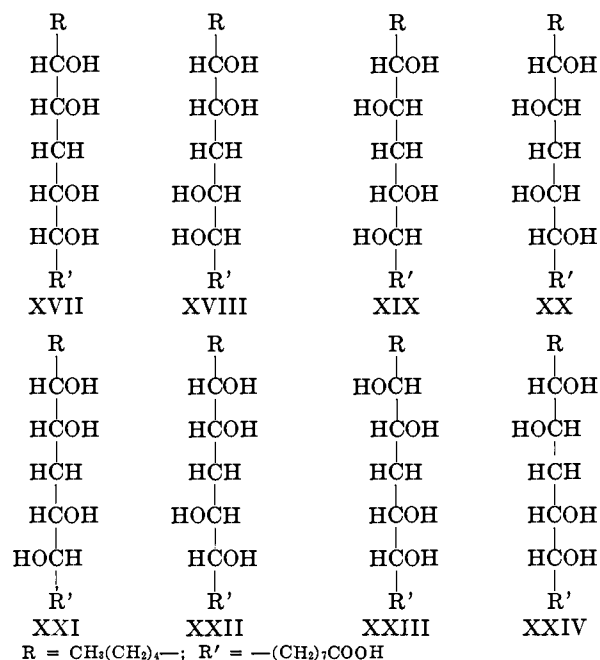
Tetrahydroxyoctadecanoic acids

XVII *erythro*-9,10-*erythro*-10,12-*erythro*-12,13-
XVIII *erythro*-9,10-*threo*-10,12-*erythro*-12,13-
XIX *threo*-9,10-*threo*-10,12-*threo*-12,13-
XX *threo*-9,10-*erythro*-10,12-*threo*-12,13-
XXI *threo*-9,10-*erythro*-10,12-*erythro*-12,13-
XXII *threo*-9,10-*threo*-10,12-*erythro*-12,13-
XXIII *erythro*-9,10-*erythro*-10,12-*threo*-12,13-
XXIV *erythro*-9,10-*threo*-10,12-*threo*-12,13-

It is obvious that a mixture of XVII and XVIII will be produced by *cis* addition to linoleic acid (*cis*-9-*cis*-12-octadecadienoic acid) and a mixture of XIX and XX by *trans* addition. There are a number of reports in the literature of the synthesis of some of these pairs of diastereoisomers, including two reports of the preparation of all eight racemates (65, 339).

Any procedure for the preparation of 9,10,12,13-tetrahydroxyoctadecanoic acids which is based upon linoleic acid and which does not provide for maintaining a fixed stereochemical relationship between the 10- and 12-carbon atoms will result in a mixture of two diastereoisomers. It would be expected that separation of such a mixture would be complicated by the formation of a eutectic which would not be susceptible to separation by fractional crystallization under equilibrium conditions. Whether this complication has been fully appreciated is not clear from the literature reports. However, a device has been employed which has made it possible to separate both components from such a eutectic mixture and thereby allowed the experimental demonstration of the existence of the eutectic.

Specifically, preparation of the tetrahydroxy acids designated above as XVII and XVIII was accomplished in the manner which will be described (441). The so-called α-linoleic acid (obtained by debromination of the 9,10,12,13-tetrabromoöctadecanoic acid, m.p. 115°) was oxidized with alkaline potassium permanganate, yielding a 9,10,12,13-tetrahydroxyoctadecanoic acid mixture, m.p. 154–163°. This crude product was first crystallized from acetic acid. The resulting crystals then were extracted with acetone until the residue melted at 168°. Recrystallization of this residue from 50 per cent ethanol yielded a tetrahydroxyoctadecanoic acid, m.p. 174°. The solid recovered from the acetone was recrystallized from 40–50 per cent ethanol and yielded an acid melting at 163.5°. A phase diagram based upon the melting points of mixtures of the 174° and the 163.5° acids showed a minimum, m.p. 156°, at 30 per cent of the former. The successful separation of the components of a eutectic in this instance can be attributed to the acetone extraction step in the process. Evidently, the component melting at 163.5° dissolved more rapidly than the material melting at 174°, and mixtures were obtained whose composition lay somewhere between that of the eutectic and each of the pure components. Having accomplished this partial separation, recrystallization of the two mixtures then yielded the pure diastereoisomers.

One of the reports of the preparation of the eight diastereoisomers of 9,10,12,13-tetrahydroxyoctadecanoic acid is based on 12,13-dibromo-9-octadecenoic acid as the starting material (339). This dibromo acid was obtained by the selective bromination of linoleic acid. Its purity is questionable (see the discussion on this point, page 114) and therefore the identity of the product may be questioned. This may account for some of the discrepancies which will be noted between this and other work. The reaction scheme employed in the preparation of the four pairs of diastereoisomers is shown in Figure 2. Separation of racemates was accomplished by a combination of extraction and crystallization. Melting points of the racemates are listed in Table 9 in comparison with those obtained by a different reaction scheme. Both sets of values will be discussed together.

The second method for the preparation of the eight diastereoisomers of 9,10,12,13-tetrahydroxyoctadecanoic acid is based upon cis-12,13-epoxy-cis-9-octadecenoic acid (XV) as starting material (65). This acid was obtained from a natural source and its configuration was proved by conversion to derivatives with known configuration. The reaction scheme is shown in Figure 3; separation of racemates also was accomplished by a combination of extraction and crystallization.

The melting points of the diastereoisomers of 9,10-12,13-tetrahydroxyoctadecanoic acid which were obtained by both of the above schemes are shown in Table 9.

With the exception of the pair XXI,XXII the higher melting-point values appear to be in good agreement. With respect to the three substances melting at 164°, produced by method A, the substance from pair XXI,-XXII did depress the melting point of the substance from pair XVII,XVIII but not that of the substance from pair XXIII,XXIV. This fact, together with the lack of agreement with the value in column B and the questionable starting material (12,13-dibromoöctadecenoic acid), suggests the possibility that the 164° substance (XVII,XVIII, method A) may not be the diastereoisomer sought. The values in column B of the lower-melting members are all appreciably lower than those in column A. The value (155.5–156.5°) for the pair XVII,XVIII closely corresponds with the value (156°) for the eutectic formed between XVII and XVIII (441). It seems very likely that although a combination of extraction and crystallization was used, the investigators who employed the epoxy compound, method B, as starting material failed in all cases to separate the lower-melting member of the pairs of diastereoisomers from the eutectic.

A study of the binary system erythro- and threo-9,10-dihydroxy octadecanoic acids has shown eutectic formation at about 25 per cent of the erythro form (594). The melting point of the eutectic is approximately 93°, only about 2° below that of the pure threo form. Obviously, the melting point is not a good criterion of purity for this substance.

(c) Epoxidation

Epoxidation of olefinic fatty acids is accomplished by treatment with organic peroxy acids, usually peroxyacetic acid (70, 165, 181, 184, 240, 290, 405, 478, 594). A general review of the subject is available (526). Epoxidation occurs without inversion; thus, cis-9-octadecenoic (oleic) acid leads to cis-9,10-epoxyoctadecanoic acid, m.p. 59.5°, and trans-9-octadecenoic (elaidic) to trans-9,10-epoxyoctadecanoic acid, m.p. 55.5° (537). Although peroxyacetic acid is the

$R = CH_3(CH_2)_4—$
$R' = —(CH_2)_7COOH$

KMnO₄ Peroxyacetic acid

↓ Zn   ↓ Zn

KMnO₄   Peroxyacetic acid   KMnO₄   Peroxyacetic acid

XVII,XVIII   XXIII,XIV   XXI,XXII   XIX,XX

Fig. 2.—Preparation of eight diastereoisomers of 9,10,12,13-tetrahydroxyoctadecanoic acid from 12,13-dibromo-cis-9-octadecenoic acid. Method A.

XIX,XX   XXI,XXII

↑ Peroxyformic acid   ↑ Peroxyformic acid

Hydrolysis   XXV   See below

↓ KMnO₄   ↓ KMnO₄

XXIII,XXIV   XVII,XVIII

cis   HBr → threo   (CH₃CO)₂O → threo   CH₃COOAg → erythro   KOH → erythro
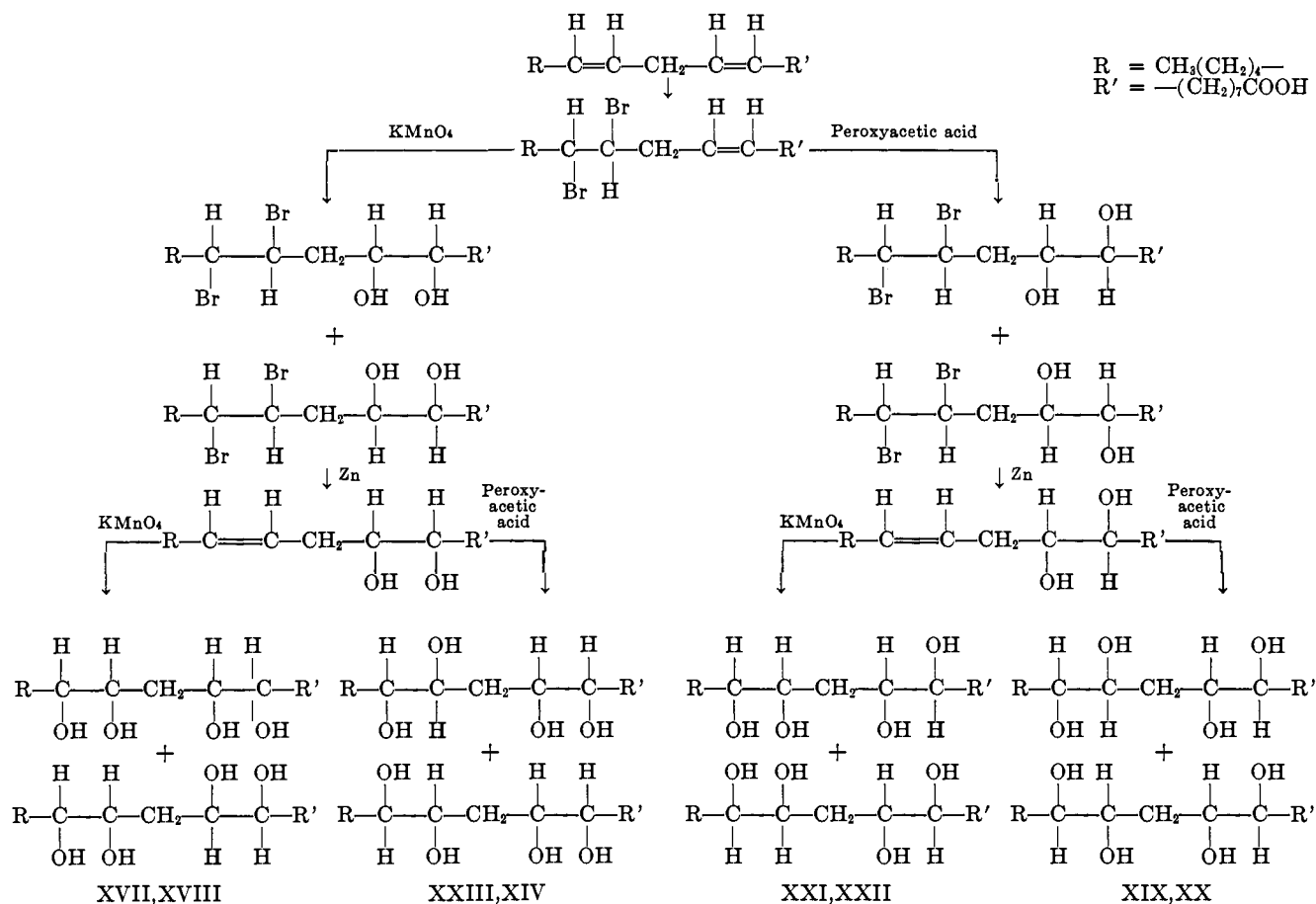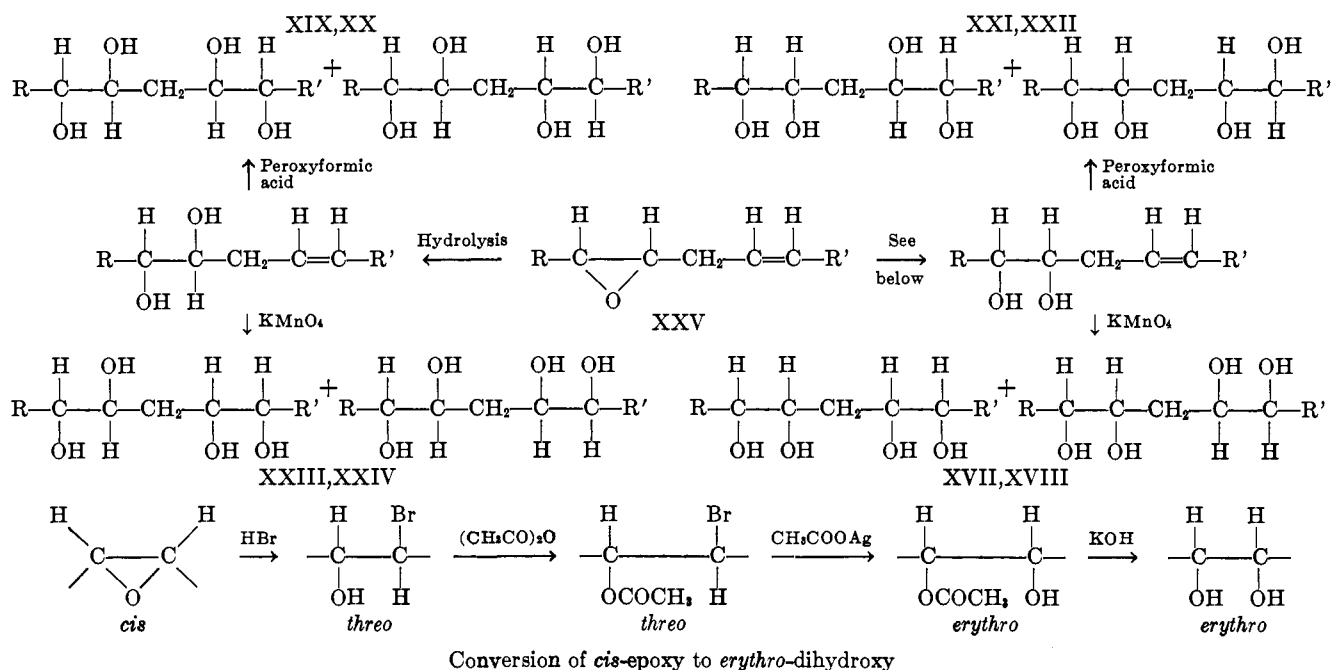
Conversion of cis-epoxy to erythro-dihydroxy

Fig. 3.—Preparation of eight diastereoisomers of 9,10,12,13-tetrahydroxyoctadecanoic acid from cis-12,13-epoxy-cis-9-octadecenoic acid. Method B.

TABLE 9

Melting Points °C. of 9,10,12,13-Tetrahydroxyoctadecanoic Acids

Pairs of diastereoisomers	Method of preparation			
	A	B	A	B
XVII,XVIII	174	176.5–177	164	155.5–156.5
XIX,XX	148	147.5–148.5	126	121–122
XXI,XXII	164	156.5–157	141.5	129.5–131
XXIII,XXIV	164	164–165	126	112–113

usual reagent for effecting epoxidation, other reagents such as peroxynonanoic acid have been used (535). The higher-molecular-weight acid is much less reactive. Epoxidation of oleic acid or its methyl ester also has been accomplished by treatment with air in the presence of aldehydes and under ultraviolet irradiation (533). Epoxidation may also be accomplished by addition of hydrogen peroxide to an acetic acid solution of the unsaturated fatty acid (181). Sulfuric acid was used as catalyst and yields were 70–85 per cent.

An investigation of the epoxidation of linolenic acid has shown that a maximum of 65 per cent of the total possible oxirane is obtained (535). It is postulated that after one double bond is epoxidized the reactivity of that (or those) adjoining will be reduced through an inductive effect. Ultimately, oxirane ring-opening by acid becomes competitive with epoxidation, and it is not possible therefore to produce 100 per cent of the triepoxy acid. 9,10,12,13,15,16-Triepoxyoctadecanoic acid was isolated, however. Epoxidation of linoleic acid produced 9,10,12,13-diepoxyoctadecanoic acid (532), and epoxidation of ricinoleic acid produced 9,10-epoxy-12-hydroxyoctadecanoic acid (407).

A phase study of the binary system *cis-* and *trans-*9,10-epoxyoctadecanoic acids showed eutectic formation at about 42 per cent of the high-melting (*cis*) isomer (594). The eutectic melting point is about 49°.
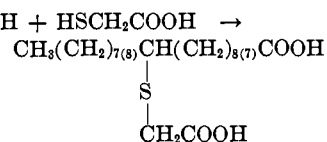
An investigation of the "monoepoxide" prepared from methyl linoleate included an attempt to establish its structure (406). Evidence based upon oxidative cleavage with alkaline permanganate, comparative rate of hydrogenation *vs.* linoleate, and properties of the aminohydroxyoctadecanoic acid prepared therefrom led to the conclusion that epoxidation occurs at the 12,13-bond. The evidence for this conclusion is unacceptable, since all products were not actually identified nor accounted for quantitatively. Nonanedioic acid and "nonenoic epoxide" were isolated from the cleavage mixture, the latter identified by neutral equivalent and analysis of barium salt. Also, apparently acetic and hexanoic acids were present.

Epoxidation of several oxoöctadecenoic acids has disclosed differences in reactivity which are attributed to steric effects (372). With alkaline hydrogen peroxide and magnesium chloride as catalyst both 12-oxo-*trans*-10-octadecenoic acid and 12-oxo-*cis*-9-octadec-

enoic acid were converted to 10,11-epoxy-12-oxoöctadecanoic acid (presumably *trans*, although not so specified). However, 12-oxo-*trans*-9-octadecenoic acid was not converted to epoxide under the same conditions. 9,12-Dioxo-*trans*-10-octadecenoic acid yielded 9,12-dioxo-*trans*-10,11-epoxyoctadecanoic acid when treated with the reagents described above.

6. Addition of Sulfur

Addition of mercaptoacetic acid to oleic acid with lauroyl peroxide as catalyst yielded carboxymethyl-thioöctadecanoic acid, substitution presumably being in the 9- and 10-positions. 10-Undecenoic acid with the same reagent yielded only 11-(carboxymethylthio)-undecanoic acid with no thio-attachment to the 10-

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH + HSCH_2COOH \rightarrow$$
$$CH_3(CH_2)_{7(8)}CH(CH_2)_{8(7)}COOH$$
$$|$$
$$S$$
$$|$$
$$CH_2COOH$$

position (301). The reaction has been extended to include a variety of mercapto compounds (302). *cis*-9-*cis*-12-Octadecadienoic acid or its methyl ester when treated with an equivalent of mercaptoacetic acid yielded only 40 per cent of the monocarboxymethyl-thio adduct; with five times the theoretical amount of reagent a 96 per cent yield of the diadduct was obtained (172).

Two procedures for producing sulfonic acids from unsaturated fatty acids have been described. 10-Undecenoic acid with sulfur dioxide plus potassium hydroxide, after acidification, yielded 11-sulfoundecanoic acid (446). Oleic acid with sulfur trioxide (in sulfur dioxide) yielded a mixture which, on the basis of analyses for the hydroxyl group and for sulfur, carbon, and hydrogen, had the following composition: 54.3 per cent 8(11)-sulfo-9-octadecenoic acid, 28.3 per cent 9(10)-sulfo-10(9)-hydroxyoctadecanoic acid, and 17.4 per cent 9,10-disulfoöctadecanoic acid (473). Propyl oleate and 10-undecenoic acid with the same reagent gave similar results.

7. Addition of Nitrogen

Relatively little has been reported on addition reactions of unsaturated fatty acids which produce carbon–nitrogen bonds. Methyl 10-undecenoate with N_2O_3 is said to yield methyl 11-nitro-10-nitrosoundecanoate, which upon hydrolysis produces nitromethane and decanedioic acid (382). With nitrogen tetroxide (N_2O_4) 10-undecenoic acid yielded 10-nitroso-11-nitrosoöxyundecanoic acid, which was hydrolyzed to 11-hydroxy-10-nitrosoundecanoic acid (573). 13-Docosenoic acid undergoes a similar reaction with N_2O_4, although the substitution presumably was random (572). The reactions of both N_2O_3 and N_2O_4 with 6-octadecenoic acid have been investigated, but the

resulting products were not fully characterized (576).

Treatment of 10-undecenoic acid with ammonium sulfide and sulfur plus ammonium thiosulfate (Willgerodt reaction) is reported to yield undecanediamide (393).

8. Addition of Phosphorus

Esters of 10-undecenoic acid with dialkylphosphonite catalyzed either by ultraviolet irradiation or tert-butyl peroxybenzoate yielded esters of 11-(dialkylphosphono)undecanoic acid (472). A variety of these esters were prepared in yields of 53–66 per cent. Alkyl oleates with dialkylphosphonite and peroxybenzoate as catalyst yielded alkyl 9(10)-(dialkylphosphono)octadecanoates in yields of 66–77 per cent.
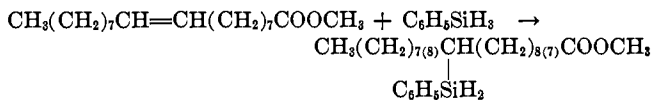
$$CH_3(CH_2)_7CH=CH(CH_2)_7COOR + (RO)_2PH\rightarrow O \rightarrow$$
$$CH_3(CH_2)_{7(8)}\underset{\underset{O\leftarrow P(OR)_2}{|}}{CH}(CH_2)_{8(7)}COOR$$
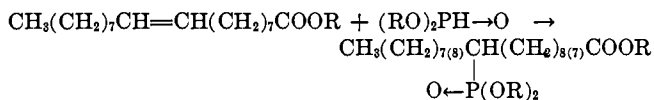
9. Addition of Silicon

The addition of a number of silane derivatives to unsaturated fatty acids has been reported. Methyl 10-undecenoate with trichlorosilane (acetyl peroxide as catalyst) yielded methyl trichlorosilylundecanoate; with triethylsilane this ester yielded triethylsilylundecanoate (104). With chlorodiethylsilane (ultraviolet irradiation) the chlorodiethylsilyl ester was produced and with dichloroethylsilane the dichloroethylsilyl ester (105). In none of these reactions was the position of substitution proved. 9-Undecenoic acid plus triphenylsilane led to triphenylsilylundecanoic acid (180). Methyl oleate plus phenylsilane (tert-butyl peroxybenzoate as catalyst) yielded methyl 9(10)-phenylsilyloctadecanoate (502).

$$CH_3(CH_2)_7CH=CH(CH_2)_7COOCH_3 + C_6H_5SiH_3 \rightarrow$$
$$CH_3(CH_2)_{7(8)}\underset{\underset{C_6H_5SiH_2}{|}}{CH}(CH_2)_{8(7)}COOCH_3$$

10. Addition of Boron

Hydroboration of certain internally unsaturated hydrocarbons and then oxidation and hydrolysis leads to terminal alcohols. This reaction has been applied to methyl oleate in an effort to produce 18-hydroxyoctadecanoic acid. Addition of diborane to the oleate yielded the expected borine derivative with boron attached at both the 9- and the 10-positions of the octadecanoate molecule (171).

$$CH_3(CH_2)_7CH=CH(CH_2)_7COOCH_3 + B_2H_6 \rightarrow$$
$$[CH_3(CH_2)_{8(7)}\underset{|}{CH}(CH_2)_{7(8)}COOCH_3]_3B$$
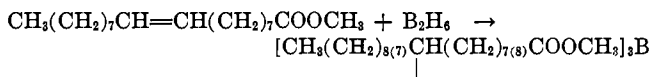
Oxidation with peroxide followed by hydrolysis yielded hydroxyoctadecanoic acid, which was oxidized with chromic oxide to the keto acid. Conversion to the oxime and Beckmann rearrangement yielded a mixture

of dibasic acids which chromatographic resolution showed to be an equimolar ratio of nonanedioic and decanedioic acids. Evidently no isomerization had occurred.

11. Addition of Mercury

Mercuration of unsaturated fatty acids is accomplished by means of mercuric acetate in methanol solution.

$$-CH=CH- + Hg(OCOCH_3)_2 + CH_3OH \rightarrow$$
$$\underset{\underset{OCH_3\ \ HgOCOCH_3}{|\ \ \ \ \ \ \ \ |}}{-CH-\!-\!-CH-}$$
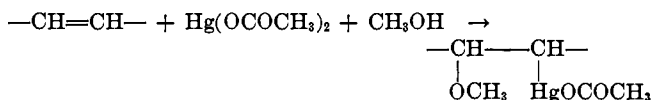
The reaction is random; it takes place with both cis and trans isomers and has been proposed as a means of estimating the composition of mixtures, since the trans olefinic acid reacts at a slower rate (131). The acetoxymercurimethoxy derivatives of unsaturated fatty acids have been suggested for the paper chromatographic analysis of mixtures (250). Addition of mercuric acetate to methyl α-eleostearate proceeded only to the extent of about 1.5 groups per molecule (412). Mercuration of 10-undecenoic acid apparently led to 11-(acetoxymercuri)-10-hydroxyundecanoic acid (251). Evidence for the assignment of structure was based on the conversion to 10-oxoundecanoic acid through a series of reactions. The experimental details were not available.

12. Addition Reactions which Produce Carbon–Carbon Bonds

A number of important addition reactions of unsaturated fatty acids result in the production of carbon-to-carbon bonds. Only those reactions will be included in the present discussion which give well-defined products. The fairly extensive literature concerning the polymerization of fatty acids and their esters for the most part is considered outside the scope of this review. Certain aspects of polymerization chemistry will be discussed briefly.

(a) Addition of Alkyl Halides

Addition of trichloromethane to methyl 10-undecenoate in the presence of benzoyl or acetyl peroxide as catalyst yielded methyl 12,12,12-trichlorododecanoate (149). Upon hydrolysis dodecanedioic acid was produced. Under the same conditions tetrachloromethane with methyl 10-undecenoate yielded methyl 10,12,12,12-tetrachlorododecanoate. With ethyl bromoacetate methyl 10-undecenoate yielded methyl ethyl 4-bromotridecanedioate.

(b) Addition of Nitriles

Additions of several nitriles to unsaturated fatty acids via the Ritter reaction have been described. The reaction is effected in 85 per cent or stronger sulfuric

TABLE 10

Addition of Aromatic Compounds to Unsaturated Acids

Fatty acid	Aromatic compound	Catalyst	Yield, %	References
10-Undecenoic	Benzene	TiX₄		224
		AlCl₃		175, 483
Oleic	Benzene, toluene, cumene, dodecylbenzene, xylene, etc.	AlCl₃ (AlBr₃, FeCl₃, ZrCl₄)	70–90	515
Oleic	Phenol, anisole, m-cresol, 2,6-di-tert-butyl-p-cresol, 6-tert-butyl-m-cresol	AlCl₃ (H₂SO₄, BF₃)	40–60	193
Oleic	Naphthalene	Acidic clay		307
Oleic	Benzene, naphthalene, biphenyl	TiX₄		224
Oleic	Phenol, m-cresol, 4-tert-butylpyrocatechol, anisole	H₂SO₄	14–49	455
Oleic	Ethyl phenyl ether	Acid-treated Permutit QH resin	11–39	455
Linoleic	Benzene	TiX₄		224
Linoleic	Phenol, resorcinol	AlCl₃		255
Ethyl erucate	Benzene, toluene, ethylbenzene, biphenyl, anisole, veratrole	AlCl₃	25–34	103

acid and leads to an amido acid. Yields are usually above 90 per cent.

$$-CH=CH- + RCN \xrightarrow[H_2SO_4]{H_2O} -CH_2CH(NHCOR)-$$
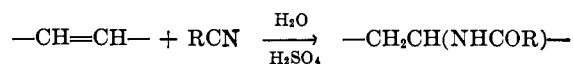
Amidoundecanoic acids have been prepared by the interaction of 10-undecenoic acid or its ester with benzonitrile (221), acrylonitrile or methacrylonitrile (413), or hydrogen cyanide (455). Amidoöctadecanoic acids have been produced from oleic acid and the following nitriles: hydrogen cyanide (455), acetonitrile, propionitrile, acrylonitrile, benzonitrile, cyanoacetic acid, and succinonitrile (454). 12-Hydroxy-9(10)-formamidoöctadecanoic acid was prepared from ricinoleic acid and hydrogen cyanide (455). Presumably addition occurs randomly and all of the above-mentioned products are mixtures of positional isomers.

(c) Addition of Aromatic Compounds

Addition of various aromatic compounds to the double bond of unsaturated fatty acids is accomplished through the use of acidic catalysts. Yields as high as 90 per cent are reported, although usually considerably lower yields are obtained (30–60 per cent or lower). A variety of catalysts have been used; aluminum chloride appears to be preferred by some. Pure individual compounds are not isolated, since under the conditions of the reaction positional isomerization occurs. Table 10 summarizes information on the addition of aromatic compounds.

A very recent report has provided significant information on the mechanism of the Friedel–Crafts reaction of olefinic fatty acids (367). Both 2-nonenoic and oleic acids were condensed with benzene, and some of the products were identified by comparison with synthesized compounds. 2-Nonenoic acid with benzene yielded 43.5 per cent of a phenylnonanoic acid whose properties, and those of the S-benzylpseudothiouronium salt, coincide with properties of synthetic 8-phenylnonanoic acid and its salt. Oxidation of the phenylnonanoic acid obtained from 2-nonenoic acid with chromium trioxide afforded a 19.4 per cent yield

of acetophenone, thus confirming the presence of at least substantial amounts of the 8-phenyl acid.

Phenylation of oleic acid yielded a liquid phenyloctadecanoic acid whose p-phenylanilide melted at 102° after ten recrystallizations from alcohol. For purposes of comparison 17-phenyloctadecanoic acid was synthesized (p-phenylanilide, m.p. 109°). Also a substance designated as 10-phenyloctadecanoic acid (p-phenylanilide, m.p. 90°) was prepared by the reaction of phenylmagnesium bromide with the oxoöctadecanoic acid produced by the hydration of stearolic acid. It is probable that this oxoöctadecanoic acid is the equimolar mixture of the 9- and 10-isomers (see page 129) and that the phenyloctadecanoic acid also is a mixture of the two positional isomers. This would account for the comparatively low melting point. Mixtures of the p-phenylanilide melting at 102° with those melting at 109° and 90° showed no depression, and no conclusions regarding the structure of the phenylation product were reached.

Oxidation of the phenyloctadecanoic acid obtained from oleic acid yielded 11 per cent of acetophenone plus a mixture of acids from which was isolated some hexadecanedioic acid. Although this dibasic acid was not pure, there is little question regarding the presence of 17-phenyloctadecanoic acid in the original product. The investigators estimate an amount as high as 50–55 per cent. It is clear, from the above-described results, that isomerization, probably involving a carbonium ion, occurs to a very considerable extent during the reaction of unsaturated fatty acids in the presence of aluminum chloride. Also there appears to be reason to conclude that migration away from the carboxyl group predominates, but this observation requires further confirmation.

(d) Hydroformylation

Hydroformylation, the "oxo" process, has been applied to unsaturated fatty acids to a limited extent. Reaction of the ethylenic linkage with carbon monoxide and hydrogen is brought about at an elevated
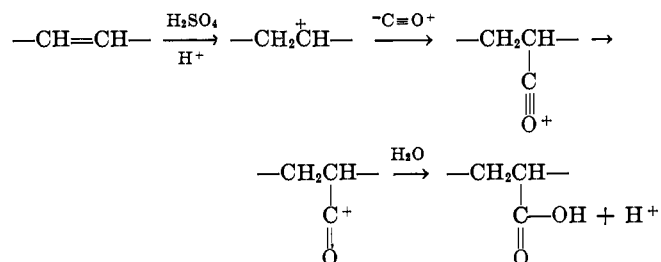
temperature (125°), a high pressure (5000 p.s.i.), and in the presence of dicobaltoctacarbonyl as catalyst.

$$-CH=CH- + CO + H_2 \xrightarrow{Co_2(CO)_8} -CH_2CH(CHO)-$$
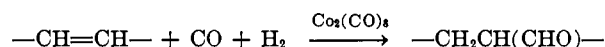
The formyl group is not hydrogenated under the conditions of the reactions. With oleic acid the addition is random and 9(10)-formyloctadecanoic acid is produced (201, 358, 359). With 10-undecenoic acid terminal addition predominated but 10-formylundecanoic acid was also produced (8, 9). Hydroformylation of methyl oleate in the presence of methanol produced the acetal, 9(10)-(dimethoxymethyl)octadecanoate (341).
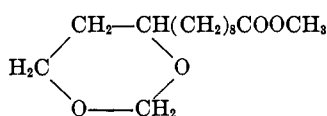
(e) Carboxylation

The introduction of a carboxyl group by the addition of carbon monoxide plus water to unsaturated fatty acids has been described recently (300, 454).

$$-CH=CH- \xrightarrow[H^+]{H_2SO_4} -CH_2\overset{+}{C}H- \xrightarrow{-C\equiv O^+} -CH_2CH- \rightarrow$$
$$\overset{|}{\underset{\overset{\|}{O^+}}{C}}$$

$$-CH_2CH- \xrightarrow{H_2O} -CH_2CH-$$
$$\overset{|}{\underset{\overset{\|}{O}}{C^+}} \qquad \overset{|}{\underset{\overset{\|}{O}}{C}}-OH + H^+$$
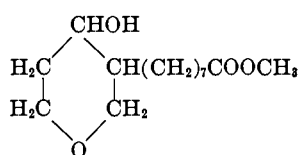
Oleic acid yielded a mixture of dicarboxylic acids in which addition of the carboxyl presumably occurred at both the 9- and 10-position; also, there were indications that isomerization had taken place. 10-Undecenoic acid apparently yielded predominantly 2-methylundecanedioic acid. Linoleic and ricinoleic acids yielded unsaturated dicarboxylic acids which appeared to be identical.

(f) Addition of Formaldehyde

The addition of formaldehyde in sulfuric acid to olefinic acids (Prins reaction) leads mainly to cyclic addition products which have been identified on the basis of their chemical reactions. The major products from 10-undecenoic acid were methyl m-dioxane-4-nonanoate (XXVI) (30 per cent) and methyl tetrahydro-4-hydroxypyran-3-octanoate (XXVII) (16 per cent) (499); some methyl undecenoate and methyl 10-hydroxyundecanoate also were found.
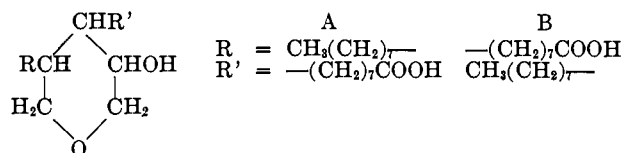
$$\begin{array}{cc}
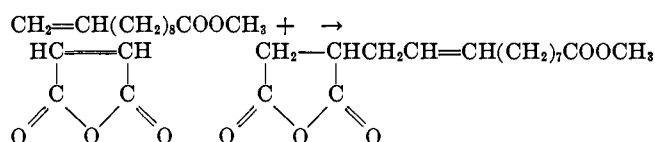\text{CH}_2\text{---CH(CH}_2\text{)}_8\text{COOCH}_3 & \text{CHOH} \\
\text{H}_2\text{C} \qquad \text{O} & \text{H}_2\text{C} \qquad \text{CH(CH}_2\text{)}_7\text{COOCH}_3 \\
\text{O---CH}_2 & \text{H}_2\text{C} \qquad \text{CH}_2 \\
 & \text{O} \\
\text{XXVI} & \text{XXVII}
\end{array}$$

Oleic acid is said to yield a mixture of two tetrahydropyran isomers, A and B (408)

$$\begin{array}{ccc}
\text{CHR'} & A & B \\
\text{RCH} \quad \text{CHOH} & R = CH_3(CH_2)_7\text{---} & -(CH_2)_7\text{COOH} \\
\text{H}_2\text{C} \quad \text{CH}_2 & R' = -(CH_2)_7\text{COOH} & CH_3(CH_2)_7\text{---} \\
\text{O}
\end{array}$$

(g) Addition of Maleic Anhydride

Maleic anhydride will add to isolated ethylenic linkages in unsaturated fatty acids or to conjugated diene systems. The latter will be discussed in the section on the Diels–Alder reaction.
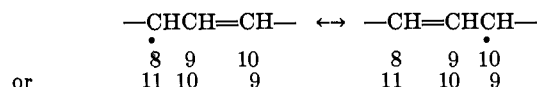
Degradation of the products of the addition of maleic anhydride to monoölefinic acids and identification of some of the degradation products have thrown light on the nature of the adducts. Methyl 10-undecenoate was treated with maleic anhydride and then with methanol plus sulfuric acid to form the tricarboxylic acid ester (461). This ester was saponified and then acidified to yield a mixture of tricarboxylic acids. From this mixture a solid acid was isolated; it was converted to a dihydroxy compound by means of hydrogen peroxide in acetic acid. The dihydroxy compound was oxidized with periodic acid to yield aldehydic substances. These were separated by extraction with ether, and the two fractions (ether extractable and aqueous) were oxidized further with hydrogen peroxide. By this treatment the ether-extractable fraction yielded nonanedioic acid, and the water-soluble fraction yielded 1,2,3-propanetricarboxylic acid. These two products indicate that the original maleic anhydride adduct consisted in part of 10-methoxycarbonyl-2-decenylsuccinic anhydride, the result of terminal addition of the anhydride with shifting of the double bond.

$$CH_2=CH(CH_2)_8COOCH_3 + \rightarrow$$
$$\begin{array}{cc}
\text{HC----CH} & \text{CH}_2\text{---CHCH}_2\text{CH=CH(CH}_2\text{)}_7\text{COOCH}_3 \\
\text{C} \quad \text{C} & \text{C} \quad \text{C} \\
\text{O} \quad \text{O} \quad \text{O} & \text{O} \quad \text{O} \quad \text{O}
\end{array}$$

From the maleic anhydride adduct of methyl oleate by a series of reactions similar to those employed with the methyl 10-undecenoate adduct the same investigators (461) isolated octanoic acid, octanedioic acid, and undecanetricarboxylic acid. According to these results it was concluded that addition had occurred at the 9- or 10-position and that the double bond had shifted to the 10- or 8-position, respectively. Recoveries were not quantitative and the methods of separation did not exclude the presence of other cleavage products. It is not possible to reconcile the above conclusion with the results now to be described.

Methyl oleate was treated with a substantial excess of maleic anhydride and, following the reaction, the adduct was purified by distillation (66). The iodine value of the adduct was close to the theoretical value. The adduct was ozonized and then cleaved by reduction

with Raney nickel to produce an aldehydic mixture, which was oxidized with peroxyacetic acid and then esterified. The esters were fractionally distilled quantitatively; four fractions were collected. The four fractions corresponded to the methyl esters of octanoic, nonanoic, octanedioic, and nonanedioic acids. The free monobasic acids were identified as the hydrazides by mixed melting points with authentic samples and the dibasic acids by direct comparison with authentic samples. Approximately equimolar amounts of each of the four fractions were obtained. These findings indicate that addition of maleic anhydride occurs equally at the 8-, 9-, 10-, and 11-positions. An intermediate free radical is proposed to account for the observed result. The radical is believed to originate at the 8- or 11-position adjacent to the double bond leading to a resonance hybrid which is equally susceptible to reaction at either of two positions (8 and 10; 9 and 11):

$$—CHCH{=}CH— \leftrightarrow —CH{=}CHCH—$$

$$
\begin{array}{ccc}
\bullet & & \bullet \\
8\ \ 9\ \ \ 10 & & 8\ \ \ 9\ \ 10 \\
\text{or} \quad 11\ 10\ \ \ 9 & & 11\ \ 10\ \ 9
\end{array}
$$

Maleic anhydride adducts of linoleic acid have also been reported but were not precisely characterized (414, 548).

(h) Diels–Alder Reaction

Reactions of polyunsaturated acids which are conjugated, or capable of undergoing conjugation readily, with a variety of dienophiles have been described. The dienophiles include maleic anhydride and acrylic acid (137, 546), maleic, chloromaleic, and methylmaleic anhydrides (67), crotonic acid and crotononitrile (551), acrylonitrile (411), diethyl azodicarboxylate (183), nitroethylene, β-nitrostyrene, acrylic acid, acrylonitrile, acrolein, methacrolein, methyl vinyl ketone, methyl vinyl sulfone, propynoic acid, and butynedioic acid (550). For the most part the adducts were not characterized; mixtures of products containing a six-membered ring are assumed. In one instance the six-membered ring was proved by the sequence of reactions shown (550)

$$CH_3(CH_2)_5CH{=}CHCH{=}CH(CH_2)_7COOH + CH{\equiv}CCOOH \rightarrow$$

Trimellitic acid
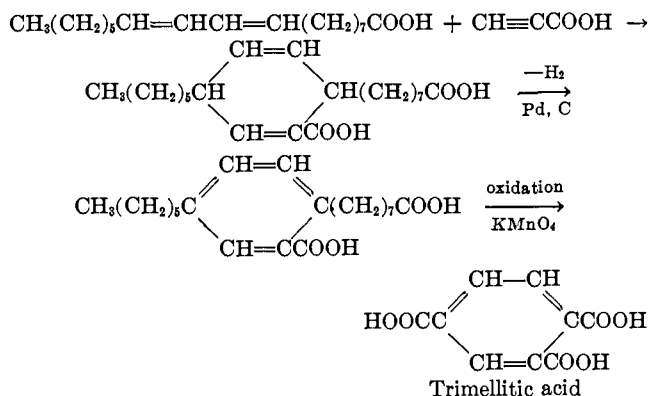
(i) Cyclization

Polyunsaturated fatty acids will undergo cyclization to a significant extent upon being heated (usually as the ester). Thus, methyl eleostearate (50 per cent α, 50 per cent β) when heated at 250° for 48 hr. in a sealed tube yielded 29 per cent of a monomer which does not form an adduct with urea (392). This monomer, when subjected to aromatization and then to oxidation, yielded phthalic acid, a result which indicates that the original monomer contained a six-membered ring. It was postulated that cyclization proceeds via the trans–cis–trans form of the triene and an ionic intermediate:
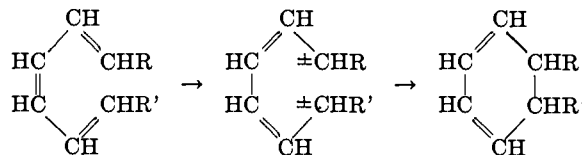
Methyl β-eleostearate yields 9 per cent of a cyclic monomer after heating at 180° for 4.5 hr. (447). Phthalic acid was obtained by an oxidative procedure similar to that described above.

Methyl linoleate when heated for 6 hr. at 270° with palladium on charcoal yielded a mixture which was estimated to contain 30 per cent aromatic compounds, 40 per cent monoölefins, 18 per cent stearate, and 7 per cent polymer (170). Further fractionation of the aromatic portion and oxidation of one of the fractions yielded phthalic acid (identified as the anhydride). It is evident that both cyclization and disproportionation occur. The mechanism of the process is not known. Conjugated methyl linoleate (90.5 per cent cis,trans conjugated diene) when heated at 250° for 4.5 hr. with selenium yielded 30 per cent of a material which did not form the urea adduct. Spectral analysis and iodine values of this material indicated that it consisted of a mixture of dialkylbenzene and dialkylcyclohexene (545). Aromatization and oxidation yielded phthalic acid.

When treated with potassium hydroxide in ethylene glycol for 7 hr. at 200°, methyl linolenate yielded 81.8 per cent of a monomer which did not form a urea adduct (479). Aromatization and oxidation of this material also yielded phthalic acid.

(j) Dimerization

The self-condensation of dienoic fatty acids to produce the so-called "dimer" acid is of some technological importance and therefore has received some attention in the scientific literature. Dimerization of monoölefinic acids has received less attention. Formation of dimers usually is accompanied by the formation of trimers or higher polymers and sometimes by side reactions.

Methyl 10-undecenoate when heated at 325° for

2.5 hr. yielded 14 per cent of a dimer and 36 per cent of higher polymers (460). Twenty per cent of a solid material was separated from the dimer ester fraction and was subjected to an investigation of its structure. Upon dihydroxylation with peroxyacetic acid followed by saponification, this solid yielded a dihydroxy acid, m.p. 141–148°, together with a saturated acid whose structure was undetermined. The dihydroxy acid was esterified and then oxidized with periodic acid to produce an aldehyde mixture which was further oxidized to a mixture of dibasic acids with peroxyacetic acid. The mixed dibasic acids were extracted with water and the insoluble fraction recrystallized, yielding tridecanedioic acid, m.p. 112–113°. The water-soluble dibasic acids were precipitated as the lead salts; the acids were liberated with hydrogen sulfide and recrystallized. Nonanedioic acid, m.p. 105.5°, was obtained. If these results are accepted at face value (approximately equimolar quantities of the two acids were obtained), it can be concluded that the original solid dimeric ester was the ester of 9-docosenedioic acid. This is substantiated by catalytic hydrogenation and saponification to yield docosanedioic (phellogenic) acid, m.p. 125°.

However, it is known that dibasic acids in the range of chain lengths under consideration form eutectic mixtures (242) and, although the C_9–C_{13} system has not been described, there is no reason to expect that it would not also form a eutectic. And, as has been pointed out previously, it is not possible to separate both components of a eutectic mixture by crystallization. No positive explanation of the results under discussion can be offered; possibly the successful separation of tridecanedioic and nonanedioic acids lies in the lead salt precipitation step. The major portion of the dimerized undecenoate was not identified.

Later work on the structure of dimerized methyl 10-undecenoate established formaldehyde and nonanedioic acid among the products of hydroxylation and oxidative cleavage (591). It is postulated that these compounds are produced from these two dibasic acid esters:

$$CH_2=CHCH(CH_2)_7COOCH_3 \qquad CH(CH_2)_7COOCH_3$$
$$CH_2(CH_2)_9COOCH_3 \qquad\quad CH(CH_2)_{11}COOCH_3$$
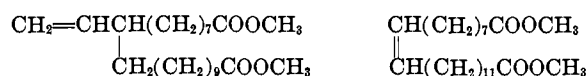
An allylic free-radical mechanism is proposed for the dimerization reaction.

Dimerization of oleic acid or its ester by heating in the presence of an acid clay (48) or boron trifluoride-phosphoric acid catalyst (555) has been reported. In the latter case oxidative cleavage of the dimer suggests the structure

$$CH_3(CH_2)_7CH=C{\longrightarrow}CH(CH_2)_7COOH$$
$$HOOC(CH_2)_7\ (CH_2)_8CH_3$$
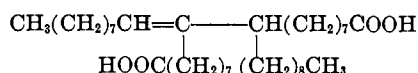
Dimerization of methyl oleate also occurs under the influence of an electric discharge (344).

Dimerization of esters of linoleic acid proceeds through what is generally believed to be a Diels–Alder type reaction (389). Conjugated dienoic esters undergo dimerization much more rapidly than do those which

$$-CH=CH-CH=CH- \rightarrow$$
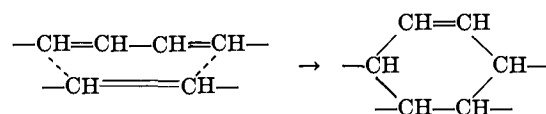
are not conjugated. It has therefore been suggested that the conjugation step limits the rate of dimerization of nonconjugated dienes (390, 391). However, rate studies of both the uncatalyzed and catalyzed reaction led to the conclusion that the dimer is formed by direct reaction between unconjugated dienes (467). A free-radical mechanism involving an α-methylene hydrogen is proposed. The cyclic nature of the dimer molecule has been confirmed by a method of ring analysis based on properties of the deoxygenated dimer (80, 579).

Dimerization of methyl β-eleostearate at 185° for 4.5 hr. yielded a dimer containing four double bonds (126). Aromatization and oxidation of this dimer produced 1,2,3,4-benzenetetracarboxylic acid. The same tetracarboxylic acid was obtained from the maleic anhydride adduct of methyl β-eleostearate, and these observations are regarded as formal proof that the dimerization is a Diels–Alder type reaction. Rate studies of the dimerization of eleostearate show the reaction to be second order, which is in agreement with the Diels–Alder mechanism (391). Ring analysis of products of the thermal polymerization of methyl eleostearate have shown that below 260° the product is chiefly a dimer containing one ring; the product from polymerization at 290° contains two rings (76).

Polymerization of polyunsaturated acids in the presence of water is said to lead to a higher dimer–trimer ratio and also to reduce decarboxylation (194, 195, 196).

B. ADDITION TO TRIPLE BONDS

The literature on addition reactions of acetylenic acids is not extensive. Principally reductive or oxidative processes are involved.

1. Addition of Hydrogen to Acetylenic Acids

Reduction of acetylenic fatty acids has been confined principally to half-hydrogenation as a means of introducing cis double bonds in the synthesis of olefinic fatty acids. This requires that the process be selective, i.e., that complete saturation be minimized and that the hydrogenation be stereospecific. These objectives have been attained to a reasonably satisfactory degree with both nickel and palladium cata-

lysts. A palladium catalyst on calcium carbonate on which a small percentage of lead has been deposited (Lindlar catalyst) has given excellent results. A small proportion of quinoline is used in conjunction with this catalyst.

A recent review on the synthesis of fatty acids (187) has covered the hydrogenation of acetylenic acids very adequately. Although additional publications have appeared, no highly significant new information was found.

Using Raney nickel as catalyst, stearolic acid was converted to elaidic acid in 2 min.; a period of 2 hr. was required to effect complete hydrogenation to stearic acid (6). Deuteration of methyl stearolate using Raney nickel yielded a product containing 94.6 per cent methyl 9-octadecenoate-9,10-d_2 (94 per cent *cis*, 6 per cent *trans*) (276). No appreciable substitution of hydrogen by deuterium occurred.

A recent synthesis of a dihydroxy acetylenic acid will illustrate complications which arise because of the formation of stereoisomers. 9,12-Dihydroxy-10-octadecynoic acid was prepared by the coupling of 1-nonyn-3-ol (IX) and ethyl 8-oxoöctanoate (X) (371). This procedure will lead to a mixture of the two enantiomorphic forms (XI and XII), each a racemic mixture. From the mixture (after saponification) was isolated by crystallization a substance, m.p. 64–65°, assumed to be one of the pure enantiomorphs. Hydrogenation of the mixture of acetylenic acids using the Lindlar catalyst produced a mixture of the enantiomorphic forms of 9,12-dihydroxy-10-octadecenoic acid (XIII and XIV) (presumably *cis*, although this was not specified), m.p. 75–79° after recrystallization. Hydrogenation of the acetylenic acid using platinum as

catalyst yielded a mixture of the 9,12-dihydroxyoctadecanoic acids (XV and XVI). By a crystallization procedure this mixture was separated into two "purified" fractions, m.p. 119–121° and 80–82°. These were assumed to be the pure isomers, but it is more likely that only the higher-melting material is a pure component (possibly *erythro* (XV) by analogy with the vicinal dihydroxoctadecanoic acids) and that the lower-melting product is the eutectic mixture of the *threo* (XV) and *erythro* forms (XVI). The configurational transformations suggested in the following scheme have not been demonstrated experimentally.

2. Addition of Halogens and Hydrogen Halides to Acetylenic Acids

A few reports of the addition of halogens or hydrogen halides to acetylenic acids have appeared.

Addition of iodine to an acetylenic acid yields the corresponding diiodoethylenic acid. Thus, 6-octadecynoic and stearolic acids yielded 6,7-diiodo-6-octadecenoic and 9,10-diiodo-9-octadecenoic acids, respectively. Similarly, 13,14-diiodo-13-docosenoic acid was obtained from 13-docosynoic acid (28).

The addition of hydrogen bromide to 10-undecynoic acid is subject to the peroxide effect (220). In the presence of an oxidant the product, m.p. 18.6°, was largely 11-bromoundecenoic acid; with an antioxidant present a product melting at 12.1° was obtained (presumably, largely 10-bromoundecenoic acid). A mixture of the two materials melted at −6°. Stearolic acid with hydrogen iodide produced iodoöctadecenoic acid or diiodoöctadecanoic acid (two isomers) (29, 30). With the latter both halogen atoms appear to add to the same carbon atom. The iodoöctadecenoic acid
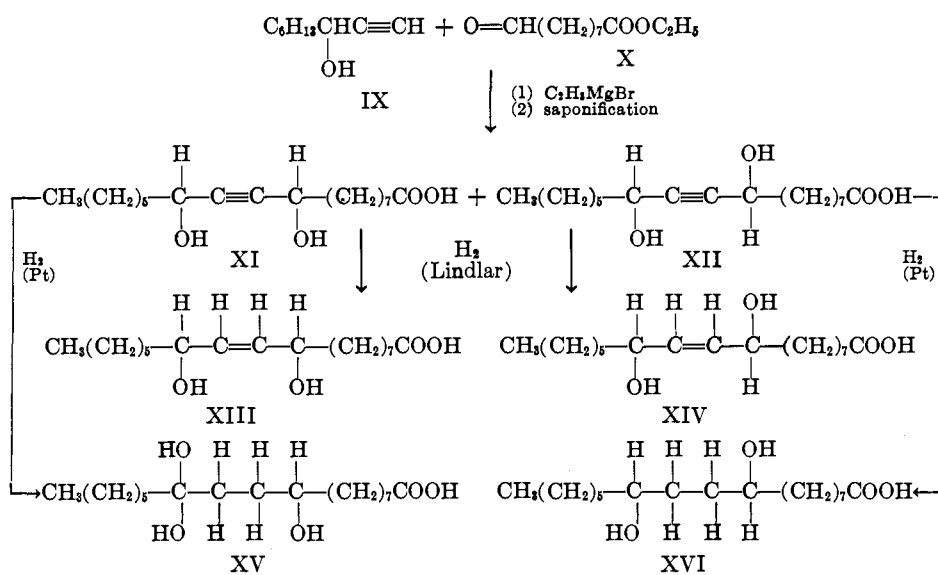
XI   *erythro*-9,12-Dihydroxy-10-octadecynoic acid
XII *threo*-9,12-Dihydroxy-10-octadecynoic acid
XIII *erythro*-9,12-Dihydroxy-*cis*-10-octadecenoic acid

XIV *threo*-9,12-Dihydroxy-*cis*-10-octadecenoic acid
XV   *erythro*-9,12-Dihydroxyoctadecanoic acid
XVI *threo*-9,12-Dihydroxyoctadecanoic acid

was separated by crystallization into two fractions, melting at 39° and 23–24°, and assumed to be positional isomers. It is unlikely that the 9- and 10-iodo acids could have been separated by crystallization or that their melting points would be as widely separated as were the reported values.

3. Addition of Oxygen to Acetylenic Acids

Oxidative reactions of acetylenic acids include hydration, oxidation, and alkoxidation; mono- or diketo acids are produced.

Hydration is accomplished by means of concentrated sulfuric acid (49, 87, 134, 287, 450) or mercuric acetate (351). The reaction may be represented as

$$-C{\equiv}C- + H_2O \rightarrow -CH{=}C- \rightarrow -CH_2C-$$
$$\underset{OH}{|} \qquad \underset{O}{\|}$$
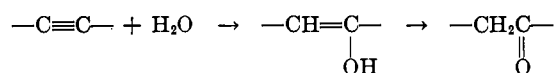
Although in an isolated system random addition of the hydroxyl to either carbon atom of the triple bond would be expected, early work indicated that the 10-carbon of stearolic acid was completely (49, 351) or partially (450) favored. In the latter case the preferential activity of the 10-carbon was attributed to an effect induced by the carboxyl group. This possibility is most unlikely, and, in fact, the earlier conclusions have been discounted recently on the basis of a study of the phase properties of the binary system consisting of 9- and 10-oxoöctadecanoic acids (127).

The directive influence of a keto group in close proximity to the triple bond has been demonstrated through the addition of methoxide to 12-oxo-9-octadecynoic acid (134). When treated with sodium methoxide, followed by reduction with potassium borohydride, this acid yielded 12-hydroxy-10-oxoöctadecanoic acid, m.p. 82–82.5°. The structure of this hydroxy keto acid was confirmed by the isolation of decanedioic acid after treatment with hydrazoic acid (Schmidt reaction) and hydrolysis. Treatment of 12-oxo-9-octadecynoic acid with ethanolic potassium hydroxide, followed in 3 min. by acidification, yielded a product which showed strong allene infrared absorption. Prolonged exposure to the alkali resulted in a change in absorption which was attributed to an enol ether. Acidification yielded a 1,3-diketone. The following
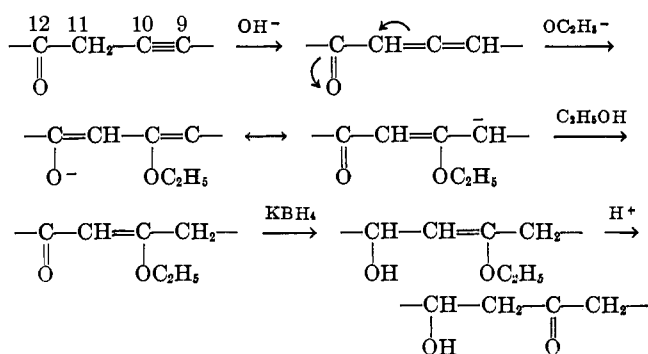
sequence of reactions was proposed to account for the directed addition to the triple bond under unusually mild conditions.

In contrast to the above, when 12-hydroxy-9-octadecynoic acid was treated with sulfuric acid a product identified as 12-hydroxy-9-oxoöctadecanoic acid, m.p. 83.5°, was obtained. This substance has been characterized previously; when mixed with the 10-oxo acid described above the melting point was lowered to 70–76°.

Oxidation of an acetylenic acid with potassium permanganate yields a diketo acid. Thus, stearolic acid was converted to 9,10-dioxoöctadecanoic acid (278, 287, 289). A yield of 90 per cent was reported.

C. ADDITION TO CARBONYL

1. Addition of Hydrogen

Reduction of keto acids is a common route to the synthesis of hydroxy acids. The subject has been discussed in a general review of the synthesis of fatty acids (187). Catalytic hydrogenation using Raney nickel is frequently employed (55, 489). Other reducing agents may be used if selectivity is required. 12-Oxo-9-octadecynoic acid has been reduced to 12-hydroxy-octadecynoic acid with potassium borohydride (134). 4-Oxohexadecanoic acid was reduced by sodium amalgam to the lactone of 4-hydroxyhexadecanoic acid (241). 6,7-Dioxoöctadecanoic acid was reduced with zinc in acetic acid to yield 6(7)-hydroxy-7(6)-oxoöctadecanoic acid (158a).

An interesting comparison of three reducing reagents has been reported in connection with work on 14-methoxy-13-oxodocosanoic acid (87). With aluminum and isopropyl alcohol this acid yielded 13-hydroxy-14-methoxydocosanoic acid together with an unidentified oil. With sodium and ethanol some 13-hydroxydocosanoic acid was produced, the methoxyl having been replaced by hydrogen. Clemmensen reduction with zinc amalgam yielded 90 per cent of 14-hydroxydocosanoic acid, the keto group having been completely reduced (see page 107).

2. Addition of Organometallics

The addition of organometallics to keto acids affords a means for introducing branching into the fatty acid chain (cf. 187). With the Grignard reagent keto acids yield a tertiary carbinol usually with an asymmetric carbon atom. Partial asymmetric synthesis has been reported as a result of the interaction of phenylmagnesium bromide with (−)-menthyl esters of keto acids of five- and six-carbon chain length (435). However, with the 9-oxodecanote evidence of asymmetric synthesis was not detected in the product.

D. ADDITION TO EPOXIDE

Epoxy fatty acids offer a convenient intermediate

for the introduction of certain groups (hydroxyl, alkoxy, halo, amino) into the fatty acid side chain. Most work has been done with epoxy acids derived from naturally occurring unsaturated fatty acids.

1. Addition of Hydrogen

Catalytic hydrogenation results in the opening of the oxirane ring to form a hydroxy compound (129). It has been reported that hydrogenation of either cis- or trans-9,10-epoxyoctadecanoic acid or ester yields almost exclusively 10-hydroxyoctadecanoic acid rather than a mixture of the 9- and 10-positional isomers (325, 462), but the evidence upon which this conclusion was based has been disputed (260). Furthermore, it has been demonstrated that 9- and 10-hydroxyoctadecanoic acids form a molecular compound at a ratio of 1:1 which cannot be distinguished from the 10-isomer by any of the criteria applied in the identification of the above-mentioned product of the hydrogenation of 9,10-epoxyoctadecanoic acid (127). Without question the reaction does proceed in a random manner. Other claims for the nonrandom opening of the oxirane ring in the fatty acid chain have been published, e.g., ethyl 13,14-epoxydocosanoate to ethyl 14-hydroxydocosanoate (409) and methyl trans-2,3-epoxyhexadecanoate, octadecanoate, and docosanoate to the corresponding 3-hydroxy esters (37). Conclusive proof of the structure of the 14-hydroxydocosanoate was not presented; probably the product is the mixture of positional isomers. Apparently, with the 2,3-epoxides the carbon–oxygen bond nearest the carboxyl is opened. Random opening of the oxirane ring in cis-6,7-epoxyoctadecanoic acid has been reported recently (171a).

2. Addition of Water

Opening of an oxirane ring in an epoxy fatty acid by the addition of water results in the formation of a dihydroxy acid (526). Inversion occurs during the process. Thus, cis-9,10-epoxyoctadecanoic acid yields the threo-dihydroxy acid and the trans-epoxy compound yields the erythro-dihydroxy acid (537) (see Figure 1). Typical illustrations of the procedure include 9,10-epoxyoctadecanoic acid (525), 2,3-epoxyoctadecanoic acid (352, 353), and cis-12,13-epoxy-cis-9-octadecenoic acid (65). Either aqueous alkali or aqueous acid is used to effect the reaction. With organic acids an intermediate acyloxyhydroxy compound may be isolated. Thus, cis-9,10-epoxyoctadecanoic acid, when refluxed with acetic acid, yields 9(10)-acetoxy-10(9)-hydroxyoctadecanoic acid (325). If the epoxy acid is heated (75°, 100°, 120°) for a prolonged period (up to 512 hr.) interaction between the carboxyl group and the oxirane ring occurs and a linear polyester is produced (528). α-Keto epoxides apparently do not add water to form the dihydroxy keto acid (372).

3. Addition of an Alcohol

When treated with an anhydrous alcohol and an acid catalyst an epoxide yields an alkoxyhydroxy compound. 9,10-Epoxyoctadecanoic acid with various low-molecular-weight alcohols and sulfuric acid as catalyst yielded esters of 9(10)-alkoxy-10(9)-hydroxyoctadecanoic acid (184, 530). The alcohols employed include methyl, ethyl, propyl, butyl, isobutyl, and allyl.

10,11-Epoxyundecanoic acid with 2-aminoethanethiol yielded 11-(2-aminoethylthio)undecanoic acid (110), the structure of which was established on the basis of infrared absorption data. Another report of the reaction of methyl 10,11-epoxyundecanoate with 2-aminoethanethiol lists as the product methyl 10-hydroxy - 11 - [2 - (2 - hydroxy - 11 - methoxycarbonylundecylamino)ethylthio]undecanoate, $CH_3OOC(CH_2)_8$-$CHOHCH_2SCH_2CH_2NHCH_2CHOH(CH_2)_8COOCH_3$ (329).

4. Addition of Hydrogen Halides

Epoxy acids are converted to halohydroxy acids by means of hydrogen halides. Inversion of configuration occurs during the process. Figure 1 shows the interrelationships among the epoxides, dihydroxy compounds, and chlorohydroxy compounds derived from oleic and elaidic acids (290, 525). Hydroxyiodo and hydroxybromo acids also have been produced (525). 11,12-Epoxyeicosanoic acid has been converted to 11(12)-chloro-12(11)-hydroxyeicosanoic acid (240) and 9,10-epoxy-12-hydroxyoctadecanoic acid to 9(10)-chloro-10-(9),12-dihydroxyoctadecanoic acid (291) by reaction with hydrogen chloride.

Separation by crystallization of the isomeric chlorohydroxyoctadecanoates, obtained by the treatment of methyl 9,10-epoxyoctadecanoate with hydrogen chloride, led to the conclusion that three times as much of the 9-chloro-10-hydroxy isomer was produced as of the 10-chloro-9-hydroxy (261). Identification of the two fractions was based on reduction of the chloro group and oxidation of the hydroxy acids to the corresponding keto acids. It has been shown, however, that the keto acid identified as the 10-isomer more closely corresponds to the eutectic mixture of the 9- and 10-isomers (127). The conclusion as to the ratio of products is invalid and there appears to be no reason to believe that the hydrohalogenation of isolated epoxides does not occur randomly.

Reaction of 10,11-epoxyundecanoic acid with hydrogen chloride (329) or hydrogen bromide (109) is reported to yield only the 11-halo-10-hydroxyundecanoic acids. A preponderance of the 11-halo acids might be predicted, but demonstration of the complete absence of the isomeric 10-halo-11-hydroxy acids was lacking.

5. Addition of Ammonia and Amines

Interaction of epoxy fatty acids with ammonia or amines leads to the formation of aminohydroxy acids. cis-9,10-Epoxyoctadecanoic acid with aqueous ammonia at 130° for 12 hr. yielded 9(10)-amino-10(9)-hydroxyoctadecanoic acid (404). The same epoxy acid with ammonium hydroxide or aqueous methyl-, ethyl-, dimethyl-, or diethylamine at 100–105° for 4 hr. yielded the corresponding amino (or substituted amino) hydroxy acid (534). The phenylaminohydroxy acid was obtained using aniline at 100° for 6 hr.

When treated with aqueous ammonium hydroxide 10,11-epoxyundecanoic acid is said to yield 11-amino-10-hydroxyundecanoic acid (109, 329). The identity of this material is based upon an alternate method of preparation from the bromohydrin (see page 115), the homogeneity of which may be somewhat questionable (see also above, section 4—Addition of Hydrogen Halides).

VI. ELIMINATION REACTIONS

A. ELIMINATION TO FORM A DOUBLE BOND

1. Elimination of Hydrogen

Some work has been done on the catalytic dehydrogenation of saturated fatty acids. The reaction is accompanied by side reactions such as decarboxylation and ketone formation; there are no indications that it is a satisfactory procedure for the preparation of unsaturated fatty acids.

After 15 hr. at 250–300° in the presence of nickel on pumice, a small increase in the iodine value of saturated acids was noted (173). With ethylene as hydrogen acceptor the degree of unsaturation increased somewhat.

Other investigators have studied the dehydrogenation process using a variety of catalysts, but of these Raney nickel was best (346, 347, 348, 432). A high proportion of catalyst was employed (50 g. of stearic acid, 8 g. of catalyst) and the reaction was run in the liquid phase at 220–240° for 20 hr. (346). In addition to stearic acid, lauric and palmitic acids were employed. The products contained only about 4 per cent of unsaturated fatty acids. In order to determine the position of unsaturation these acids were subjected to cleavage by ozonolysis and the mono- and dibasic acids resulting therefrom were isolated. The results indicated that with palmitic and stearic acids unsaturation occurred at the 4- to 5-position, whereas with lauric acid it occurred at the 3- to 4-position. These conclusions should be accepted with reservations until they have been substantiated by more rigorous analytical methods.

2. Elimination of Water

A number of attempts to produce dienoic acids from dihydroxy fatty acids have been reported. Under proper conditions some degree of success is attained. Conversion of 9,10-dihydroxyoctadecanoic acid by heating at 290–300° with p-toluenesulfonic acid catalyst to 70 per cent unsaturated acid (50 per cent diene) is reported (365). Other products (keto and epoxy acids) also were formed (363). Conjugated dienes up to as high as 60 per cent of the theoretically possible amount were formed by the pyrolysis of diacyloxy-, acyloxyhydroxy-, or epoxyoctadecanoates (135). Temperatures ranging from 285 to 360° were employed. No pure substances were isolated from any of the reaction products mentioned above.

Ricinoleic acid, the major constituent of castor oil, is a raw material for the production of a dienoic acid. There are many reports in the older technical literature relating to the dehydration of ricinoleic acid or castor oil. Many of the conclusions drawn from this work are highly speculative, and actually even today relatively little is known concerning the products of the reaction. Reported yields of conjugated diene vary considerably, but 30–40 per cent is a reasonable average. Dehydration may be accomplished directly using catalysts such as maleic anhydride adducts (205), sodium bisulfate or zinc (303), or alumina (330). Acetylated ricinoleic acid has also been used with various catalysts (204). Acidic catalysts gave best results.

The dehydration of ricinoleic acid is assumed to result in a mixture of 9,11- and 9,12-octadecadienoic acids. However, a dienoic acid, m.p. 55.5–56.5°, was isolated, via a solid dibromide, from the products of dehydration (345). The properties of this acid corresponded to those of a conjugated diene. Oxidation with permanganate in acetone yielded octanedioic acid, which suggests that the original acid was 8,10-octadecadienoic acid. This is a reasonable conclusion, although the possibility of degradation during the oxidative cleavage was not eliminated.

3. Elimination of Halogen

Elimination of bromine from vicinal dibromides is a common procedure for generating (or regenerating) olefinic fatty acids. Elimination is accompanied by inversion; thus a threo dibromide will yield a cis olefin and an erythro dibromide will yield a trans olefin. The reaction, however, is not completely stereospecific (23). Vicinal dichlorides do not react under the conditions employed for the dibromides (zinc plus alcoholic hydrogen chloride) (324). With more drastic treatment of the dichloride some unsaturation is accomplished.

Typical examples of the synthesis of monoölefinic fatty acids from vicinal dibromides by means of zinc and alcoholic hydrogen chloride are listed in Table 11.

The bromination–debromination procedure is commonly employed for the preparation of pure linoleic

TABLE 11

Dehydrobromination of Vicinal Dibromo Acids

Dibromo acid	Unsaturated acid	References
threo-9,10-Dibromotetradecanoic.....	*cis*-9-Tetradecenoic	96
erythro-9,10-Dibromotetradecanoic...	*trans*-9-Tetradecenoic	96
erythro-9,10-Dibromohexadecanoic ...	*trans*-9-Hexadecenoic	96
erythro-4,5-Dibromoöctadecanoic.....	*trans*-4-Octadecenoic	96
erythro-9,10-Dibromoöctadecanoic....	*trans*-9-Octadecenoic	84
threo-9,10-Dibromöctadecanoic......	*cis*-9-Octadecenoic	20, 58
erythro-11,12-Dibromoöctadecanoic...	*trans*-11-Octadecenoic	85
erythro-9,10-Dibromoeicosanoic......	*trans*-9-Eicosenoic	96
threo-9,10-Dibromoeicosanoic........	*cis*-9-Eicosenoic	96
threo-13,14-Dibromodocosanoic......	*cis*-13-Docosenoic	84
erythro-13,14-Dibromodocosanoic.....	*trans*-13-Docosenoic	84, 87

acid (335), since the solid 9,10,12,13-tetrabromoöcta-decanoic acid, m.p. 115°, is separated readily in the pure state. The purity of the final product, *cis*-9-*cis*-12-octadecadienoic acid, has been questioned (18). Apparently, it is not possible to obtain a product entirely free of *trans* double bonds. Amounts varying from a trace to as high as 15 per cent are reported (13, 23, 244, 340, 380).

Debromination has also been applied in the preparation of methyl 8,11-heptadecadienoate (59) and linolenic acid (335, 376). 9,10,16-Tribromohexadecanoic acid with zinc in methanol (HBr catalyst) yielded 16-bromo-9-hexadecenoic acid (74, 247). In the same manner 9,10,16-triiodohexadecanoic acid led to 16-iodohexadecenoic acid (247).

A tetrabromo acid produced by allylic bromination of oleic acid with *N*-bromosuccinimide (see page 103), followed by addition of bromine to the remaining double bond, was debrominated to yield a mixture of dienoic acids (216). *trans*-8-*trans*-10-Octadecadienoic acid was isolated from this mixture after ultraviolet irradiation in the presence of iodine.

4. Elimination of Hydrogen Halide

(a) Elimination of Hydrogen Chloride

Unsaturated fatty acids have been produced by the elimination of hydrogen chloride from chloro alkanoic acids. The chloro acids were the products of the chlorination of saturated fatty acids or the products of the addition of chlorine (367, 564, 565) or of hydrogen chloride (570) to unsaturated fatty acids. Dehydrochlorination was effected at 220–315° over cobalt chloride on pumice under reduced pressure (564, 565). Other catalysts which have been used include cadmium, mercury, copper, iron, and zinc chlorides (366) and nickel carbonate (570). Definite products from these reactions were not identified, but analytical data show the presence of relatively high unsaturation with some conjugated diene. Oxidation of a product from chlorinated palmitic acid (2 equivalents of chlorine) yielded a mixture of dibasic acids, indicating that unsaturation occurs at all positions (564). Lactone

formation and polymerization also take place.

A slightly different method for introducing double bonds, one intended to increase unsaturation, involves allylic chlorination then dehydrochlorination. *tert*-Butyl hypochlorite was used as the chlorinating agent and dehydrochlorination was accomplished by heating (52, 185, 544, 549) or by heating in the presence of catalysts (366).

Several alkenoic acids have been reported which were produced by treatment of a chloro acid with alkali. 17-Octadecenoic acid was prepared from 18-chloroöctadecanoic acid (214). 12,12,12-Trichloro-10-dodecenoic acid was obtained from 10,12,12,12-tetrachlorododecanoic acid (149). Both methyl 12-chloro-*cis*-9-octadecenoate and the *trans* isomer yielded *trans*-9-*trans*-11-octadecadienoic acid (203). 9(10)-Chloro-10(9)-hydroxyoctadecanoic acid is said to yield some 9(10)-hydroxy-10(8)-octadecenoic acid when treated with sodium carbonate at 80° (364). Methyl 3-chloro-nonanoate upon treatment with sodium acetate produced only methyl 2-nonenoate (207); no substitution occurred.

(b) Elimination of Hydrogen Bromide

Dehydrobromination of 2-bromo acids with base leads to the formation of 2-alkenoic acids in only fair yields at best. 2-Bromotetradecanoic acid with quinoline at 200° for 5 hr. is reported to give a 59.4 per cent yield of 2-tetradecenoic acid (308). 2-Bromododecanoic and 2-bromohexadecanoic acids with aqueous potassium hydroxide yielded no more than 36 per cent of the unsaturated acid (474). Dimethylaniline gave unsatisfactory results. 2-Bromohexadecanoic acid (33) and 2-bromodocosanoic acid (34) with 30 per cent alcoholic potassium hydroxide produced small amounts of the corresponding 2-alkenoic acids together with substantial amounts of the ethoxy acid and some hydroxy acid.

Dehydrobromination of 10-bromo-12-oxoöctadec-anoic acid yielded 12-oxo-*trans*-10-octadecenoic acid (153, 294).

Dehydrobromination of the products of the allylic bromination of unsaturated fatty acids has been employed as a means of increasing unsaturation. In a few instances products of the reaction have been identified. The mixture of methyl 9-bromo-10-undecenoate and 11-bromo-9-undecenoate which is obtained by the reaction of methyl 10-undecenoate with *N*-bromosuccinimide when treated with quinoline at 120–130° yielded 50 per cent methyl 8,10-undecadienoate (223). This result can be explained according to the scheme shown, involving a carbonium ion which exists as a resonance hybrid.

9,11-Octadecadienoic acid, m.p. 32–33°, has been isolated from the products of the dehydrobromination with collidine of the bromoöctadecenoic acids obtained by treatment of elaidic acid with *N*-bromosuccinimide

BrCH₂CH=CHCH₂—   CH₂=CHCHBrCH₂—

$\downarrow$ —Br⁻ $\downarrow$ —Br⁻

⁺CH₂CH=CHCH₂—   ⟷   CH₂=CHĊHCH₂—

                                $\downarrow$ —H⁺

                        CH₂=CHCH=CH—
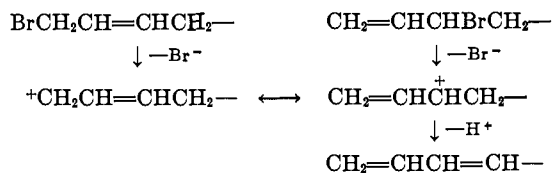
(477). In the same manner 13,15-docosadienoic acid, m.p. 53–54°, was obtained from brominated *trans*-13-docosenoic acid. The two dienoic acids were identified by ozonolysis and isolation of heptanoic and nonanedioic acids and of heptanoic and tridecanedioic acids, respectively.

Investigators from two laboratories have concluded that the allylic methylene farthest from the carboxyl group in a monoölefinic acid is most susceptible to bromination with *N*-bromosuccinimide. In both instances dehydrobromination followed by oxidative cleavage and partial identification of the products is the basis for the conclusion. *cis*-6-Octadecenoic acid was converted to the monobromoöctadecenoic acid, then dehydrobrominated with collidine (125). The resulting octadecadienoic acid was cleaved by ozonolysis and from the cleavage products were isolated decanoic acid (36 per cent by steam distillation) and a dibasic acid fraction (by extraction, 29 per cent as methyl hexanedioate). Hexanedioic acid (amount unspecified) was obtained by sublimation of the acids obtained from the diester. Disregarding possible differences in the reactivity of the two allylic methylene groups, allylic monobromination should yield a mixture of two pairs of tautomers. Dehydrobromination and cleavage of these would yield a mixture of three monobasic (C₁₀, C₁₁, C₁₂) and three dibasic (C₄, C₅, C₆) acids. The procedure used to isolate the decanoic and hexanedioic acids in the work described above would tend to fractionate these acids from the overall mixture. Without more complete information regarding all of the products of cleavage of the dienoic acid selective allylic bromination at the 8-position of 6-octadecenoic acid cannot be considered as an established fact.

The second instance of apparent selective allylic bromination involved both oleic acid and *cis*-6-octadecenoic acid (356). The experimental procedures were similar to those described above for 6-octadecenoic acid, except that no dibasic acids were actually isolated. Heptanoic acid (39 per cent) was isolated from the dienoic acid obtained from oleic acid and decanoic acid (35 per cent) from the dienoic acid obtained from *cis*-6-octadecenoic acid. As a basis for concluding that selective allylic bromination takes place, this work is subject to the same criticism as given above.

Other work on the dehydrobromination of the products of the allylic bromination of unsaturated fatty acids or esters has utilized a variety of organic and inorganic bases. These include Co₂O₃ (366), pyridine, potassium carbonate, ammonia, sodium acetate, am-

monium carbonate, calcium oxide, and magnesium oxide (383). Individual products of these reactions were not reported.

(c) Elimination of Hydrogen Iodide

In contrast with the 2-bromo compound, which yielded little or no olefinic acid, 2-iodohexadecanoic acid with 6.5 per cent ethanolic potassium hydroxide yielded 57 per cent 2-hexadecenoic acid with the 2-hydroxy acid as a by-product (524).

B. ELIMINATION TO FORM A TRIPLE BOND

Dehydrobromination of vicinal dibromo acids leads to the formation of acetylenic acids. This is the classical procedure for the preparation of stearolic acid from *threo*-9,10-dibromoöctadecanoic acid through the action of potassium hydroxide in amyl alcohol (7). Sodamide in liquid ammonia also has been used in the preparation of acetylenic acids from dibromo acids (119, 278, 283, 287). Potassium 11-bromo-10-undecenoate was converted to 10-undecynoic acid by heat (501).

C. ELIMINATION TO FORM A CARBONYL GROUP

1. Elimination of Hydrogen

Keto acids commonly are produced by the oxidation of hydroxy acids. Chromium trioxide (CrO₃) is frequently the oxidizing agent. Some keto acids which have been prepared in this way are listed in Table 12.

TABLE 12

Keto Acids Prepared from Hydroxy Acids

Keto acid	Melting point, °C.	References
10-Formyldecanoic	—	119
3-Oxohexadecanoic	94	37
3-Oxoöctadecanoic	98.2	37
9-Oxoöctadecanoic	82	21
10-Oxoöctadecanoic	82	21
12-Oxoöctadecanoic	82	134
	80–81	206
12-Oxo-9,10-epoxyoctadecanoic	84	291
3-Oxodocosanoic	105	37
6,7-Dioxoöctadecanoic	97–98	158a
9,10-Dioxoöctadecanoic	85–86	336
9,12-Dioxoöctadecanoic	95–96	371
13,14-Dioxoöctadecanoic	93–94	336
12-Oxo-*cis*-9-octadecenoic	39	153
12-Oxo-*trans*-9-octadecenoic	73	153, 294

Fusion of 10- and 12-hydroxyoctadecanoic acids with potassium hydroxide or with mixtures of potassium and sodium hydroxides at temperatures ranging from 200° to 360° produced the corresponding keto acids in yields of from 30 to 76 per cent (150). Ricinoleic acid was oxidized with sodium dichromate or aluminum isopropoxide to produce 9,12-dioxo-*trans*-10-octadecenoic acid (XXVIII) (304, 371). This substance was also obtained from 12-oxo-*cis*(or *trans*)-9-octadecenoic acid (XXIX) by oxidation with sodium dichro-

mate, from 9,12-dihydroxy-10-octadecenoic acid (XXX) by oxidation with chromium trioxide, and from 9,12-dioxoöctadecanoic acid (XXXI) by dehydrogenation with selenium dioxide (371).

R = CH₃(CH₂)₅—; R' = —(CH₂)₇COOH
R—CHOHCH₂CH₂CHOH—R'

↓ CrO₃

R—C—CH₂CH₂—C—R'
   ‖   ‖
   O   O

XXXI

SeO₂ ↓   ↑ H₂—Pd or SnCl₂

          H
          | trans
┌───→R—C—C══════C—C—R'←───┐
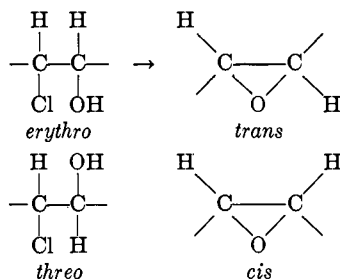│   ‖ | ‖   │
│   O   H O   │
Na₂Cr₂O₇   XXVIII   CrO₃

cis or trans   R—CHOHCH═CHCHOH—R'
R—C—CH₂CH═CH—R'   XXX
   ‖
   O   ↑
XXIX   Na₂Cr₂O₇

                    cis
        R—CHOHCH₂C═══C—R
                  | |
                  H   H
            Ricinoleic acid
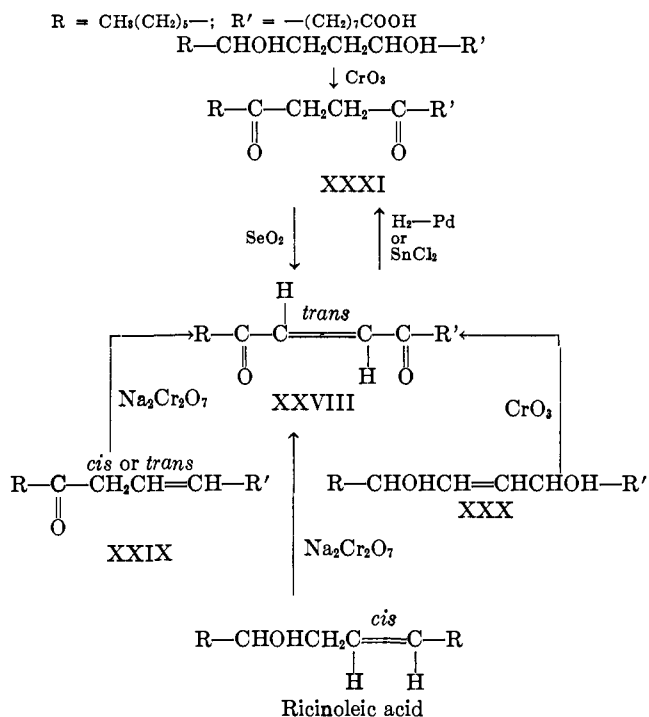
With sodium dichromate 12-hydroxy-9-octadecynoic acid yielded 12-oxo-9-octadecynoic acid (371).

2. Elimination of Water

Methyl 9,10-dihydroxyoctadecanoate when heated at 290–300° yielded mainly the 9(10)-oxoöctadecanoate (599); some diene was formed.

D. ELIMINATION TO FORM AN EPOXIDE

One method for the preparation of epoxy acids is through the dehydrochlorination of vicinal chloro-hydroxy acids with base. Both cis- and trans-9,10-epoxyoctadecanoic acids have been prepared by this method, although yields are only fair at best (40). Inversion of configuration occurs during the process (525).

          H H   H
          | | \   /
        —C—C—   →   C———C
          | | / \ / \
          Cl OH   /   O   H
         erythro   trans

          H OH   H   H
          | | \   /
        —C—C—   →   C———C
          | | / \ / \
          Cl H   /   O   \
          threo   cis

Reduced yields are the result of side reactions, including the formation of keto acids, dihydroxy acids, and hydroxyalkenoic acid (364).

Epoxy acids also have been prepared from the mixed chlorodihydroxy acids obtained by the addition of hypochlorous acid to 12-hydroxy-cis-(and trans)- octadecenoic acids (291), and also from vicinal acetoxy-bromo acids by treatment with alkali (353, 541); inversion also occurs in the latter case.

          H H   H
          | | NaOH   \   /
        —C—C—   ───────→   C═══C
          | | / \ / \
          Br OCOCH₃   H   O
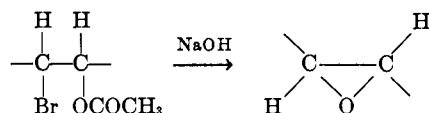
VII. ISOMERIZATION

Most naturally occurring unsaturated fatty acids are in the cis form with the double bond(s) in a specific location(s) in the hydrocarbon chain. Frequently, laboratory reactions or industrial processing will result in isomerization, either as a side effect or as an effect essential to the utility of the product of the reaction. Consequently, some aspects of the phenomena of isomerization have been investigated fairly extensively.

This discussion will be confined to those reactions whereby geometrical or positional isomerization of unsaturated fatty acids is effected. Positional isomerization probably always is accompanied by geometrical isomerization, although the converse is not true. Therefore, the latter will be considered first. The Varrentrapp reaction, which involves both a double-bond shift and the loss of two carbon atoms, will be discussed in the section on cleavage reactions (see page 138).

A. GEOMETRICAL ISOMERIZATION

Most symmetrically disubstituted ethylene derivatives are capable of existing in both the cis and trans forms. Interconversion may be effected by various catalysts and, with those pairs of geometrical isomers in which there is not a great difference in the degrees of stability, an equilibrium mixture is obtained which contains substantial amounts of both isomers. Mono-olefinic fatty acids with isolated double bonds apparently belong in this category. Properties of the geometrical isomers of polyolefinic acids of more complex structure have been less well defined. The process of converting oleic acid to elaidic acid is called elaidinization, and the term frequently is extended to include all cis-to-trans isomerization of unsaturated fatty acids.

In 1932 was published a report of the estimation of the composition of the equilibrium mixture of oleic and elaidic acids and of cis- and trans-6-octadecenoic and -13-docosenoic acids (202). The method was based upon the separation of trans-9-octadecenoic acid as its lead salt, a method shown to be reliable with mixtures high in the trans isomer. For the other two acids the composition of isomerized products was

estimated on the basis of phase diagrams determined from mixtures of the pure components. Using oxides of nitrogen as catalyst a mixture of *cis* and *trans* acids was obtained, plus a component described as an addition compound. The percentage values for the composition of this mixture were based on the starting material. The maximum amount of elaidic acid obtained was in the neighborhood of 66 per cent (somewhat lower values for the other two acids), and this value was assumed to represent the amount of *trans* isomer in the equilibrium mixture. It would seem more logical to estimate the composition of the equilibrium mixture on the basis of the total *cis* plus *trans* present in the product. If this is done, higher values for the percentage of *trans* isomer are obtained.

Other work which will be discussed in the section on isomerization during hydrogenation (see page 136) tends to support the value of 66 per cent *trans* in the equilibrium mixture. However, although this value has come to be generally accepted, a reëxamination of the matter is needed.

Various catalysts have been employed for the conversion of *cis* to *trans* unsaturated acids. These include oxides of nitrogen produced from nitric acid plus mercury, copper, or arsenic trioxide or from sodium nitrite plus sulfuric acid (202). Nitric acid plus sodium nitrite has also been used (291) as well as N_2O_3 (556). An investigation of several oxides of nitrogen has shown that NO_2 is most effective (282, 285, 286). Ethyl nitrite is also effective (427, 428). Of a series of lower alkyl nitrites, isopropyl nitrite was best (429).

Elemental selenium is now considered the best catalyst for the isomerization (*cis–trans*) of unsaturated fatty acids (14, 166, 168, 179, 245). A catalyst concentration of 0.1–1.0 per cent is usually employed and a temperature of about 200°. One report claims no isomerization with 0.15–0.30 per cent selenium after 1 hr. at 210° (486). Under conditions which are effective with selenium, tellurium gives no isomerization (426). Sulfur also has been used (202).

Iodine plus ultraviolet light is an effective catalyst for isomerizing unsaturated fatty acids (216). With 10,12-octadecadienoic acid a 2-min. exposure to a No. 2 photoflood lamp is sufficient to attain equilibrium (554). At equilibrium the dienoic acid contained 32 per cent *cis-trans* and 64 per cent *trans-trans* with no more than 5–10 per cent of the *cis-cis* form present. Other investigators found 71 per cent of the *trans-trans* form at equilibrium (120). Other catalysts include sulfur dioxide (81) and mercaptoacetic acid (172); irradiation with cathode rays has induced the formation of up to about 14 per cent of the *trans* isomer in oleic acid (385).

Various mechanisms for the elaidinization of unsaturated fatty acids have been proposed, including the postulation of addition compounds and "transitional forms" which even account for the 2:1 ratio of

trans to *cis* (71). It is more probable that *cis–trans* interconversions may proceed by more than one mechanism, but that free radials sometimes are involved. Obviously an intermediate is required which permits free rotation, which is capable of regenerating a double bond, and which does not induce migration of the double bond. Both free-radical and ionic mechanisms have been suggested which fulfill these requirements.

B. POSITIONAL ISOMERIZATION

From the point of view of usefulness, positional isomerization is almost entirely limited to the conjugation of polyunsaturated fatty acids. Many publications have appeared which pertain to this process as an analytical procedure for the estimation of polyunsaturated acids; some of the more recent investigations will be cited. After conjugation the amount of polyene is measured by ultraviolet spectrophotometry. Dienes, trienes, *etc.*, each have distinctive absorption bands and can be quantitatively differentiated by this means.

Some of the chemistry of the conjugation of linoleic acid has been elucidated (373). Conjugation of the pentadiene system of linoleic acid was assumed to be the result of the attack of the base (the usual reagent) upon the central methylene group, producing a carbanion. A shift of electrons will produce the conjugated diene. These reactions may be illustrated as shown.
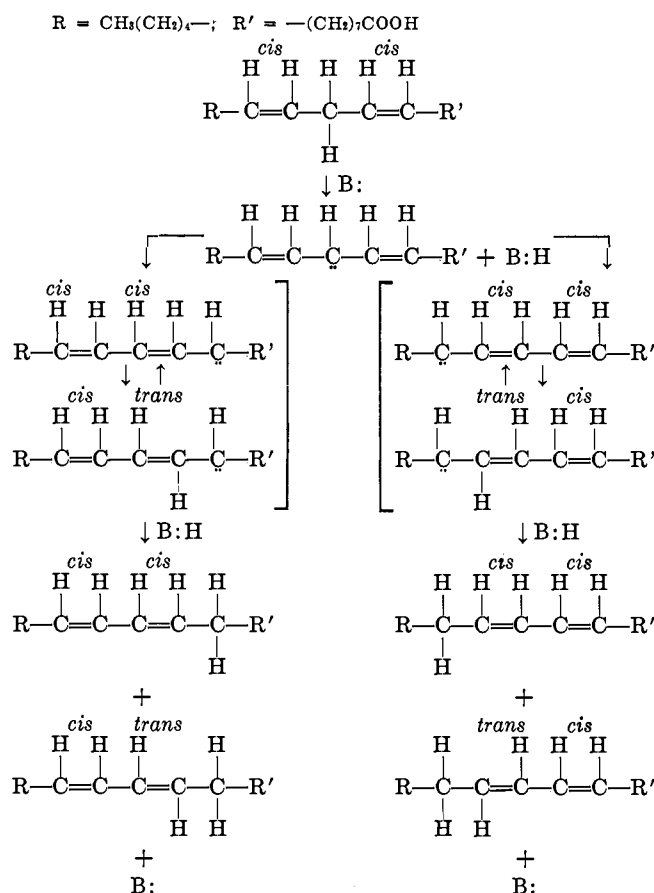
The carbanion is a resonance hybrid which presumably exists in a coplanar configuration. On the basis of molecular models it was predicted that *trans* double bonds would be generated predominantly from *cis* during the conjugation process because of spacial limitations for some of the theoretically possible arrangements of the coplanar configuration of the carbanion. Therefore, it was concluded that from *cis*-9-*cis*-12-octadecadienoic acid, mainly *cis*-9-*trans*-11- and *trans*-10-*cis*-12-octadecadienoic acids would be formed. As evidence for the validity of this deduction, linoleic acid was isomerized with alkali, esterified, and fractionated by crystallization. Among the fractions were two which, after saponification and elaidinization, proved to be *trans*-9-*trans*-11-octadecadienoic acid, m.p. 54°, and *trans*-10-*trans*-12-octadecadienoic acid, m.p. 57°. Also, alkali-isomerized linoleic acid after elaidinization yielded 60 per cent of the theoretical amount of these two *trans-trans* acids in a ratio of 1 to 1. Actually none of this evidence eliminates the possibility that the *cis-cis* configurations were present in the mixture of conjugated acids. This work, however, did show that there are significant differences in the ultraviolet absorption curves for the *trans-trans* and the *cis-trans* isomers. Others have obtained much lower absorption coefficients for conjugated acids derived from *trans*-9-*trans*-12-octadecadienoic acid (linelaidic) (140, 144).

Various procedures for the conjugation of polyunsaturated fatty acids have been described. These include potassium hydroxide in ethylene glycol (217, 228, 237, 552, 569) or water (60) and potassium *tert*-butoxide in *tert*-butyl alcohol (140, 505, 506, 588). Sodamide is partially effective with methyl linoleate, although the product is a mixture of ester and amide (2). The conjugated product is said to consist mainly of the *cis-trans* configuration, although some *trans-trans* is present.

Conjugation of unconjugated polyunsaturated fatty acids can also be effected by means of metal catalysts. Nickel on carbon after 6 hr. at 170° resulted in 30–34 per cent conjugation (421). Nickel on kieselguhr also exerts a large isomerizing effect (318). Palladium on carbon resulted in a maximum conjugation at 24

per cent after 4 hr. at 200°, after which period of time conjugation decreased because of random isomerization and polymerization (540).

An entirely different type of isomerization is the conversion of ricinoleic acid or its ester to 12-oxoöctadecanoic acid. This has been accomplished by heating the barium salt (401) or by heating the methyl ester

$$—\underset{\underset{OH}{|}}{C}HCH_2CH=CH— \xrightarrow[Ni]{Base\ or} —\underset{\underset{O}{|}}{C}CH_2CH_2CH_2—$$
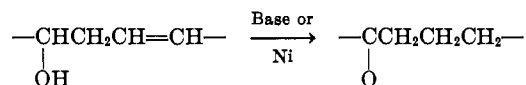
with Raney nickel (130). 12-Oxo-*cis*(or *trans*)-9-octadecenoic acid or its ester has been isomerized to 12-oxo-*trans*-10-octadecenoic acid or its ester by treatment with sulfuric acid in acetic acid (371) or simply by heating at 80° (294). An equilibrium is said to exist which contains 60–70 per cent of the 10-isomer.

C. ISOMERIZATION DURING HYDROGENATION

The fact has been recognized for many years that isomerization occurs during the process of catalytic hydrogenation of unsaturated fatty acids but, with the advent of better analytical techniques (spectrophotometry and later chromatography), investigations in this area have been intensified (139, 314, 331). It soon was recognized that both geometrical and positional isomerization were taking place; from products of the partial hydrogenation of triolein were isolated *trans*-8-octadecenoic and *trans*-9-octadecenoic acids as well as *cis*-9-octadecenoic acid (53). Isolation of these substances was accomplished by crystallization of lead and mercury soaps.

In actual fact the validity of the conclusions which can be reached regarding positional isomerization is entirely dependent upon the validity of the analytical results. Positions of double bonds are determined by oxidative cleavage and quantitative estimation of the amounts of the fragments produced. The limitations of procedures available at the time of this writing will be discussed more fully in the section on oxidative cleavage reactions (see page 140). Suffice it to say that analytical errors will be reflected in erroneous conclusions, and many of the conclusions which will be stated here should be accepted with this reservation in mind.
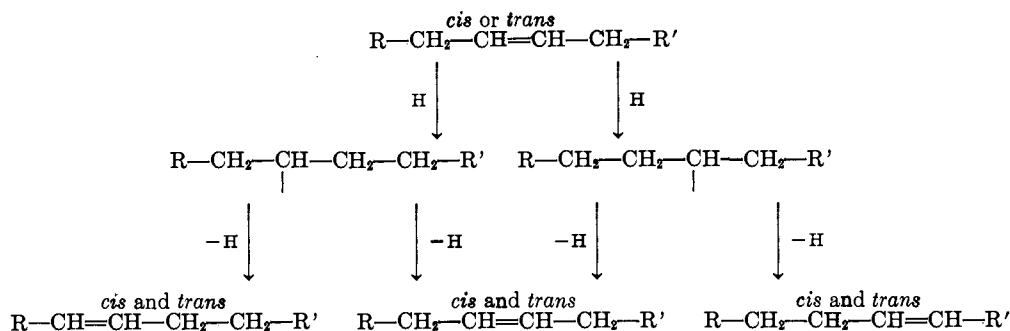
The actual mechanism of the catalytic hydrogenation of ethylenic bonds is perhaps somewhat apart from the major interests of investigators in the field of fatty acid chemistry. However, some speculation has been directed toward explaining experimental observations. Systems involving a fatty acid–hydrogen complex (567) and partial hydrogenation–partial dehydrogenation have been suggested (17, 72). These simplified model systems are not explicit as to the role of the catalyst, although absorption of both fatty acid and hydrogen is implied. The partial hydrogenation–partial dehydrogenation scheme offers a reasonable explanation of isomerization effects which are observed. Presumably the unattached carbon bond in the intermediate form represents attachment to the catalyst. This scheme explains both positional and geometric isomerization. Experimental findings of a number of investigators are in agreement with this scheme, which suggests that migration occurs equally away from the original double-bond position and that the ratio of *cis* to *trans* will tend toward the equilibrium mixture (17, 73, 133, 161, 296, 538). All published data, however, are not in accord with the above simple scheme.

Previously, the isolation of *trans*-8-octadecenoic acid and *cis*- and *trans*-9-octadecenoic acids after the partial hydrogenation of triolein was mentioned (53). No 10-octadecenoic acid was found. In the light of later work it probably is safe to conclude that failure to find the 10-isomer was due to the inadequacies of the procedure used (crystallization of metal soaps). Another investigation of double-bond displacement during the hydrogenation of methyl oleate, elaidate, *cis*-6-octadecenoate, and linoleate showed migration in both directions but mainly away from the carboxyl group (77). Positions of the double bond were determined by permanganate cleavage and chromatography of the dicarboxylic acids. Other workers have reached similar conclusions, *i.e.*, that under certain conditions migration away from the carboxyl group predominates (73, 78, 161). In order to establish these conclusions beyond question it will be necessary to devise an analytical method which is free from side effects, such as degradation of the products of cleavage, and which also gives quantitative recovery of all cleavage products.

The extent of isomerization is dependent upon the conditions of the reaction, the catalyst used, and whether solvents are employed. The *cis–trans* equilibrium ratio apparently is temperature dependent, decreasing with increased temperature (162). Electrolytic nickel and palladium are said to induce equal migration in both directions from the original position of the double bond, whereas Raney nickel favors migration away from the carboxyl group (161). With palladium as catalyst either with or without solvent the amount of *trans* formed reaches 76–79 per cent, whereas with Raney nickel values as low as 20.7 per cent were

obtained (132). Without solvent extensive migration was observed with both palladium and Raney nickel. With Raney nickel and solvents a large proportion of the double bonds remained in the original position.

Obviously, the catalytic hydrogenation of olefinic bonds is a complicated process and much regarding it remains to be learned. Isomerization reactions which occur during the hydrogenation of polyunsaturated fatty acids are of course complicated (or sometimes simplified) by interaction of the double bonds. Both positional and geometric isomerization occur (318, 485, 601).

In a study of isomerization during the hydrogenation of linoleic acid monoenes corresponding to each bond position within the original pentadiene system were found after partial hydrogenation, but no migrations to positions outside this system were reported (18). This result may simply be due to limitations of the analytical procedure in detecting the small amounts of other isomers which might have been produced. Later work by other investigators showed migration outside the original pentadiene system (133). The pattern of double-bond distribution appeared to be symmetrical, with the highest concentration at the 10-position under some conditions. No explanation for this is apparent and, as with other anomalous findings, the adequacy of the analytical procedure must be questioned.

Geometrical isomerization accompanies the positional isomerization described above. After the partial hydrogenation of conjugated linoleic acid a *trans* content of 85 per cent was found (480). This probably does not represent an equilibrium value.

VIII. CLEAVAGE REACTIONS

Several reactions which involve cleavage of the fatty acid hydrocarbon chain are important as either industrial or laboratory processes. Cleavage is accomplished by pyrolytic or chemical means, the latter usually through an oxidative procedure. The more important cleavage reactions are concerned directly or indirectly with unsaturated fatty acids.

A. PYROLYTIC CLEAVAGE

Pyrolytic reactions by definition are effected at elevated temperatures. Usually also catalysts or other special conditions are required. Alkali fusion is included in this section, although oxidation does occur during the process.

1. Cleavage of Saturated Acids

No highly significant work on the pyrolysis of unsubstituted saturated acids has been reported recently. Catalytic decomposition of caprylic acid at 445° over cracking catalysts produced a mixture containing

acid, ketone, and alkene as well as carbon dioxide and monoxide (143).

A study of the alkali fusion of keto and hydroxy acids has clarified the principal reactions which occur during this process (150). Fission of a ketone in strong alkali is postulated as occurring according to the scheme

$$R—\underset{\underset{O}{\|}}{C}—R' \xrightarrow{OH^-} R—\underset{\underset{O^-}{|}}{\overset{\overset{OH}{|}}{C}}—R' \xrightarrow{OH^-} R—\underset{\underset{O^-}{|}}{\overset{\overset{O^-}{|}}{C}}—R'$$

$$\begin{bmatrix} R^- + HO_2C—R' \\ R—CO_2H + R'^- \end{bmatrix} \qquad \begin{bmatrix} R^- + \ ^-O_2C—R' \\ R—CO_2^- + \ R'^- \end{bmatrix}$$

$$H_2O \Big\downarrow OH^- \qquad\qquad H_2O \Big\downarrow$$

$$R—H + \ ^-O_2C—R'$$
$$R—CO_2^- + \ R'—H$$
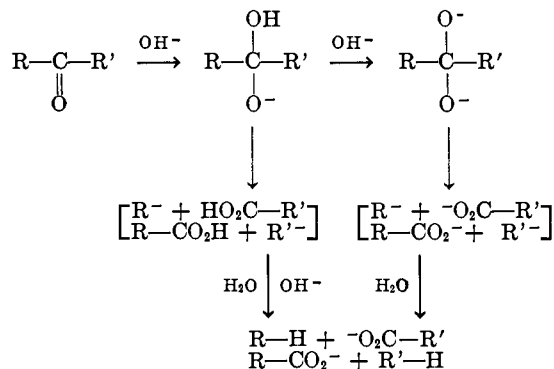
The major products predicted according to this scheme were obtained by the fusion of 10- and 12-oxoöctadecanoic and 10-oxoheptadecanoic acids with potassium hydroxide at 300 and 360°. Thus, from 10-oxoöctadecanoic acid [R = $CH_3(CH_2)_7$—, R' = —$(CH_2)_8COOH$] were obtained nonanoic (by fission at either side of the carbonyl group) and decanedioic acids; from 12-oxoöctadecanoic acid [R = $CH_3(CH_2)_5$—, R' = —$(CH_2)_{10}COOH$] were obtained heptanoic, undecanoic, and dodecanedioic acids; from 10-oxoheptadecanoic acid [R = CH_3-$(CH_2)_6$—, R' = —$(CH_2)_8COOH$] were obtained octanoic, nonanoic, and decanedioic acids. Small amounts of other products were isolated, including branched acids. These were explained as resulting from secondary reactions as, for instance, interaction of a carbanion with the keto acid. Fusion of the corresponding hydroxy acids with alkali yielded essentially the same results obtained with the keto acids. This is to be expected, since under the conditions hydroxy acids are dehydrogenated to yield keto acids.

Alkali fusion of 5-oxoheptadecanoic and 6-oxoöctadecanoic acids produced less or none of the products predicted by the above scheme. Apparently, the proximity of the carboxyl group influences the direction of the reaction. A "retro-Michael" type reaction with the 5-oxoheptadecanoic acid and a cyclization with the 6-oxoöctadecanoic acid are among the possibilities suggested.

Alkali fusion of 9(10)-cyano-10(9)-hydroxyoctadecanoic acid is said to produce a mixture of nonanedioic and decanedioic acids (442).
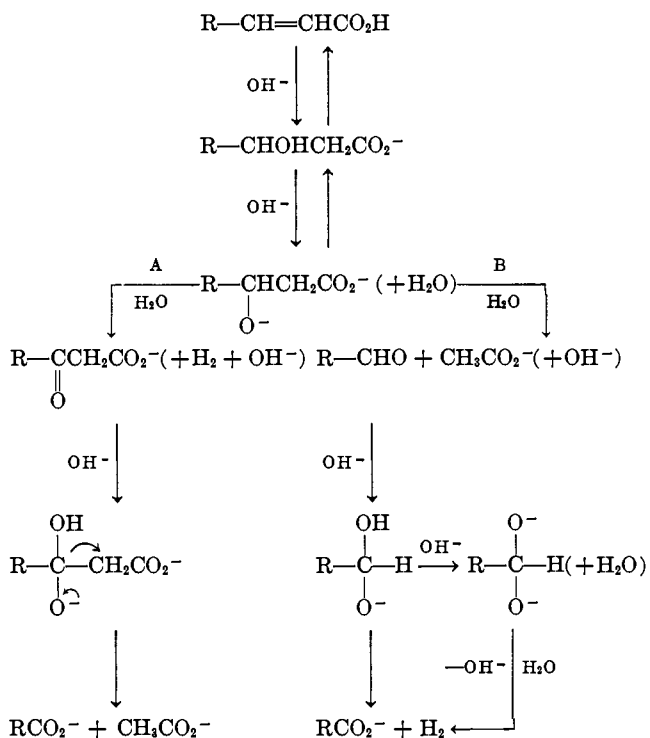
2. Cleavage of Unsaturated Acids

Degradation of olefinic acids by fusion with alkali was first described by Varrentrapp in 1840. From a monoölefinic acid is produced a saturated acid containing two fewer carbon atoms. Although the literature on the subject is fairly extensive, only recently have

data been published which clearly indicate the probable mechanism of the reaction (5, 323). The recent reports summarize adequately the earlier literature.

A study of the alkali fission of 2-, 6-, and 9-octadecenoic, 2-nonenoic, and 10-undecenoic acids involved analysis of the fusion mixture for positional isomers after progressively longer heating times or progressively higher temperatures (5). Analysis was accomplished by ozonolysis followed by gas chromatography of esters of the monobasic acids and paper chromatography of the dibasic acids. Taking into account the limitations of the analytical procedure it was clear that during alkali fusion reversible shifting of the double bond occurs in both directions from the original position. Shifts into the 2-position are followed by irreversible fission and ultimately good yields of the saturated acid are obtained. The length of time required for completion of the reaction is dependent upon the position of the original double bond and the length of the carbon chain. Opportunity to move away from the carboxyl group prolongs the reaction. Results are summarized in Table 13.

Shifting of double bonds under the influence of base has been discussed (see page 136). Fission of a 2-alkenoic acid is postulated as occurring according to the scheme

$$R—CH=CHCO_2H$$

$$OH^- \Big\updownarrow$$

$$R—CHOHCH_2CO_2^-$$

$$OH^- \Big\updownarrow$$

$$\overset{A}{\underset{H_2O}{\longleftarrow}} R—\underset{\underset{O^-}{|}}{CH}CH_2CO_2^- \ (+H_2O) \overset{B}{\underset{H_2O}{\longrightarrow}}$$

$$R—\underset{\underset{O}{\|}}{C}CH_2CO_2^-(+H_2 + OH^-) \qquad R—CHO + CH_3CO_2^-(+OH^-)$$

$$OH^- \Big\downarrow \qquad\qquad OH^- \Big\downarrow$$

$$R—\underset{\underset{O^-}{|}}{\overset{\overset{OH}{|}}{C}}CH_2CO_2^- \qquad R—\underset{\underset{O^-}{|}}{\overset{\overset{OH}{|}}{C}}—H \xrightarrow{OH^-} R—\underset{\underset{O^-}{|}}{\overset{\overset{O^-}{|}}{C}}—H(+H_2O)$$

$$\Big\downarrow \qquad\qquad \Big\downarrow \qquad —OH^- \Big| H_2O$$

$$RCO_2^- + CH_4CO_2^- \qquad RCO_2^- + H_2 \longleftarrow\!\!\!\dashv$$

Treatment of 10-undecenoic acid at lower temperatures than those indicated above has shown that the Varrentrapp reaction will take place at 250°, but not at 220° (323).

Products of the alkali fusion of olefinic acids contain small amounts of unsaturated acids, unsaturated

TABLE 13

Alkali Fission of Olefinic Acids (5)

Acid	Conditions °C.	min.	Product	Yield, %
2-Octadecenoic	360	60	Hexadecanoic	83
6-Octadecenoic	360	30	Hexadecanoic	78
9-Octadecenoic	360	60	Hexadecanoic	80-85
2-Nonenoic	300	5	Heptanoic	~80
10-Undecenoic	360	30	Nonanoic	80

polymers, and saturated acids containing two fewer carbon atoms than the main product (5). It is postulated that the lower saturated acid is produced by dehydrogenation of the main product and fission of the resulting 2-alkenoic acid. Other trace impurities in the fusion product have not been identified.

Studies of the fusion of dienoic and acetylenic acids with alkali have been reported recently (4). Alkali fusion of linoleic acid yields about 60 per cent myristic acid plus about 5 per cent palmitic acid. Acetic acid also was produced, but no butyric acid was detected. The formation of myristic acid is attributed to fission of either a 2,4-dienoic acid or to two successive fissions of 2-alkenoic acids produced by independent migration of the double bonds into the 2-position. The presence of palmitic acid was explained as having resulted from a transfer of a hydride ion to the diene prior to fission, with subsequent fission of the resulting monoene.

Alkali fusion of stearolic acid also yielded myristic acid (57 per cent) and a small amount of palmitic acid. A sequence of reversible acetylene–allene rearrangements is postulated to explain the migration of the triple bond. Alkali fusion of 10-undecynoic acid yielded heptanoic acid (12–26 per cent) and nonanoic acid (2–9 per cent), and 9-undecynoic acid gave essentially the same yields of these products. Extensive polymerization accounted for the low yields. 6,12-Tridecadiynoic acid polymerized completely upon fusion with alkali (300°, 60 min.). 2-Decynoic acid gave a low yield of octanoic acid.

Pyrolytic reactions of ricinoleic acid are of special interest because of the industrial importance of the products. Depending upon the conditions of the pyrolysis three different pairs of products are formed. These reactions may be summarized as shown (219)
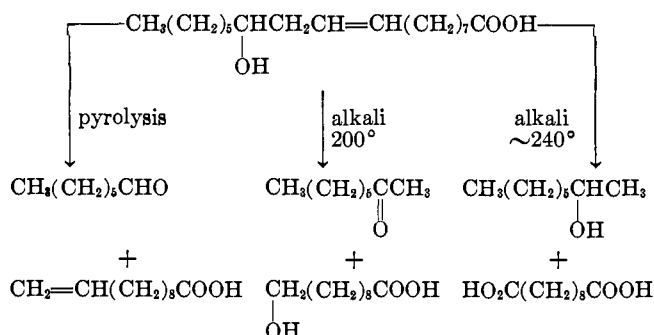
Speculation as to the mechanisms of these three reactions has provided reasonable schemes. For the simple pyrolysis of ricinoleic acid a cyclic transition state was postulated (32):
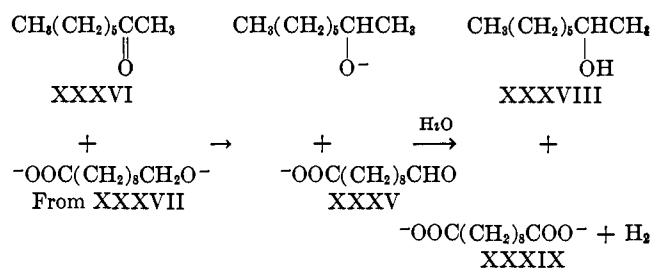
$R = CH_3(CH_2)_5—; \quad R' = —(CH_2)_7COOH$
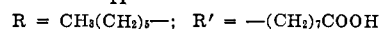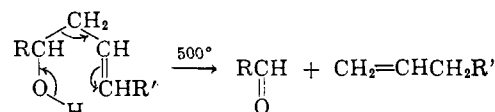
Supporting evidence for this mechanism was supplied through the pyrolysis of model compounds. Also in support of the cyclic mechanism pyrolysis of methyl 12-hydroxy-12-methyl-*cis*-9-octadecenoate yielded 2-octanone and methyl 10-undecenoate, showing that the hydrogen atom at the 12-position is not involved in the cleavage of methyl ricinoleate (188).

The mechanism for the alkaline fission of ricinoleic acid (XXXII) must account for the temperature dependence of the reaction. Two schemes have been proposed. One entails positional isomerization of the double bond to the 10-position (219); the other, and probably the more likely, suggests dehydrogenation of the carbinol function and isomerization of the β-unsaturated ketone (XXXIII) to the α-unsaturated ketone (12-oxo-10-undecenoic acid, XXXIV) (150). A "retro-aldol" type fission of the latter keto acid would yield 2-octanone (XXXVI) and 9-formylnonanoic acid (XXXV). The actual isolation of 10-hydroxydecanoic acid (XXXVII) is ascribed to the aldo acid (XXXV) acting as a hydride-ion acceptor during the initial dehydrogenation of a ricinoleic acid molecule. Both 12-oxo-*trans*-9-octadecenoic acid (XXXIII) and 12-oxo-*trans*-10-octadecenoic acid (XXXIV) have been shown to yield 2-octanone upon treatment with alkali (153, 294).
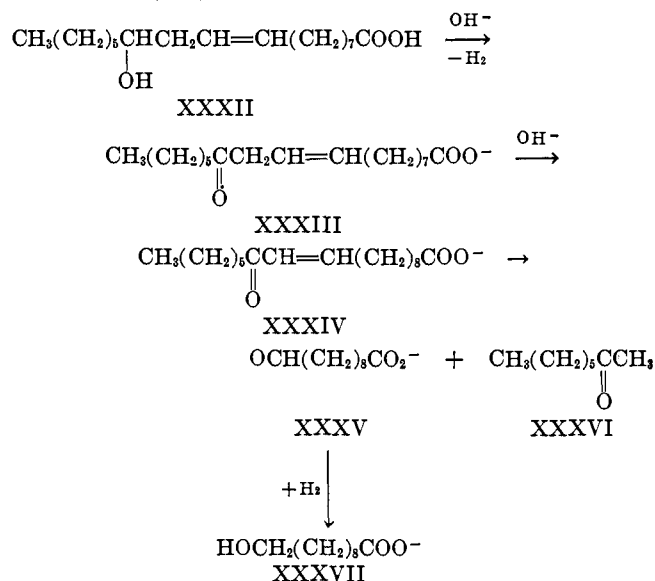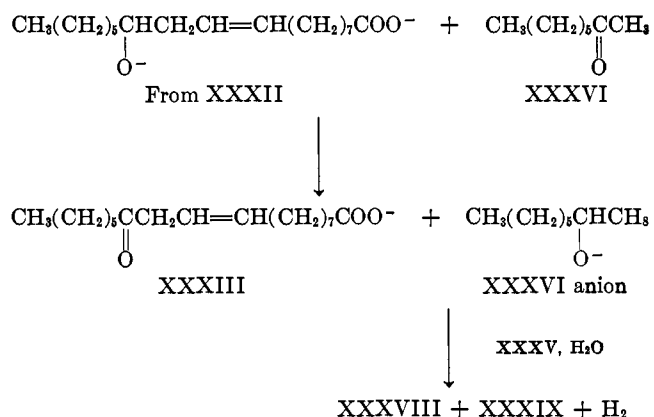
Support for this mechanism was provided by the fact that addition of an aldo acid to the fusion mixture

promotes the reaction (219). It also was demonstrated that the products of the higher-temperature fission of ricinoleic acid are formed from the products of the lower temperature fission:

$$CH_3(CH_2)_5CCH_3 \quad\quad CH_3(CH_2)_5CHCH_3 \quad\quad CH_3(CH_2)_5CHCH_3$$
$$\underset{\overset{\|}{O}}{} \quad\quad\quad\quad \underset{\overset{|}{O^-}}{} \quad\quad\quad\quad \underset{\overset{|}{OH}}{}$$
$$XXXVI \quad\quad\quad\quad XXXVIII \quad\quad\quad\quad XXXVIII$$

$$+ \quad\rightarrow\quad + \quad\overset{H_2O}{\longrightarrow}\quad +$$

$$^-OOC(CH_2)_8CH_2O^- \quad\quad ^-OOC(CH_2)_8CHO$$
From XXXVII   XXXV

$$^-OOC(CH_2)_8COO^- + H_2$$
XXXIX

An alternate route for the higher-temperature reaction does not require the intermediate formation of the hydroxy acid (XXXVII). Both routes may be followed.

$$CH_3(CH_2)_5CHCH_2CH=CH(CH_2)_7COO^- + CH_3(CH_2)_5CCH_3$$
$$\underset{\overset{|}{O^-}}{} \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad \underset{\overset{\|}{O}}{}$$
From XXXII   XXXVI

$$\downarrow$$

$$CH_3(CH_2)_5CCH_2CH=CH(CH_2)_7COO^- + CH_3(CH_2)_5CHCH_3$$
$$\underset{\overset{\|}{O}}{} \quad\quad\quad\quad\quad\quad\quad\quad\quad\quad \underset{\overset{|}{O^-}}{}$$
XXXIII   XXXVI anion

$$\downarrow \quad XXXV, H_2O$$

$$XXXVIII + XXXIX + H_2$$

Another route which might be proposed for the fission of ricinoleic acid includes as a first step the isomerization to 12-oxoöctadecanoic acid (401) (see page 136). If this isomerization occurred to any significant extent, products of the alkaline fusion of the 12-oxo-acid, namely, heptanoic, undecanoic, and dodecanedioic acids (150), would be found among the fission products of ricinoleic acid. This is not the case, and therefore it can be concluded that other routes are followed.

B. OXIDATIVE CLEAVAGE

It is expedient to discuss the oxidative cleavage of fatty acids in terms of the reagent employed. Most of the interest in this type of cleavage has centered in the determination of structure; therefore, the quantitative aspects of the reactions are especially important. Oxidative cleavage is used in one commercial process. A general review is available on oxidizing agents used in organic chemistry, many of which have been applied to fatty acids (580).

1. Cleavage with Oxygen

The degradation which occurs during autoxidation

will be mentioned later. Several recent investigations have been concerned with the oxidation of fatty acids with oxygen at elevated temperatures. The oxidation of ethyl caprate, ethyl palmitate, and palmitic acid by air was studied at 100°, using nickel phthalocyanine or potassium palmitate as catalyst (386). Lower saturated fatty acids and oxalic acid were identified among the products. It was concluded that β-oxidation occurs and that decarboxylation and ketone formation are favored by the alkaline catalyst. The treatment of methyl laurate, stearate, and oleate with oxygen at 200° yielded a variety of volatile products containing carbonyl and carboxyl functions (425). A random attack was indicated and a free-radical mechanism was proposed. The longer-chain esters appeared to be more susceptible to oxidation. Among the products of the oxidation of oleic acid by air, using uranium oleate as catalyst, nonanoic acid was identified (387).

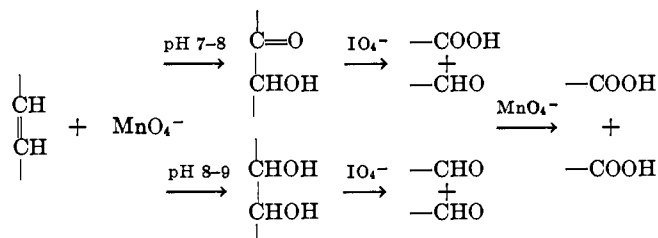#### 2. Cleavage with Permanganate

For many years permanganate has been used for the cleavage of double bonds in fatty acids as a means of locating their position, and numerous reports have appeared in the literature. The principal products of the reaction when applied to a monoölefinic acid are a monobasic and a dibasic acid.

$$CH_3(CH_2)_mCH=CH(CH_2)_nCOOH \xrightarrow{KMnO_4}$$
$$CH_3(CH_2)_mCOOH + HOOC(CH_2)_nCOOH$$
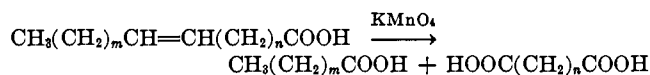
With the development of methods capable of giving better resolution of the products of the reaction it was found that use of permanganate in acetone resulted in considerable degradation of the primary products of the cleavage (51). Use of acetic acid as solvent yielded good results with relatively little degradation (51, 77). Others have failed to obtain results which were completely satisfactory, in that degradation of dicarboxylic acids occurred with permanganate in acetic acid (272, 296). Permanganate oxidation of ester, including triglycerides, has not yielded satisfactory results (156). The rate of oxidation of esters of oleic and elaidic acids by permanganate in acetone decreased with increase in molecular weight (99); esters of oleic acid were oxidized more rapidly than those of elaidic acid. At pH 12 aqueous permanganate cleaved stearolic acid to yield 80 per cent nonanedioic acid (289); at a lower pH cleavage did not occur, but the diketo acid was produced.

3. Cleavage with Permanganate–Periodate

An improvement on the permanganate cleavage of olefinic acids is provided through the use of a combination of permanganate with periodate (311, 465), and a sequence of reactions was suggested

$$
\begin{array}{c}
\overset{|}{CH} \\
\overset{\parallel}{CH} \\
\overset{|}{}
\end{array}
+ \; MnO_4^- \;
\begin{array}{l}
\xrightarrow{pH\ 7\text{--}8}
\begin{array}{c}
\overset{|}{C}=O \\
\overset{|}{C}HOH \\
\overset{|}{}
\end{array}
\xrightarrow{IO_4^-}
\begin{array}{c}
-COOH \\
+ \\
-CHO
\end{array}
\\[8pt]
\xrightarrow{pH\ 8\text{--}9}
\begin{array}{c}
\overset{|}{C}HOH \\
\overset{|}{C}HOH \\
\overset{|}{}
\end{array}
\xrightarrow{IO_4^-}
\begin{array}{c}
-CHO \\
+ \\
-CHO
\end{array}
\end{array}
$$

$$
\xrightarrow{MnO_4^-}
\begin{array}{c}
-COOH \\
+ \\
-COOH
\end{array}
$$

Permanganate is not reduced beyond manganate and is regenerated by the periodate; equivalent amounts are not required. Quantitative yields (± 2 per cent) of the expected mono- and dibasic acids were obtained from oleic, elaidic, linoleic, eicosenoic, and 10-undecenoic acids. For acids containing more than eighteen carbon atoms pyridine was added to aid in effecting solution. For esters and triglycerides, pyridine or *tert*-butyl alcohol was recommended (466). The quantitative estimation of 10-undecenoic acid has been reported, using permanganate–periodate for cleavage and then steam distillation of the formaldehyde which is produced (93). At pH 7 only 73 per cent of the formaldehyde was recovered; at pH 10 (then lowered to 7) 97 per cent was recovered (312).

A more recent critical study of the permanganate-periodate procedure for locating double bonds failed to confirm the quantitative recovery of cleavage products first reported (259). Modifications of the procedure resulted in the recovery of over 90 per cent. Oleic and elaidic acids of relatively high purity showed small amounts of 8- and 10-octadecenoic acids. Although gas chromatographic analysis of the products of the permanganate–periodate oxidation of oleic, linoleic, and linolenic acids showed the presence of unexpected products (379), this is probably the cleanest procedure available today for the location of double bonds in fatty acids.
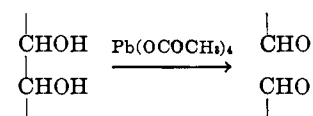
4. Cleavage with Periodic Acid

Vicinal dihydroxy acids are cleaved by periodic acid to yield a mixture of aldehyde and aldo acid. Frequently this mixture is oxidized further with permanganate to produce mono- and dibasic acids. The structure of various dihydroxyoctadecanoic acids has been established by this procedure (85, 100, 158a, 179, 245, 292, 462, 596). It apparently is satisfactory, although it has not been examined as critically as the procedures for cleavage of double bonds.

Sodium bismuthate (443, 444) and manganese dioxide (384) also cleave vicinal dihydroxy acids to yield aldehyde and aldo acid.
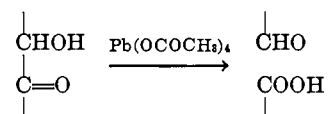
5. Cleavage with Lead Tetraacetate

Lead tetraacetate is a common reagent for the cleavage of glycols. A mixture of aldehydes is produced from unsymmetrical glycols. The method has been used for the determination of the structure of vicinal

dihydroxy fatty acids (14, 15, 53, 119). Further oxida-

$$
\begin{array}{c}
\overset{|}{C}HOH \\
\overset{|}{C}HOH \\
\overset{|}{}
\end{array}
\xrightarrow{Pb(OCOCH_3)_4}
\begin{array}{c}
CHO \\
CHO
\end{array}
$$

tion is required to convert the aldehyde and aldo acid to mono- and dibasic acids.

Cleavage of a ketol with lead tetraacetate yields a mixture of aldehyde and acid.

$$
\begin{array}{c}
\overset{|}{C}HOH \\
\overset{|}{C}=O \\
\overset{|}{}
\end{array}
\xrightarrow{Pb(OCOCH_3)_4}
\begin{array}{c}
\overset{|}{C}HO \\
COOH
\end{array}
$$

The identity of 6-hydroxy-7-oxo- and 7-hydroxy-6-oxoöctadecanoic acids was established by this method of cleavage (158a). The former yielded a mixture of lauric and 5-formylpentanoic acids, and the latter gave dodecanal and hexanedioic acid. Cleavage of a vicinal diketo acid with lead tetraacetate leads to a mixture of mono- and dibasic acids. Thus, 6,7-diöxoctadecanoic acid yielded lauric and hexanedioic acids.

6. Cleavage with Ozone

Ozonolysis is a classical method for the cleavage of double bonds. Cleavage actually is effected by hydrolysis of the ozonide which is formed by the addition of ozone to the double bond.

$$
-CH=CH- + O_3 \; \rightarrow \;
\begin{array}{c}
O \\
/ \; \backslash \\
-CH \qquad CH- \\
\backslash \qquad / \\
O-O
\end{array}
\xrightarrow{H_2O}
$$

$$
-CHO + OHC- + H_2O_2
$$
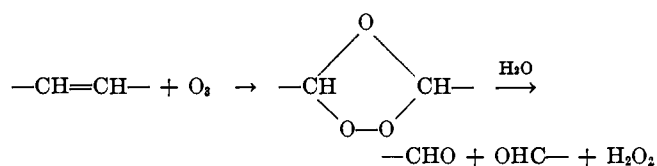
In applying the process to fatty acids the ozonide usually is not isolated. However, the infrared absorption characteristics of the ozonide of oleic acid and ester have been reported (95, 115). If actual isolation of the aldehydes is desired, the ozonide is decomposed in the presence of a reducing agent such as zinc. 9-Formylnonanoic acid has been produced by this means (219, 323). Reduction of the ozonide of oleic acid with sodium borohydride yielded a mixture of 1-nonanol and 9-hydroxynonanoic acid (500). More commonly an oxidizing agent such as hydrogen peroxide is used, and from a monoölefinic fatty acid is obtained a mixture of mono- and dibasic acids. The hydrogen peroxide may be generated from ozone and water; this is the basis for a commercial process for the production of azelaic and pelargonic acids from oleic acid (197).
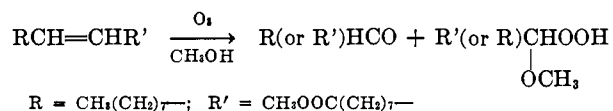
Ozonolysis is a very satisfactory method for establishing the position of a double bond in a pure unsaturated fatty acid and many examples of this application have appeared in the literature. These include monoölefinic acids (51, 125, 272), diolefinic acids (142,

272), and an acetylenic acid (287). The main products of the reaction are a monobasic acid and one or sometimes more than one (from polyolefinic acids) dibasic acids. These usually are readily separated and purified, and the position of the double bond in the original pure acid is thus established. Secondary or side reactions are not important because the main products are assumed to reflect the original structure.

For the analysis of a mixture of olefinic acids, such as those produced during isomerization reactions or those found in natural products, it is important that secondary or side reactions be reduced to a minimum during cleavage. Although ozonolysis has been widely employed for the analysis of mixtures of olefinic acids and especially of the mixtures resulting from partial hydrogenation (16, 17, 18, 19, 132, 133, 161, 296), the method does have limitations. Failure to recognize these limitations may lead to questionable or incorrect conclusions. Some of these have been mentioned in the discussion of isomerization (see page 136).

Earlier applications of ozonolysis and other cleavage reactions to the analysis of mixtures of olefinic acids lacked precise methods for the quantitative separation of the cleavage products. With the development of chromatographic procedures, which give highly reproducible and close to theoretical results with synthetic mixtures of mono- or dibasic acids, other reasons for anomalous findings must be sought. Unfortunately, however, few investigators appear to have actually established the precision of their procedure for the analysis of mixtures of positional isomers of unsaturated fatty acids. One source of error apparently lies in failure to achieve clean decomposition of the ozonide (54). Another difficulty is in the separation of longer-chain dicarboxylic acids ($>C_{12}$) from monocarboxylic acids and in the chromatography of these dibasic acids (5).

A recent study of the ozonization of methyl oleate has demonstrated the effect of the solvent on the nature of the products (420a). Use of methanol as solvent and then reduction with zinc and acetic acid resulted in yields of over 90 per cent of the aldehydes (slightly less actually isolated). Catalytic hydrogenation using palladium on charcoal was somewhat less effective. Ozonolysis in the presence of methanol led to a mixture of carbonyl compound and methoxy hydroperoxide

$$RCH=CHR' \xrightarrow[CH_2OH]{O_3} R(or\ R')HCO + R'(or\ R)CHOOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad OCH_3$$

R = CH$_3$(CH$_2$)$_7$—;   R' = CH$_3$OOC(CH$_2$)$_7$—

In the work described, analytical data indicated that the hemiacetals of the aldehydes actually were formed.

7. Cleavage with Nitric Acid

A number of reports of the oxidative cleavage of both saturated and unsaturated fatty acids with nitric acid have appeared in the recent literature. Most of these are found in less accessible journals or in the patent literature and relatively few experimental details are available. It is fairly obvious, however, that cleavage with nitric acid gives low yields of dibasic acids and that considerable degradation occurs.

Oxidation of stearic acid with fuming nitric acid in concentrated sulfuric acid yielded a mixture of dibasic acids of all chain lengths (157). Oxidation of methyl stearate with a 1:1 mixture of sulfuric and nitric acids yielded essentially the same result (399, 400). With nitric acid (10–30 per cent) at elevated temperatures and pressures saturated fatty acids yielded a mixture of mono- and dibasic acids (154). 12-Hydroxyoctadecanoic acid when oxidized with concentrated nitric acid, using copper plus ammonium vanadate as catalyst, is reported to yield a mixture of undecanedioic and dodecanedioic acid (510). These products, however, were not well characterized. 9,10-Dihydroxystearic acid is said to yield 61 per cent nonanedioic acid when treated with nitric acid, using ammonium vanadate as catalyst (38).
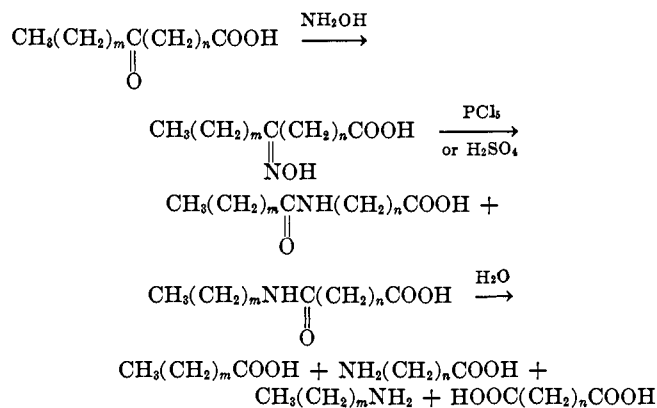
Oleic acid yielded nonanoic and nonanedioic acids when oxidized with nitric acid under various conditions: 95% HNO$_3$ at 20–25° or with manganese dioxide as catalyst at 105–110° (295); with ammonium vanadate as catalyst (38); dilute nitric acid, 125–200°, 10–500 p.s.i. (154); dilute nitric acid plus air at 15 p.s.i. (321). Ricinoleic acid with concentrated nitric acid (263) or 40–90 per cent nitric acid with ammonium vanadate as catalyst (252) yielded nonanedioic acid.

8. Cleavage with Miscellaneous Reagents

Oxidative cleavage of fatty acids by means of several other reagents has been reported. None of these is important at the present time. Chromium oxides have been used for the cleavage of hydroxy acids (342) and unsaturated acids (167). The latter was at one time a commercial process. Use of dichromate also has been reported (107). Hydrogen peroxide has been used for the cleavage of vicinal diketo acids (336) and of unsaturated acids (107, 462). Fusion of polyhydroxy acids with sodium hydroxide in the presence of air or oxygen is said to yield mono- and dibasic acids (320). Bombardment of oleic acid with deuterons yielded a variety of hydrocarbon fragments plus polymerized acid and some stearic acid (101).

C. CLEAVAGE BY BECKMANN REARRANGEMENT

Cleavage of the fatty acid hydrocarbon chain through Beckmann rearrangement of ketoximes has been used as a means of establishing the structure of keto acids.

$$CH_3(CH_2)_mC(CH_2)_nCOOH \xrightarrow{NH_2OH}$$
$$\qquad \overset{\parallel}{O}$$

$$CH_3(CH_2)_mC(CH_2)_nCOOH \xrightarrow[or\ H_2SO_4]{PCl_5}$$
$$\qquad \overset{\parallel}{NOH}$$
$$CH_3(CH_2)_mCNH(CH_2)_nCOOH\ +$$
$$\qquad \overset{\parallel}{O}$$

$$CH_3(CH_2)_mNHC(CH_2)_nCOOH \xrightarrow{H_2O}$$
$$\qquad\qquad \overset{\parallel}{O}$$

$$CH_3(CH_2)_mCOOH\ +\ NH_2(CH_2)_nCOOH\ +$$
$$CH_3(CH_2)_mNH_2\ +\ HOOC(CH_2)_nCOOH$$

Although all of the products can be isolated, frequently only the mono- and dicarboxylic acids are identified and sometimes only the latter. The length of the dicarboxylic acid carbon chain coincides with the original position of the keto group. Examples of the use of the Beckmann rearrangement for locating keto groups include 9-oxoöctadecanoic acid (210), 12-oxoöctadecanoic acid (462), and a mixture of the 9- and 10-oxo acids (171, 451).
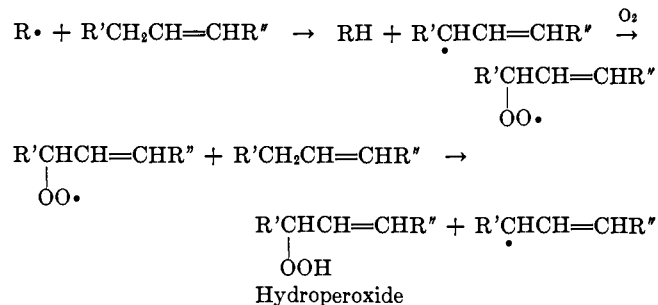
IX. Autoxidation

In the field of fatty acid chemistry probably more literature has been published pertaining to autoxidation than to any other single area of chemistry. This is in part a result of the many problems which arise in the processing of fats and in the manufacture of fat-derived products which can be attributed to the action of oxygen. Chemical changes, degradation, and development of undesirable odors and color are involved. On the other hand, the polymerization of "drying" oils is also a result of autoxidation, and a better understanding of the process is sought.

The term autoxidation is applied to comparatively slow oxidative processes which occur at moderate temperatures with free oxygen. A detailed knowledge of the chemical reactions which take place during the autoxidation of unsaturated fatty acids is still to be gained. The final result usually can be explained as resulting from a combination of substitution, addition, elimination, or cleavage reactions.

A number of fairly recent excellent reviews covering the autoxidation of fats and fatty acids are available (236, 520, 531). More general theoretical discussions of the subject also have been published (580). The treatment of autoxidation in the present review therefore will be limited to a brief recapitulation of the present state of knowledge plus some additional mention of very recent developments.

It is now generally believed that the autoxidation of ethylenic compounds is a free-radical chain reaction which involves a methylene group adjacent to the double bond. The reaction is initiated by a radical-producing catalyst (R·) (or a photochemically activated

oxygen molecule) which abstracts a hydrogen atom from a methylene group. The allylic radical formed combines with an oxygen molecule to produce a peroxide radical which can in turn dehydrogenate olefin, thus continuing the chain reaction.

$$R\cdot\ +\ R'CH_2CH{=}CHR''\ \rightarrow\ RH\ +\ R'\overset{\cdot}{C}HCH{=}CHR''\ \xrightarrow{O_2}$$
$$\qquad\qquad R'CHCH{=}CHR''$$
$$\qquad\qquad \overset{|}{O}O\cdot$$

$$R'CHCH{=}CHR''\ +\ R'CH_2CH{=}CHR''\ \rightarrow$$
$$\overset{|}{O}O\cdot$$

$$\qquad R'CHCH{=}CHR''\ +\ R'\overset{\cdot}{C}HCH{=}CHR''$$
$$\qquad \overset{|}{O}OH$$
$$\qquad Hydroperoxide$$

With monoölefinic acids such as oleic, abstraction of the hydrogen may occur at either position 8 or position 11. The allylic radical is actually a resonance hybrid and, in the case of autoxidized oleic acid, should consist of two such hybrids.

$$R' = CH_3(CH_2)_7{-};\quad R'' = {-}(CH_2)_7COOH$$
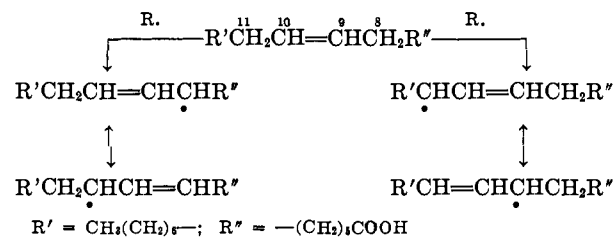
Such a mixture should produce four peroxide radicals when treated with oxygen and finally should yield a mixture of 8-, 9-, 10-, and 11-hydroperoxyoctadecenoic acids.

An attempt to realize this prediction has been reported (462). The hydroperoxide of methyl oleate was prepared, and then reduced to the mixture of hydroxy esters. Hydrogenation yielded a mixture of methyl hydroxyoctadecanoates which were oxidized to the oxoöctadecanoates. An attempt then was made to separate the four oxoöctadecanoic acids by fractional crystallization. Two fractions described as pure were obtained: 9-oxoöctadecanoic acid, m.p. 82°, and 10-oxoöctadecanoic acid, m.p. 72.3°. It has been shown subsequently that these two substances form a eutectic mixture, m.p. 73.2°; consequently, they are not separable by crystallization (127). 10-Oxoöctadecanoic acid actually melts at 83.2° and the 9-isomer melts at 82.6°; the fraction melting at 72.3° was no doubt a mixture of the two. Two other impure fractions were obtained. Three of the four fractions (the 9-oxo was excluded) were converted to the oximes; these then were subjected to the Beckmann rearrangement and the dibasic acids were isolated. From each of the three fractions was isolated some of the dibasic acid which corresponds with the keto acid believed by the investigators to be present in that fraction. Thus, the 8-
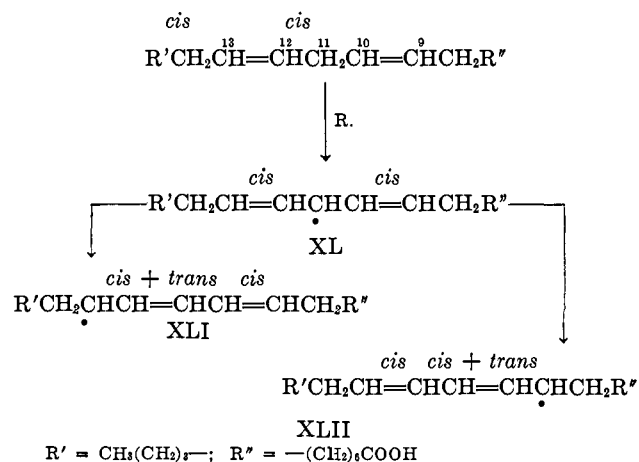
oxoöctadecanoic acid fraction yielded octanedioic acid, the 10-oxoöctadecanoic acid fraction (which has been shown to be a mixture) yielded decanedioic acid, and the 11-oxoöctadecanoic acid fraction yielded undecanedioic acid. Although the procedures described for fractionating both the keto acids and the dibasic acids could not have been truly effective because of eutectic formation, there appears to be no doubt that three dibasic acids, chain length 8, 10, and 11, were obtained and that the original hydroxyoctadecenoic acid mixture contained acids with the hydroxyl group in the 8-, 10-, and 11-positions. Properties of the substance described as 9-oxoöctadecanoic acid and its semicarbazone coincide with literature values for the synthetic compound (127); therefore, the presence of 9-hydroxyoctadecenoic acid in the original mixture can also be assumed.

Further evidence regarding the composition of the mixture of hydroxyoctadecenoates was provided by treatment with performic acid. This treatment produced a mixture of trihydroxyoctadecanoates and also resulted in cleavage, presumably at the double bond. From the cleavage products were isolated by fractional crystallization substances identified as octanedioic, nonanedioic, and decanedioic acids. The presence of the last was not explained; the first two would be expected if the free-radical reaction follows the scheme shown above. However, a question must be raised regarding the apparent success in separating by crystallization into pure components a mixture of three substances which as pairs form three eutectics (242). Cleavage of the methyl trihydroxyoctadecanoate with periodate yielded, after further oxidation of the aldehyde mixture and saponification, a mixture of dibasic acids. These were separated by extraction followed by recrystallization into substances identified as octanedioic and nonanedioic acids. These dibasic acids coincide with predictions regarding the composition of the original mixture of hydroxyoctadecenoates. Also the method of separation is capable of succeeding.

In spite of the criticisms which have been leveled at the work which has just been described and although a contrary view has been expressed (280), it does seem reasonably certain that during the autoxidation of oleic acid attack is at the 8-, 9-, 10-, and 11-positions. Whether the attack occurs equally at these positions remains to be demonstrated. (See discussion below concerning autoxidation during irradiation.)

If the concepts presented above for the autoxidation of isolated double bonds are applied to the 1,4-pentadiene system which exists in linoleic and linolenic acids, it is obvious that the possibility of several reactions exist. However, it has been shown that the relative rates of autoxidation of oleate, linoleate, and linolenate are 1:12:$ca.$ 25 (212). This suggests that the diene and triene systems have reaction sites which are considerably more reactive than are present in the

monoene. Furthermore, with linoleate the increase in peroxide parallels the increase in conjugated diene. These facts are in agreement with the postulation that attack is principally at the central methylene group.

$$cis \qquad cis$$
$$R'CH_2\overset{13}{C}H{=}\overset{12}{C}H\overset{11}{C}H_2\overset{10}{C}H{=}\overset{9}{C}HCH_2R''$$

$$\downarrow R.$$

$$cis \qquad cis$$
$$R'CH_2CH{=}CHCHCH{=}CHCH_2R''$$
$$\overset{\bullet}{\text{XL}}$$

$$cis + trans \quad cis$$
$$R'CH_2CHCH{=}CHCH{=}CHCH_2R''$$
$$\overset{\bullet}{\text{XLI}}$$

$$cis \quad cis + trans$$
$$R'CH_2CH{=}CHCH{=}CHCHCH_2R''$$

$$\text{XLII}$$
R' = CH₃(CH₂)ᵣ—; R" = —(CH₂)ₛCOOH

The radical exists as the resonance hybrid of the three structures shown (XL, XLI, XLII). The existence of both the 9- and the 13-hydroperoxy acid has been established (481), and there is a report of the isolation of the 11-hydroperoxy acid (288). However, it appears that structure XL contributes little to the resonance hybrid. During the conjugation process the double bond that migrates undergoes geometrical isomerization and the result is a mixture in which the $cis,trans$ conjugated configuration predominates (279, 280, 281, 288, 482). As autoxidation proceeds, $trans,trans$ conjugated acid is also formed (288, 419). In the $cis,trans$ hydroperoxy acid the hydroperoxy group is said to be nearest the $trans$ double bond. The autoxidation of linolenic acid follows the same pattern as for linoleic acid (279, 280, 420). The peroxide obtained by the oxidation of methyl stearolate has been concentrated and partially characterized (284).

A mechanism has been proposed for the autoxidation of olefinic compounds which does not involve free radicals but which proceeds through interaction of activated states of the reactants (280, 281). This proposal does not appear to have been generally accepted (597).

Under the influence of high-energy radiation (Co⁶⁰ source, 100 reps/sec.) the autoxidation of oleic acid and methyl oleate appears to proceed in the same manner as the nonirradiated reaction (490). Conversion of the hydroperoxy ester mixture to the mixture of keto acids was accomplished in the manner described above. The oximes of the keto acids were subjected to the Beckmann rearrangement and the resulting mixture was steam distilled to recover the monobasic acids. Elution chromatography of these showed the presence of nonanoic, octanoic, decanoic, and undecanoic acids with relative amounts in that order. These findings suggest that the original hydroperoxyocta-

decenoates were formed in the following relative amounts 10- > 11- > 9- > 8-. Whether these quantitative differences are significant is questionable. The analytical procedure is complicated; details are not reported and it is possible that some fractionation occurred during the process. Other investigators have suggested that oxidation under the influence of high-energy radiation proceeds in a manner differing somewhat from that which occurs in the absence of radiation (121).

Various studies of the autoxidation of monoölefinic fatty acids have been reported which have identified products of the reaction other than peroxides (159, 177, 198, 293, 487, 488, 490). Among the products are monobasic acids of various chain lengths, keto acids, dihydroxy acids, dibasic acids, epoxy acids, aldehydes, and polymeric substances. The *cis* configuration is more susceptible to autoxidation than the *trans*.

The structure of the polymers which form as the autoxidation of polyunsaturated fatty acids progresses is not known. Several approaches to the study of the problem have been reported (50, 273, 274). Evidence has been presented that monomers are linked through carbon–carbon (593) and through carbon–oxygen (114) bonds. Probably the reaction is very complex and both types of linkage are involved. Degradation products resulting from the autoxidation of oleic acid include propanal, heptanal, nonanal, 8-formyloctanoic acid, and dioxoöctadecanoic acid (378); products from ethyl linoleate include propanal, pentanal, hexanal, 2-pentenal, and 2-butanone (113, 256); and from linolenate were obtained ethanal, propanal, and 2-pentenal with indications of the presence of 3-hexenedial (270).

Methyl stearolate is also capable of undergoing autoxidation (284). The hydroperoxide was converted to the hydroxy-9-octadecynoate by reduction with stannous chloride.

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