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I. Introduction

A significant amount of new information on the synthesis of fatty acids has accumulated since Gunstone in 1953 (148) and Breusch in 1950 (58) published their reviews. It seemed desirable, accordingly, to make available a more up-to-date summary of the field. The first steps were taken in connection with a talk given by the author at a Gordon Research Conference on Fats and Oils in September, 1955. The present paper is a formalized and considerably expanded version of this talk.

The chemistry of fatty acid synthesis is treated here in two parts, the first dealing with pertinent methods and the second with specific acids. Emphasis is placed on the literature of 1950 through 1955, although by no means to the exclusion of other relevant material. Syntheses of and synthetic methods for the preparation of linear, branched, ethylenic, acetylenic, hydroxy, cyclic, and various other kinds of fatty acids containing ten or more carbon atoms are included. The synthesis of polybasic or of aromatic acids has not been covered.

From the synthetic point of view, probably the most interesting development in the last ten years is the increasing importance of the acetylenic bond. The synthesis of fatty acids has leaned heavily on acetylene chemistry. Some idea of how extensive this application of acetylene chemistry is may be obtained from the fact that approximately one out of every three papers consulted for this review in some way involved the triple bond. A recent book by Raphael (232) ably summarizes the chemistry of acetylenic compounds and makes available an authoritative and timely compilation of useful information.

The overwhelmingly preponderant part of the total fatty acids in nature is accounted for by a small number of acids, such as oleic, linoleic, palmitoleic, palmitic, and a few others (158). These fatty acids are all more or less similar in structure. Considerable diversity in fatty acid structure is found, however, in the many acids comprising but a minor percentage of the total. Many in this group of minor fatty acids, the members of which occur often in only a single plant or animal species and there, not infrequently, in surprisingly high concentration, are interestingly and significantly different from the predominant acids. These minor acids have attracted much attention and, as is evident in the following pages, have stimulated much synthetic work.

The nomenclature of fatty acids is encumbered with trivial names. A list of the more common names used in this report together with their systematic equivalents follows.

Common Name	Systematic Equivalent
Elaidic acid	*trans*-9-Octadecenoic acid
Linoleic acid	*cis*-9,*cis*-12-Octadecadienoic acid
Oleic acid	*cis*-9-Octadecenoic acid
Palmitic acid	Hexadecanoic acid
Palmitoleic acid	*cis*-9-Hexadecenoic acid
Stearic acid	Octadecanoic acid
Stearolic acid	9-Octadecynoic acid
Undecylenic acid	10-Undecenoic acid

Generally, numbering in the names of fatty acids starts with the carboxyl carbon, which is assigned the 1-position. However, no hesitation has been felt in writing α, β, γ to designate the 2-, 3-, and 4-positions, respectively, when usage or clarity affords a reason for so doing.

II. Synthetic Methods

A. Introduction of Carboxyl Group

Oxidative processes have been involved in forming the carboxylic function. For example, 10-undecenoic acid (*cf.* 63) and 10-undecynoic acid (39) have been converted, respectively, to 9-decenoic acid and 9-decynoic acid by Grignard addition to the ester, dehydration, and oxidative cleavage (Barbier–Wieland degradation). Saturated acids are converted cleanly to the next lower homologs by the following steps: α-bromination, hydrolysis (directly or indirectly) to α-hydroxy acid, and finally oxidative cleavage with excess lead tetraacetate in the presence of air (162a, 203b; also see 115a; *cf.* Section II,O,3). Oxidation of aldehydes or of primary alcohols can give the corresponding carboxylic acids. A mixture of dilute sodium hydroxide and silver nitrate constitutes the favorite reagent for the oxidation of aldehydes (33, 218, 236, 287). Permanganate has been used in the oxidation of 6-methyloctyl alcohol to 6-methyloctanoic acid (111), but the more common alcohol-oxidizing reagent is hexavalent chromium (38, 47, 60, 61, 96, 177, 192). Formulas I and II show how acetylenic and even ethylenic unsaturation can survive the conditions of such oxidation. The oxidation of primary alcohols to aldehydes is discussed in Section II,B.

$$\underset{\text{I}}{CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCH_2OH} \xrightarrow{CrO_3} \underset{\text{II}}{CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOH}$$

With alkyl halide available, carbonation of the Grignard derivative or combination with cyanide followed by hydrolysis constitutes two familiar methods

of extending the chain by one carbon atom while introducing carboxyl. These two methods, together with the malonate sequence, probably are the most frequently encountered reactions in the entire field of acid synthesis. Both the Grignard carboxylation and the nitrile synthesis afford opportunity for the introduction of isotopic carbon, not only in the carboxyl position but also in the hydrocarbon chain of the fatty acid (*cf.* 165; also Section II,O,5). For example (116), 6-labeled palmitic acid (III) was prepared by carbonating decylmagnesium bromide with radioactive carbon dioxide, and then adding five carbon

$$CH_3(CH_2)_9MgBr \xrightarrow[(2)\ H_2O]{(1)\ C^{14}O_2} CH_3(CH_2)_9C^{14}OOH \rightarrow \cdots \rightarrow \underset{\text{III}}{CH_3(CH_2)_9C^{14}H_2(CH_2)_4COOH}$$

atoms by standard methods. Carbonation of acetylenic Grignard reagents (or their sodium derivatives) is a reliable and convenient method of adding carboxyl to a terminal acetylene group and simultaneously of introducing α,β-unsaturation. Closely related to carbonation is the reaction of Grignard reagents, either saturated or acetylenic, with ethyl orthoformate to give (after hydrolysis) aldehydes containing one more carbon atom than the starting material (see Section II,B). Whether the carbonation of alkenyllithium (56; also *cf.* 57) or alkenyl Grignard derivatives (220) receives extensive use in the synthesis of fatty acids remains to be seen. In reactions of sensitive alkyl bromides, substitution of cuprous cyanide in an inert solvent for the more usual alkali metal cyanide in aqueous alcohol has proved expedient (92). Another modification is the reaction with sodium cyanide in slightly acid medium (45). For example, the conversion

$$\underset{\text{IV}}{HC\equiv C(CH{=}CH)_2CH_2Br} \xrightarrow[\text{pH 3–6}]{NaCN\ (Cu)} \underset{\text{V}}{HC\equiv C(CH{=}CH)_2CH_2CN}$$

of the triunsaturated allyl bromide IV to nitrile V called for the use of sodium cyanide in the presence of copper powder in aqueous tetrahydrofuran at pH 3–6.

Arndt–Eistert homologation provides a method for extending the carbon chain at the carboxyl end of an acid, which may be either saturated or unsaturated (22, 33, 123, 182, 195, 225, 226, 284, 297). The noteworthy possibility of introducing α-methyl by the use of diazoethane is illustrated by the conversion of acid chloride VI to α-methyl acid VII (32).

$$\underset{\text{VI}}{RCOCl} \xrightarrow{CH_3CHN_2} \underset{\displaystyle CH_3}{RCOCN_2} \xrightarrow{C_6H_5NH_2\ (Ag_2O)} \underset{\displaystyle CH_3}{RCHCONHC_6H_5} \xrightarrow{H_2O,\ H^+} \underset{\displaystyle \underset{\text{VII}}{CH_3}}{RCHCOOH}$$

Another method for extending an acid chain by one carbon atom and at the same time introducing a branch at the new α-position proceeds by decarboxylation by means of a silver salt and bromine, followed by a malonic ester sequence with *methylmalonic* ester (*cf. inter alia* 69, 77, 177, 290). In this way, for example, 3-methylundecanoic acid (VIII) was converted to 2-methyldecyl bromide and

$$\underset{\text{VIII}}{\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{CH}_3)\text{CH}_2\text{COOH}} \xrightarrow[(2)\ \text{Br}_2]{(1)\ \text{silver salt}}$$

3-Methylundecanoic acid

$$\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{CH}_3)\text{CH}_2\text{Br} \xrightarrow{\text{NaC}(\text{CH}_3)(\text{COOC}_2\text{H}_5)_2,\ \text{etc.}} \underset{\text{IX}}{\text{CH}_3(\text{CH}_2)_7\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}(\text{CH}_3)\text{COOH}}$$

2,4-Dimethyldodecanoic acid

then with diethyl sodiomethylmalonate to 2,4-dimethyldodecanoic acid (IX) (69). Use of unsubstituted malonic ester results in overall simple homologation.

Olefins (X) or alcohols with carbon monoxide and water under pressure and in the presence of nickel or nickel carbonyl give carboxylic acids (XI and XII).

$$\underset{\text{X}}{\text{RCH}{=}\text{CHR}'} + \text{CO} + \text{H}_2\text{O} \xrightarrow{\text{Ni(CO)}_4} \underset{\text{XI}}{\text{RCH}(\text{COOH})\text{CH}_2\text{R}'} + \underset{\text{XII}}{\text{RCH}_2\text{CH}(\text{COOH})\text{R}'}$$

Other variations lead directly to acid derivatives such as esters, amides, anhydrides, etc. (3; 99, p. 266; 238, 239). Nickel carbonyl with acetylenes gives α,β-unsaturated carboxylic acids (179, 237). In a related process olefins with carbon monoxide and hydrogen in contact with cobalt carbonyl give saturated aldehydes (154; 99, p. 280).

Many of the reactions discussed in the following pages result in insertion of the carboxyl group. It is more convenient to consider these methods under other section headings; hence such methods are not treated here.

B. REACTIONS WITH ALDEHYDES

Long-chain aldehydes can be used for the preparation of fatty acids or more generally for chain extension. Thus, oxidation gives the corresponding carboxylic acid (Section II,A). Reformatsky condensation gives β-hydroxy esters (Section III,H,5). Condensation with malonic acid gives α,β-unsaturated acids (Section II,O,3). Combination with alkylidene-triphenylphosphine in the Wittig–Geissler process gives olefins (Section II,N). Reaction with propargylmagnesium or zinc

derivatives gives hydroxy acetylenes (Section II,D). Grignard addition offers the possibility of combining two large fragments. In this last way, for example, 5,5-dimethylhexylmagnesium chloride (XIII) with 15-carbethoxypentadecanal gave a hydroxy ester (XIV), which could be converted in a straightforward

$$(CH_3)_3C(CH_2)_4MgCl + O{=}CH(CH_2)_{14}COOC_2H_5 \longrightarrow$$

XIII

$$(CH_3)_3C(CH_2)_4CHOH(CH_2)_{14}COOC_2H_5$$

XIV

(1) saponification
(2) PBr_3
(3) 20% alcoholic KOH
(4) H_2, Pt

$$(CH_3)_3C(CH_2)_{19}COOH$$

21,21-Dimethyldocosanoic acid

manner to 21,21-dimethyldocosanoic acid (259; also *cf.* 13, 159, 184, 286). The analogous series starting with a ketone instead of an aldehyde produces a branched-chain acid (*cf.* 118).

The last stages in an elegant synthesis of oenanthetol (XVI) provide a good example of extension of a chain by Grignard addition. Heptylmagnesium bro-

$$CH_3(CH_2)_6MgBr + O{=}CHCH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OCOC_6H_5 \longrightarrow$$

XV

$$CH_3(CH_2)_6CHOHCH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OH \xrightarrow{CH_3C_6H_4SO_3H \text{ in toluene}}$$

$$CH_3(CH_2)_5(CH{=}CH)_2(C{\equiv}C)_2CH{=}CHCH_2OH$$

XVI

Oenanthetol

mide (in excess) with aldehyde XV gave a dihydroxy intermediate. Acid-catalyzed elimination of water then gave oenanthetol (XVI) (159).

A method not yet applied extensively to the synthesis of fatty acids may be illustrated by the formation of 12-oxostearic ester (XVII) (63), which was pro-

$$CH_3(CH_2)_5CHO + CH_2{=}CH(CH_2)_8COOC_2H_5 \xrightarrow{(C_6H_5COO)_2}$$

Heptanal Ethyl 10-undecenoate

$$CH_3(CH_2)_5COCH_2CH_2(CH_2)_8COOC_2H_5$$

XVII

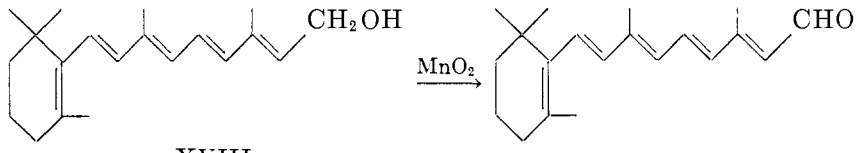
Ethyl 12-oxostearate

duced in low yield when a mixture of heptanal (excess) and 10-undecenoic ester was exposed to the action of benzoyl peroxide.

The use of aldehydes presents two problems: (*a*) preparation of the aldehyde, a procedure which is not always uncomplicated, and (*b*) the tendency of the aldehyde once formed to deteriorate by autoxidation, condensation, or trimerization. Proper handling and storage of the aldehydes and the possibility of thermal

depolymerization of the trimer help to minimize loss by deterioration. Some useful or suggestive preparations for long-chain aldehydes are summarized in the following paragraphs (*cf.* 214).

Controlled oxidation of alcohols to aldehydes is feasible. Manganese dioxide has become a more or less standard reagent in converting *allyl* alcohols to α,β-unsaturated aldehydes, e.g., vitamin A (XVIII) to vitamin A aldehyde (241;



XVIII

Vitamin A — Vitamin A aldehyde

also *cf.* 44, 47, 159, 242). Hexavalent chromium under carefully specified conditions has also been used for the same purpose (174, 263), as well as for the oxidation of nonallylic alcohols to the corresponding aldehydes.

An oxidative process by which RCH_2COOH can be degraded to RCHO is formulated in Section II,O,3 (190).

Other methods used for the preparation of aldehydes include Rosenmund hydrogenation of an acid chloride over a poisoned palladium catalyst (71, 80, 150, 176, 213, 259) and the controlled reduction of an amide by lithium aluminum hydride (*cf.* 218). A two-stage process (e.g., XIX to XX) of combining ethyl orthoformate with a Grignard reagent, either alkyl or acetylenic, to yield an acetal, followed by hydrolysis with dilute acid, has proved effective in preparing

$$\underset{\text{XIX}}{CH_3CH_2CH_2CH{=}CH(CH_2)_4MgBr} \xrightarrow{HC(OC_2H_5)_3}$$

$$CH_3CH_2CH_2CH{=}CH(CH_2)_4CH(OC_2H_5)_2 \xrightarrow{H_2O,\ H^+}$$

$$\underset{\text{XX}}{CH_3CH_2CH_2CH{=}CH(CH_2)_4CHO}$$

6-Decenal

a variety of saturated and unsaturated aldehydes (100; also *cf.* 4, 101, 104, 114, 236, 263). The oxo or hydroformylation process utilizes cobalt or cobalt carbonyl in the addition of carbon monoxide and hydrogen to an olefin to form a saturated aldehyde (154; 99, p. 280).

The addition of ethoxyacetylene to carbonyl compounds, half-hydrogenation of the triple bond, and acid hydrolysis of the resulting vinyl ether furnish an

$$R_2CO \xrightarrow{C_2H_5OC{\equiv}CMgBr} R_2\overset{OH}{\overset{|}{C}}C{\equiv}COC_2H_5 \xrightarrow{H_2,\ Pd}$$

$$R_2\overset{OH}{\overset{|}{C}}CH{=}CHOC_2H_5 \xrightarrow{H^+} \underset{\text{XXI}}{R_2C{=}CHCHO}$$

α,β-unsaturated aldehyde (XXI) (*cf.* 122; 232, p. 72). In a related process the lithium derivative of ethoxyvinylacetylene (XXIII) was used to transform aldehyde XXII to aldehyde XXIV (159; also *cf.* 203a). The reduction of lauronitrile to dodecanal with stannous chloride and hydrogen chloride in ether (Stephen reduction) has been studied (193). The sequence formulated in Section III,B by

$$\underset{\substack{\text{XXII}\\ \text{2-Hexenal}}}{CH_3CH_2CH_2CH{=}CHCHO} \xrightarrow{C_2H_5OCH{=}CHC{\equiv}CLi\ (XXIII)}$$

$$CH_3CH_2CH_2CH{=}CHCHOHC{\equiv}CCH{=}CHOC_2H_5 \xrightarrow[(2)\ H_2O,\ H^+]{(1)\ H_2,\ Pd} CH_3CH_2CH_2(CH{=}CH)_3CHO$$

XXIV

which RC≡CH is converted to RCH_2CHO appears to be general (232, p. 44; also *cf.* 25), as does the method described in Section III,H,1 for converting RC≡CH to $RCH{=}CHCH_2CHO$. The general process of converting a carbonyl compound to the homologous aldehyde is accomplished by the Darzens method, that is, by condensing the carbonyl compound with chloroacetic ester and sodium ethoxide, and by saponifying and decarboxylating the resulting glycidic ester (XXV) (217).

$$R_2CO \xrightarrow[C_2H_5ONa]{ClCH_2COOC_2H_5} \underset{\text{XXV}}{R_2C\overset{O}{\diagdown\diagup}CHCOOC_2H_5} \xrightarrow[(2)\ \text{decarboxylation}]{(1)\ \text{saponification}} R_2CHCHO$$

C. EXTENSION OF THE CHAIN BY TWO CARBON ATOMS

Reaction of a Grignard reagent or a metal acetylide (*cf.* 85, 101, 259) with ethylene oxide adds two carbon atoms and gives a product terminating in a primary hydroxyl group. Reaction of an alkyl halide or of a carbonyl with sodium acetylide extends the chain by two carbon atoms and presents a terminal acetylenic group for further operations. By condensing an aldehyde or a ketone with zinc and bromoacetic ester the Reformatsky process adds two carbon atoms to the chain and forms a β-hydroxy ester (Section III,H,5). Substitution of α-bromopropionic ester for bromoacetic ester places a branch on the new α-position. Condensation of aldehydes with malonic acid in pyridine solution containing piperidine (i.e., under Doebner conditions) gives an α,β-unsaturated acid containing two more carbon atoms than the starting aldehyde (Section II,O,3). An acid containing n carbon atoms can be converted to a β-keto ester containing $(n + 2)$ carbon atoms by methods outlined in Section II,J. The Kolbe cross product from a monobasic acid and methyl hydrogen succinate has two carbon atoms more than the original monobasic acid (*cf.* 288; also Section III,A).

The familiar malonic ester synthesis has been used repeatedly and efficiently

for converting RX to RCH_2COOH. Secondary as well as primary alkyl bromides can be used; in one case optically active 2-bromodecane was converted to opti-

$$CH_3(CH_2)_7\underset{\displaystyle CH_3}{\underset{|}{C}}HBr \xrightarrow{NaCH(COOC_2H_5)_2,\ \text{etc.}} CH_3(CH_2)_7\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH$$

2-Bromodecane — XXVI — 3-Methylundecanoic acid

cally active 3-methylundecanoic acid (XXVI) with only minor racemization (229). Repeated sequences of the type $RBr \rightarrow RCH_2COOH \rightarrow RCH_2CH_2OH \rightarrow RCH_2CH_2Br$, etc. are not uncommon. Probably the best example—one in which the sequence is used no less than six times—is in the elaboration of 15-methylpalmitic acid (XXVII) from isovaleric acid (290). Lithium aluminum hydride

$$(CH_3)_2CHCH_2COOH \rightarrow \left[\begin{array}{l}(1)\ LiAlH_4\\(2)\ P + I_2\\(3)\ NaCH(COOC_2H_5)_2,\ \text{etc.}\end{array}\right]_6 \rightarrow (CH_3)_2CH(CH_2)_{13}COOH$$

XXVII

15-Methylpalmitic acid

has been widely accepted as a convenient and effective reagent for the reduction of an acid (or ester) to an alcohol, although sodium and alcohol or high-temperature high-pressure hydrogenation (1) over a Cu-Cr-O catalyst still finds application.

Branching can be introduced by the dialkylation of malonic ester (22) or more generally by the alkylation of a monoalkylmalonic ester. For example, the series of 2-alkylstearic acids (XXVIII) in which the alkyl group ranged from methyl to dodecyl was prepared by this method (289; see also 21, 70, 76, 86, 290). 2,3-

$$CH_3(CH_2)_{15}I \xrightarrow{NaCR(COOC_2H_5)_2,\ \text{etc.}} CH_3(CH_2)_{15}CHRCOOH$$

XXVIII

Dialkyl acids have been obtained by alkylating monoalkylmalonic ester with secondary alkyl bromides (120). Methylmalonic ester has been of special interest in connection with synthetic approaches to the acids from the tubercle bacillus. Here, methylmalonic ester has been used not only for introduction of the terminal $—CH(CH_3)COOH$ unit but, by a repeating series entirely analogous to that described for the synthesis of 15-methylpalmitic acid (XXVII), for the introduction of methyl branching in the middle of the chain (*cf.* Section III,F and 27, 73, 130).

Application of the malonic ester process after degradation of RCOOH to RBr by means of a silver salt and bromine can lead to RCH_2COOH or, if monoalkylmalonic ester is involved, to RCH(R')COOH (Section II,A).

The sodium derivative (XXIX) of ethoxyacetylene, prepared from dichloroethyl ethyl ether, has been combined with butyl bromide to give an acetylenic

ether (XXX), which was hydrolyzed readily, although in low yield, to ethyl hexanoate (122). The reactions constitute an alternative to the more conventional malonic ester synthesis. The reaction of ethoxyacetylene with carbonyl

$$CH_2ClCHClOC_2H_5 \xrightarrow{3NaNH_2} NaC{\equiv}COC_2H_5 \xrightarrow{CH_3(CH_2)_3Br}$$

XXIX

$$CH_3(CH_2)_3C{\equiv}COC_2H_5 \xrightarrow{H_2O,\ H^+} CH_3(CH_2)_4COOC_2H_5$$

XXX

Ethyl 1-hexynyl ether — Ethyl hexanoate

compounds, e.g., methyl vinyl ketone (XXXI), is also possible (122, 180; see also 251 and 232, p. 82). The product with dilute aqueous acid smoothly gives an α,β-unsaturated ester (XXXIII). This process is an attractive alternative to

$$CH_2{=}CHCOCH_3 \xrightarrow{BrMgC{\equiv}COC_2H_5}$$

XXXI

Methyl vinyl ketone

$$CH_2{=}CHC(CH_3)(OH)C{\equiv}COC_2H_5 \xrightarrow{2\ N\ H_2SO_4} CH_2{=}CHC(CH_3){=}CCOOC_2H_5$$

XXXII — XXXIII

Ethyl 3-methyl-2,4-pentadienoate

the Reformatsky process. Half-hydrogenation of the intermediate acetylenic ether (e.g., XXXII) to the corresponding vinyl ether, followed by hydrolysis, yields an α,β-unsaturated aldehyde (Section II,B).

D. EXTENSION OF THE CHAIN BY THREE CARBON ATOMS

Although various three-carbon bifunctional units have been used to lengthen the chain by three carbon atoms, propargyl derivatives have been favored. For example, propargyl bromide in the presence of cuprous copper couples with

$$CH_3(CH_2)_3C{\equiv}CMgBr + BrCH_2C{\equiv}CH \xrightarrow{CuCl}$$

Propargyl bromide

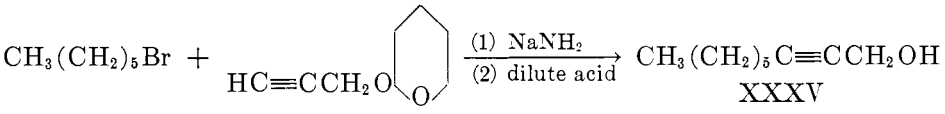
$$CH_3(CH_2)_3C{\equiv}CCH_2C{\equiv}CH$$

XXXIV

1,4-Nonadiyne

acetylenic Grignard derivatives to give terminally unsaturated, "skipped" diynes (e.g., XXXIV) (139). Propargyl bromide with *alkyl* Grignard derivatives, however, gives mainly terminal allenes (*cf. inter alia* 223). Propargyl alcohol, with or without the hydroxyl group masked, presents the acetylenic hydrogen as a point of combination. Thus, in the synthesis of linolenic acid

(Section III,B) one pair of skipped unsaturations was developed by coupling 1-bromo-2-pentyne with the Grignard derivative of propargyl alcohol carrying a tetrahydropyranyl blocking group (218). The same tetrahydropyranyl compound, as the sodium derivative, combines smoothly with alkyl bromides to give products which with dilute sulfuric acid give 1-hydroxy-2-alkynes (e.g.,



$$CH_3(CH_2)_5Br + HC{\equiv}CCH_2O\text{-}(C_5H_9O) \xrightarrow[(2)\ \text{dilute acid}]{(1)\ NaNH_2} CH_3(CH_2)_5C{\equiv}CCH_2OH$$

XXXV

2-Nonyn-1-ol

XXXV) in 60–80 per cent overall yield (98). The di-Grignard derivative of propargyl alcohol in tetrahydrofuran has been combined with crotonaldehyde to yield the expected dihydroxy compound (XXXVI) (45).

$$CH_3CH{=}CHCHO + BrMgC{\equiv}CCH_2OMgBr \rightarrow CH_3CH{=}CHCHOHC{\equiv}CCH_2OH$$

Crotonaldehyde — XXXVI

Propargyl bromide after reaction with magnesium or with zinc can be combined at the bromide end of the molecule with carbonyls or with active halogen compounds. In this way, for example, propargylmagnesium bromide with an allyl halide (XXXVII) gave 5-nonen-1-yne (114; see also 101). Carbonyl com-

$$CH_3CH_2CH_2CH{=}CHCH_2X + BrMgCH_2C{\equiv}CH \rightarrow CH_3CH_2CH_2CH{=}CHCH_2CH_2C{\equiv}CH$$

XXXVII — 2-Hexenyl halide — 5-Nonen-1-yne

pounds to which propargylmagnesium bromide has been added to give 4-hydroxy-1-alkynes (e.g., XXXVIII) include heptanal (113), hexanal (104), acetaldehyde

$$CH_3(CH_2)_5CHO + BrMgCH_2C{\equiv}CH \rightarrow CH_3(CH_2)_5CHOHCH_2C{\equiv}CH$$

Heptanal — XXXVIII — 1-Decyn-4-ol

(98), and acetone (98). Preference for zinc instead of magnesium has been expressed (104, 112, 113; 232, p. 13). In all cases more or less of the isomeric terminal allene is produced.

The acetal of propargyl aldehyde forms a Grignard derivative that adds to carbonyl compounds in the normal manner (155). Methyl propiolate in liquid ammonia containing sodium amide has added to cyclohexanone (24). However, Michael addition of other ketone compounds, acting as active hydrogen compounds, to the methyl propiolate is a complication. No information on the behavior with aldehydes is available. Methyl propiolate has been used effectively

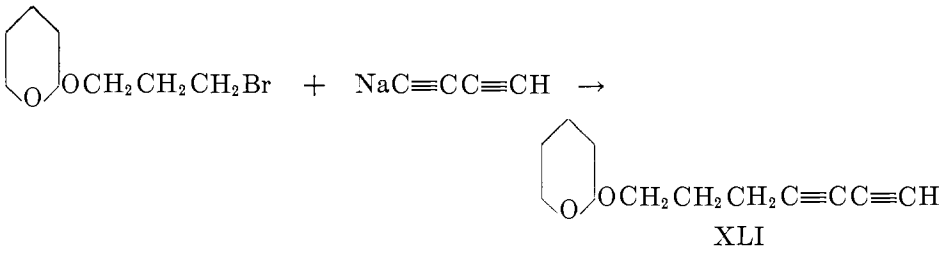
in mixed Glaser coupling (Section II,L). For example, polyunsaturated ester XL was prepared as the cross product from methyl propiolate and acetylene XXXIX (43).

$$\underset{\text{XXXIX}}{CH_3CH{=}CHC{\equiv}CC{\equiv}CH} + \underset{\text{Methyl propiolate}}{HC{\equiv}CCOOCH_3} \xrightarrow{O_2\ (CuCl)} \underset{\text{XL}}{CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCOOCH_3}$$

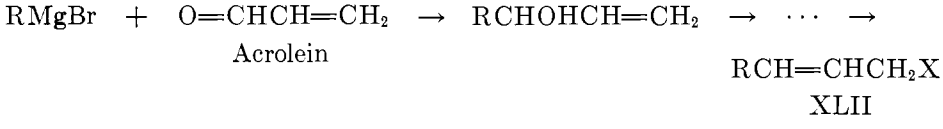
2-Hepten-4,6-diyne

Methyl 8-decen-2,4,6-triynoate

Allyl bromide couples readily with Grignard reagents to give terminally unsaturated chains. Peroxidic addition of hydrogen bromide affords a terminal bromide suitable for further reaction (*cf.* 286). The tetrahydropyranyl derivative of 3-bromo-1-propanol has been combined with the monosodium derivative of diacetylene to form XLI, which offered possibilities for reaction at either end

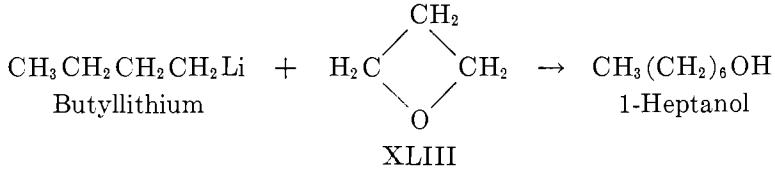


of the molecule (159). Acrolein reacts with Grignard derivatives to give alkylvinylcarbinols, which can be transformed by a 1,3-shift to a primary allyl derivative (XLII). Finally, 1-heptanol is formed from the interaction of butyllithium and trimethylene oxide (XLIII), but the low yield is discouraging (250).



Acrolein

XLII



Butyllithium

XLIII

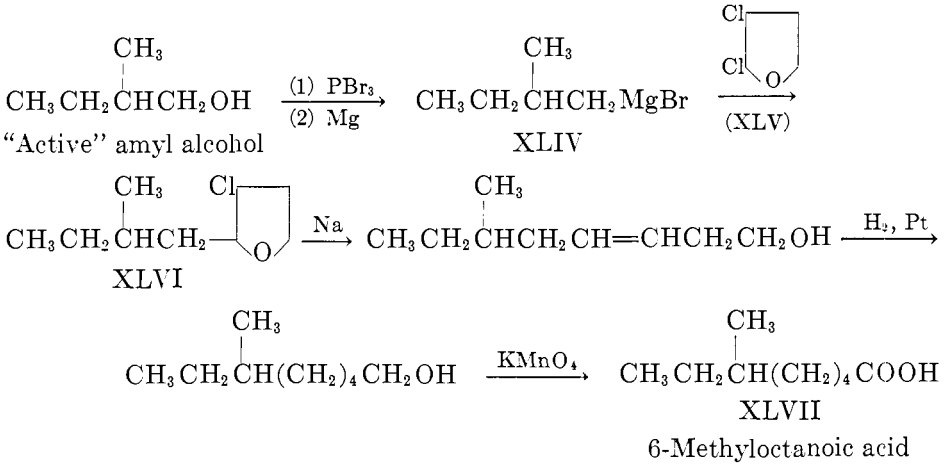
Trimethylene oxide

1-Heptanol

E. EXTENSION OF THE CHAIN BY FOUR CARBON ATOMS

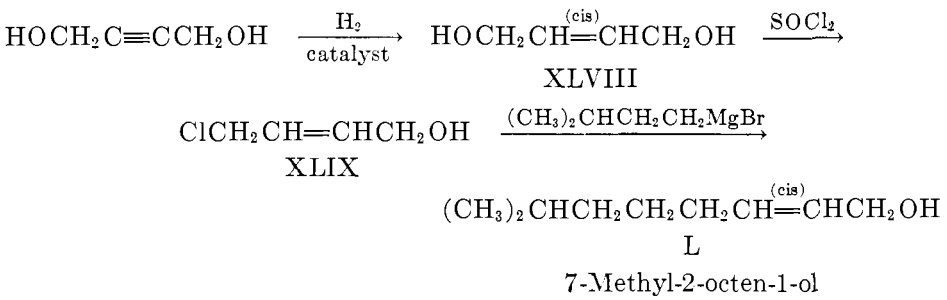
The chlorination of tetrahydrofuran as well as the addition of chlorine to 2,3-dihydrofuran (108) gives 2,3-dichlorotetrahydrofuran (XLV), which may be regarded as a cyclic analog of the α-halo ethers used in the Boord–Swallen synthesis of olefins (*cf.* 260). When this cyclic compound is used in the Boord–

Swallen synthesis, the olefinic product contains a new chain of four carbon atoms terminating in a useful hydroxyl function (*cf.* 108, 110). The accompanying formulations show how this scheme was applied to the synthesis of dextrorotatory 6-methyloctanoic acid (XLVII), one of the hydrolysis products from the antibiotic polymyxins. Grignard reagent XLIV, derived from fusel oil "active" amyl



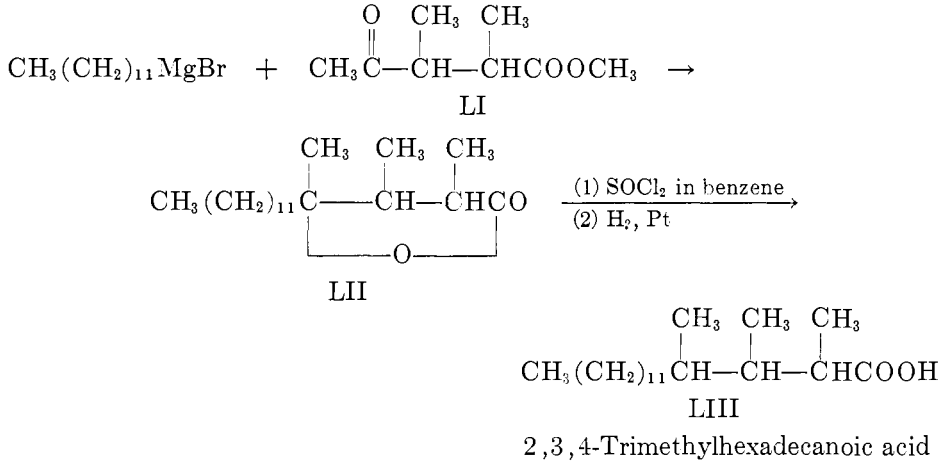
alcohol, was coupled with 2,3-dichlorotetrahydrofuran (XLV) to give (52 per cent) a mixture of cis and trans coupling products (XLVI). Powdered sodium converted XLVI to a mixture of *cis*- and *trans*-6-methyl-3-octen-1-ols, which was first hydrogenated to 6-methyl-1-octanol and then oxidized (acid permanganate) to optically active 6-methyloctanoic acid (XLVII) (111). Although *trans*-2-alkyl-3-chlorotetrahydrofuran, e.g., XLVI, gives rise mainly to the trans olefin, the cis form gives rise to comparable amounts of the cis and trans olefins (108, 110). Accordingly, a mixture of olefins is formed. Saturation of the double bond, as in the example shown, or conversion of the double bond to a triple bond by bromination followed by dehydrobromination (101) will lead to homogeneous material.

Reaction of an excess of a Grignard reagent, e.g., isopentylmagnesium bromide, with *cis*-4-chloro-2-buten-1-ol (XLIX) adds four carbon atoms to the chain of the Grignard reagent and provides not only a reactive terminal allylic function but one entirely in the cis configuration, as in L (97). The chlorobutenol was prepared by the half-hydrogenation of 2-butyne-1,4-diol, and treatment of the

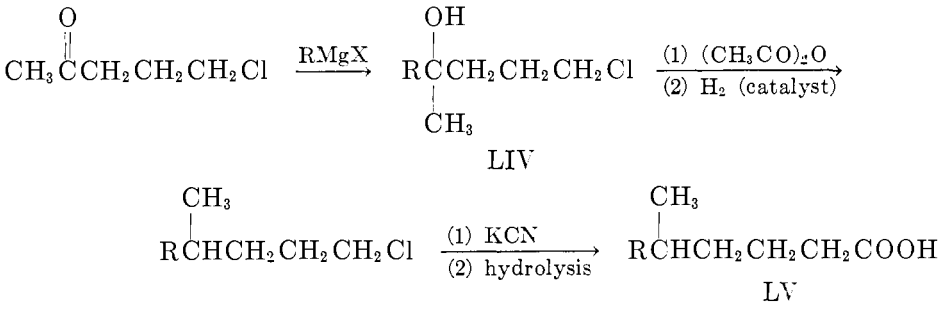


cis-diol XLVIII under controlled conditions with thionyl chloride. A reagent related to 4-chloro-2-buten-1-ol (XLIX) is the tetrahydropyranyl derivative of 4-bromo-2-butyn-1-ol (129).

Another method lengthens the chain by four carbon atoms by combining a Grignard reagent with levulinic ester or a derivative. For example, dodecylmagnesium bromide with 2,3-dimethyllevulinic ester (LI) gave the γ-lactone LII. The γ-oxygen was removed by treatment first with thionyl chloride to form



an unsaturated intermediate and then with hydrogen over platinum to saturate the double bond and to furnish 2,3,4-trimethylhexadecanoic acid (LIII) (72). When levulinic ester itself is one of the reactants, the final product is a 4-methylalkanoic acid (72, 199). Also useful is 5-chloro-2-pentanone, which with a Grignard reagent gives a tertiary alcohol (LIV). Dehydration with acetic anhydride

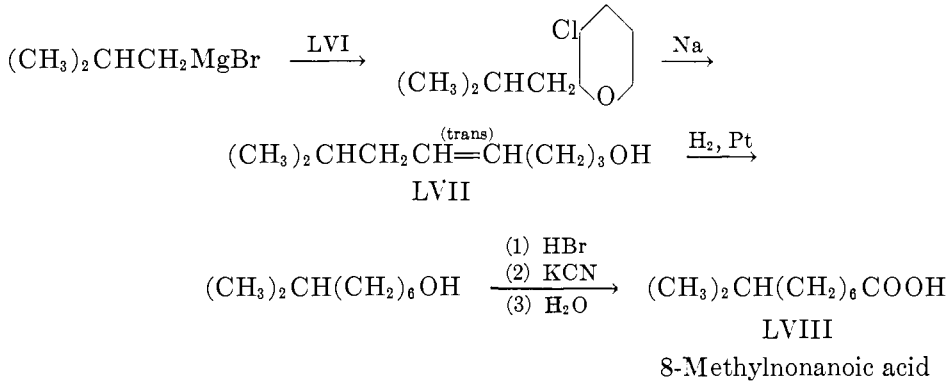


and catalytic hydrogenation gives a long-chain alkyl chloride. Standard methods can convert the chlorides to a series of methyloctadecanoic acids (85). For example, when R = tridecyl, the nitrile synthesis led to 5-methylstearic acid (LV: R = tridecyl).

The addition of ethoxyvinylacetylene to aldehydes to lengthen the chain by four carbon atoms is shown in Section II,B

F. EXTENSION OF THE CHAIN BY FIVE AND SIX CARBON ATOMS

Just as 2,3-dichlorotetrahydrofuran (XLV) in the Boord–Swallen synthesis extends the chain by four carbon atoms, so 2,3-dichlorotetrahydropyran (LVI) or the 2,3-dibromo compound extends the chain by five (*cf. inter alia* 55, 108, 110, 111). The process was applied in the synthesis of 8-methylnonanoic acid (LVIII) (163), as follows: Coupling of isobutylmagnesium bromide with 2,3-dichlorotetrahydropyran gave a mixture of *cis*- and *trans*-3-chloro-2-isobutyl-

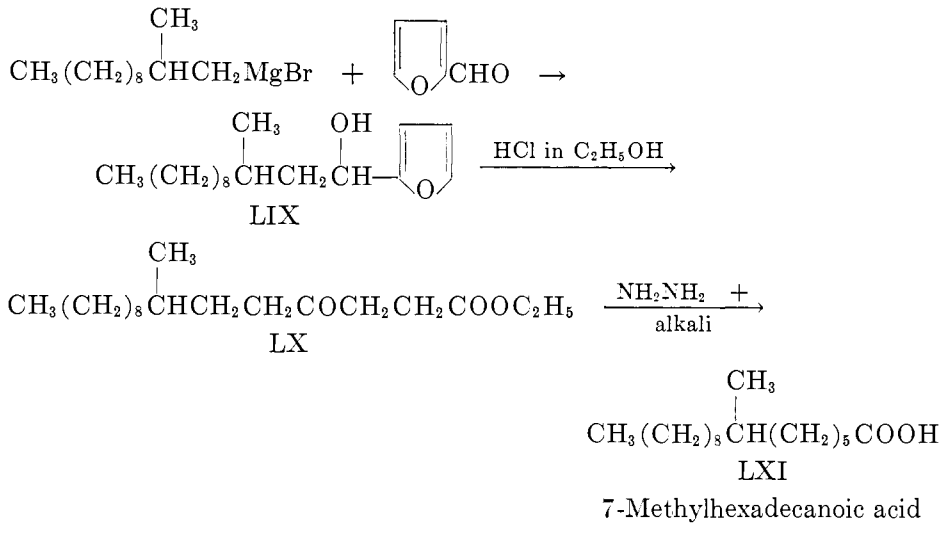


tetrahydropyrans. Sodium powder converted the mixture to a *single* product, *trans*-7-methyl-4-octen-1-ol (LVII), which on hydrogenation and attachment of carboxylic acid in a standard nitrile synthesis gave the desired product (LVIII). If the ethylenic bond is retained so as to give unsaturated final products, the method constitutes a stereospecific mode of introducing the trans double bond (*cf.* 100, 101, 107). Two successive applications of the process, as in the conversion of butyl bromide to *trans*-4,*trans*-9-tetradecadien-1-ol (overall yield 12 per cent), adds ten carbon atoms to the chain (108).

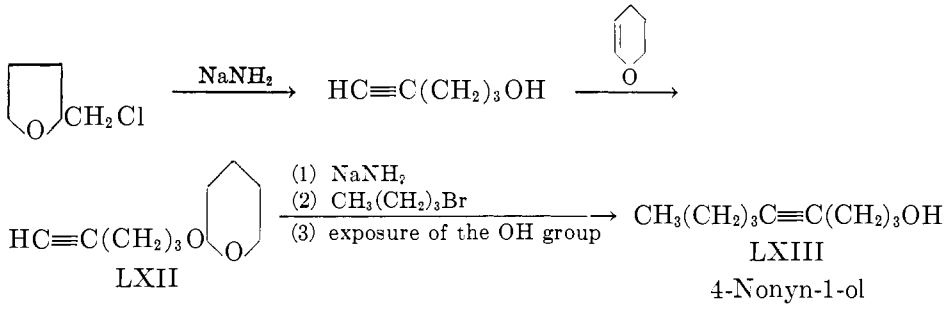
Condensation of an aldehyde with 3-methylglutaconic ester lengthens the aldehyde chain by attaching an unsaturated five-carbon unit bearing carboxyl groups as well as a side-chain methyl group (88, 89, 242; also *cf.* Section III,G).

A standard process by which a furfuryl alcohol in contact with mineral acid produces a γ-substituted levulinic acid has been largely neglected in the synthesis of long-chain acids. One application is in the elaboration of 2-methylundecyl bromide to 7-methylhexadecanoic acid (LXI) (290). In this synthesis 2-methylundecylmagnesium bromide with furfural gave furfuryl alcohol (LIX). The substituted levulinic ester LX was produced in 70 per cent yield when the furfuryl alcohol was treated with ethanolic hydrochloric acid. Wolff–Kishner reduction (281) completed the synthesis and gave 7-methylhexadecanoic acid (LXI).

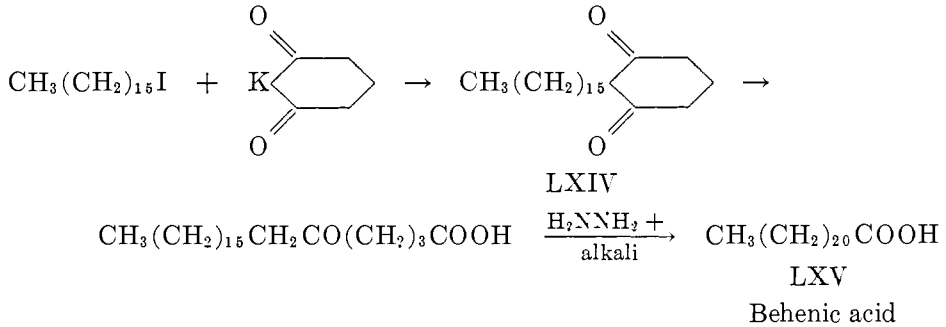
With 4-pentyn-1-ol readily available from tetrahydrofurfuryl chloride and sodium amide, another way to extend the chain by five carbon atoms presents itself (98, 178). After protecting the hydroxyl group of the 4-pentyn-1-ol with tetrahydropyranyl, the resulting monosubstituted acetylene (LXII) is alkylated in the usual manner. With butyl bromide, for example, the product after re-



moving the blocking group is 4-nonyn-1-ol (LXIII). Analogous chain extension has been realized with other hydroxyalkylacetylenes (98, 104).



A series of reactions described by Stetter and his coworkers (272) extends the chain by six carbon atoms. For example, behenic acid (LXV) was prepared in this way by alkylating potassium 1,3-cyclohexadione with hexadecyl iodide, cleaving the resulting monoalkylated diketone (LXIV) with alkali to give 5-oxo-

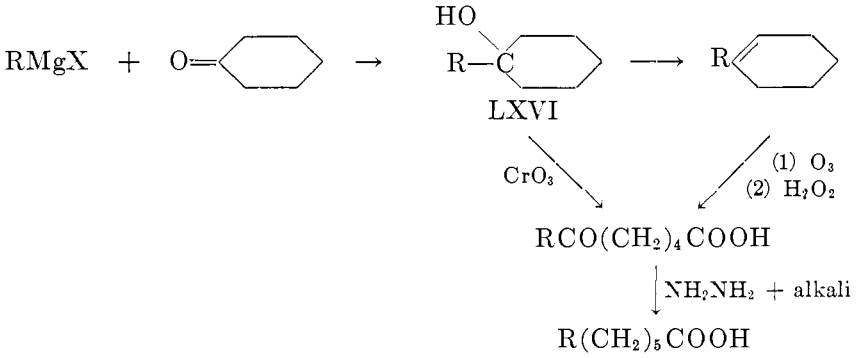


behenic acid, and removing the ketonic oxygen with hydrazine and alkali. The alkylation step is not too satisfactory, inasmuch as considerable *O*-alkylation occurs.

Stetter and his associates have described many variations of this method (for Paper XII see reference 273), which, however, have been applied not so much to the synthesis of monocarboxylic acids as to that of polycarboxylic acids.

G. OXIDATION OF 1-ALKYL-1-CYCLOALKENES

Alkylmagnesium halides add to cyclic ketones to form 1-alkyl-1-hydroxycycloalkanes (e.g., LXVI). Such compounds are oxidized either directly with chromic oxide in acetic acid (127) or, after dehydration to the alkylcycloalkene,



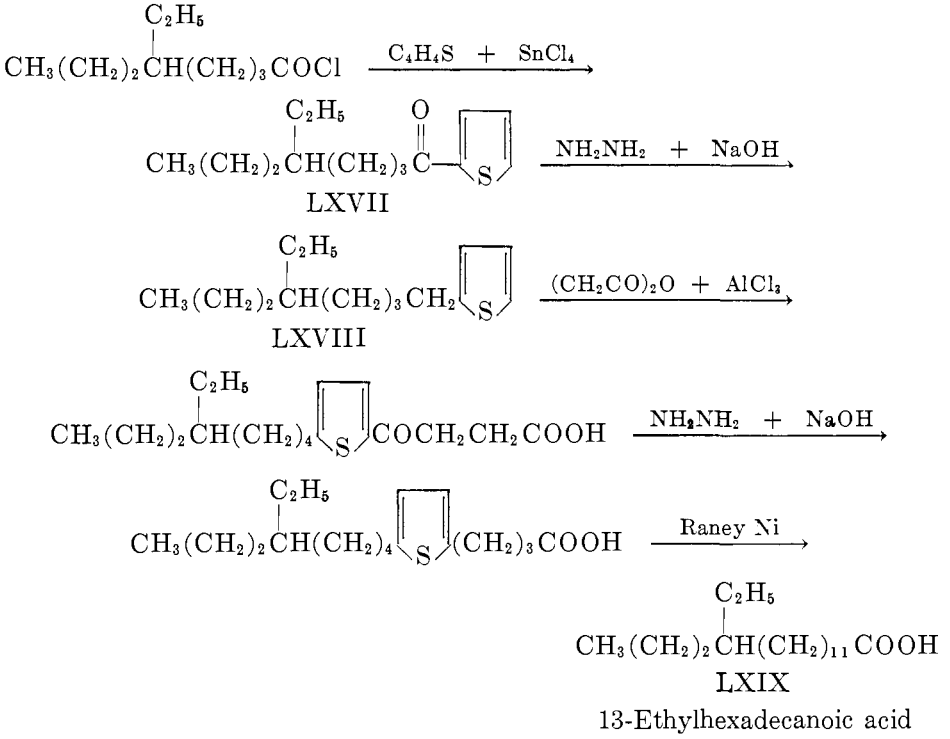
with ozone and peroxide or with chromium oxide (248) to form acyclic keto acids. Wolff–Kishner reduction completes the preparation of the long-chain acid. Application of the alcohol oxidation technique has permitted conversion of octadecyl bromide to 5-oxotetracosanoic acid and thence to tetracosanoic acid (lignoceric acid) (127), and of decyl bromide to hexadecanoic acid (185). Conversion of the tertiary alcohol from octadecylmagnesium bromide and 3,5-dimethylcyclohexanone to the acyclic keto acid failed (27). A series of "anteiso" keto acids and the corresponding "anteiso" acids were obtained by starting with 3-methylpentylmagnesium bromide and such ketones as cyclopentanone, cyclohexanone, cycloheptanone, and cyclopentadecanone (221).

In a study of the dehydration–ozonolysis method yields of cycloalkene ranged from 25 to 56 per cent, and yields of keto acid from 43 to 76 per cent (119). Examples of the dehydration–ozonolysis method would include the conversion of 3,7-dimethyloctyl bromide (tetrahydrogeranyl bromide) by reaction with cyclopentanone to 9,13-dimethyltetradecanoic acid (279), as well as the conversion of butyl bromide by reaction with cycloheptanone to undecanoic acid (119).

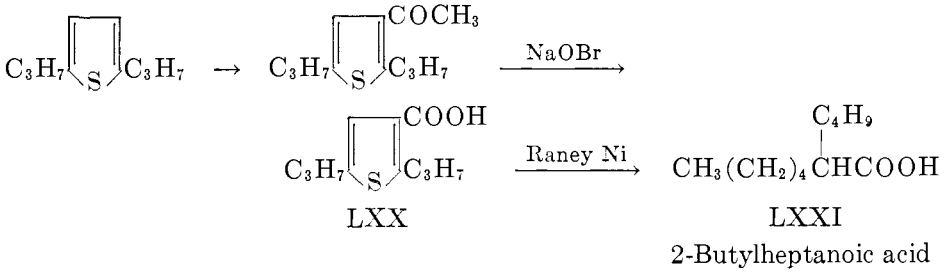
H. DESULFURIZATION OF ACID DERIVATIVES OF THIOPHENE

Raney nickel not only desulfurizes thiophenes but also reduces the ring unsaturation. If the carboxylic acid function is present either on the thiophene nucleus or on a substituent group, the desulfurization product is a fatty acid. Since alkyl groups, with or without a carboxylic acid group, can be easily attached to the thiophene nucleus, this process offers the possibility of preparing

both normal and branched-chain acids. The overall yield is reasonable, and in only two cases was resistance noted to the desulfurization step (278). Two examples from the many reported (40, 65, 131, 168, 256, 276, 278, 299) are formulated below. The synthesis of 13-ethylhexadecanoic acid started with the acylation of thiophene with 5-ethyloctanoyl chloride in the presence of stannic chloride. Reduction of the resulting ketone (LXVII) by the Wolff–Kishner procedure gave the 2-alkylthiophene (LXVIII) in an uncomplicated manner. Acylation with succinic anhydride placed the succinyl group as expected in the 5-position, and finally Wolff–Kishner reduction and desulfurization completed the synthesis of 13-ethylhexadecanoic acid (LXIX) (26).



Another synthesis started with 2,5-dipropylthiophene, which by acetylation followed by haloform oxidation furnished 2,5-dipropylthiophene-3-carboxylic acid (LXX). Raney nickel converted this acid to 2-butylheptanoic acid (LXXI) (277).



I. COUPLING OF AN ACID CHLORIDE WITH DIALKYLCADMIUM (255)

Grignard reagents react with cadmium chloride to form dialkylcadmium compounds, which combine readily and reliably with carbethoxy-substituted acyl chlorides to give keto esters. The keto esters are easily converted to the ketone-free acid, generally with hydrazine and alkali, but sometimes also with amalgamated zinc and hydrochloric acid. The process has found much application in the synthesis of acids (*cf.* 36, 71, 116, 121), especially branched-chain acids. For example, 3-methyl-5-oxopentadecanoic methyl ester (LXXIII) could be ob-

$$[CH_3(CH_2)_9]_2Cd + ClCOCH_2\underset{\text{LXXII}}{\overset{CH_3}{\overset{|}{C}}}HCH_2COOCH_3 \rightarrow$$

$$CH_3(CH_2)_9\overset{O}{\overset{\|}{C}}CH_2\overset{CH_3}{\overset{|}{C}}HCH_2COOCH_3$$
LXXIII

tained (82 per cent yield) from didecylcadmium and acid chloride LXXII (73). The branching can be in the dibasic acid moiety as in LXXII (*cf.* 71, 76, 77) or, as is more often the case, in the organocadmium moiety (74, 78, 79, 126, 229, 279). Unsaturation poses no problem; for example, undecenylcadmium reacts smoothly with the acid chloride from ethyl hydrogen heptanedioate to give 7-oxo-17-octadecenoic ester and, after reduction, 17-octadecenoic acid (167).

Coupling of acid chlorides with organozinc compounds to give ketones is possible (203, 209, 225, 226) but in recent years has been largely supplanted by the organocadmium method. The organozinc reaction, however, should be kept in mind as a practical alternative to the organocadmium method; in at least one case coupling with the zinc derivative was successful, while coupling with the cadmium derivative failed (247).

J. EXTENSION OF THE CHAIN BY THE ATTACHMENT OF GROUPS TO AN ACTIVE METHYLENE POSITION

1. Methods utilizing acetoacetic ester

Two methods of some flexibility incorporate the methylene group of malonic ester or of acetoacetic ester in the middle of a carbon chain by making the methylene group serve as the point of attachment of two larger groups. Both methods lead to intermediate keto acids, which can be reduced by standard processes to long-chain fatty acids. The first stages of the acetoacetic ester process produce long-chain β-keto esters which are themselves of some interest. The acetoacetic process is described here in terms of a specific example: namely, the conversion of undecylenic acid to 22-tricosenoic acid (271). The β-keto ester (LXXV) was prepared by acylating sodioacetoacetic ester in benzene with the acid chloride (LXXIV) of undecylenic acid, and then deacetylating by methanolysis. The β-keto ester (LXXV) was then alkylated with an ω-iodo ester, in this case 11-iodoundecanoic ester, in the presence of potassium carbonate in

boiling 2-pentanone. Saponification and decarboxylation of the alkylation product (LXXVI) gave the keto acid LXXVII, which was reduced by heating with potassium hydroxide and hydrazine in triethylene glycol to 22-tricosenoic acid

$$CH_2{=}CH(CH_2)_8COCl \xrightarrow[\text{in benzene}]{NaCH(COCH_3)COOC_2H_5}$$

LXXIV

$$CH_2{=}CH(CH_2)_8CO\underset{\displaystyle COCH_3}{\underset{|}{C}}HCOOC_2H_5 \xrightarrow{CH_3OH,\ CH_3ONa}$$

$$CH_2{=}CH(CH_2)_8COCH_2COOCH_3 \xrightarrow[+\ K_2CO_3]{I(CH_2)_{10}COOC_2H_5}$$

LXXV

$$CH_2{=}CH(CH_2)_8CO\underset{\displaystyle COOCH_3}{\underset{|}{C}}H(CH_2)_{10}COOC_2H_5 \xrightarrow[(2)\ \text{decarboxylation}]{(1)\ \text{saponification}}$$

LXXVI

$$CH_2{=}CH(CH_2)_8COCH_2(CH_2)_{10}COOH \xrightarrow{NH_2NH_2\ +\ KOH}$$

LXXVII

$$CH_2{=}CH(CH_2)_{20}COOH$$

LXXVIII

22-Tricosenoic acid

(LXXVIII). The order of constructing the chain may be reversed; that is, the acid chloride of a half-ester can be joined to acetoacetic ester to form a β-keto α,ω-dicarboxylic ester, which is then alkylated with a simple alkyl iodide. This variation was applied to the synthesis of 3-methyldocosanoic acid (LXXXI)

$$ClCOCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOCH_3 \xrightarrow[(2)\ CH_3ONa\ \text{in}\ CH_3OH]{(1)\ NaCH(COCH_3)COOC_2H_5}$$

LXXIX

$$CH_3OOCCH_2COCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOCH_3 \xrightarrow[(2)\ KOH\ \text{in}\ CH_3OH\ +\ H_2O]{(1)\ CH_3(CH_2)_{15}I\ +\ K_2CO_3}$$

LXXX

$$CH_3(CH_2)_{15}CH_2COCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH \xrightarrow{Zn(Hg)\ +\ HCl}$$

$$CH_3(CH_2)_{18}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2COOH$$

LXXXI

3-Methyldocosanoic acid

(268). The acid chloride of methyl hydrogen 3-methylglutarate (LXXIX) was used in the acylation of sodioacetoacetic ester. Deacetylation of the product gave the β-keto diester LXXX. Alkylation with hexadecyl iodide, saponification, decarboxylation, and Clemmensen reduction completed the synthesis.

The use of optically active methyl hydrogen 3-methylglutarate in the example just described furnished optically active products. One or the other of these procedures has been used effectively in the synthesis of a variety of fatty acids (*cf.* 14, 15, 36, 86, 130, 161, 203, 258, 269). Further examples will be found in Sections III,F and III,G.

2. Methods utilizing malonic ester

In the malonic ester method pictured below the methylene group of malonic ester takes over the function of the methylene group of acetoacetic ester. While in the acetoacetic ester method the characteristic and distinctive feature is clean-cut acylation and deacetylation of the ester, the essential feature in the malonic ester method is decarboxylation of the intermediate acylmalonic ester (LXXXII) without loss of the acyl group. The main difficulty lies in the fact that any at-

$$RX + \begin{matrix} COOR' \\ | \\ CH_2 \\ | \\ COOR' \end{matrix} + ClCO(CH_2)_nCOOR'' \rightarrow$$

$$\begin{matrix} COOR' \\ | \\ RCCO(CH_2)_nCOOR'' \\ | \\ COOR' \end{matrix} \rightarrow RCH_2CO(CH_2)_nCOOH$$

LXXXII

tempt at ester *hydrolysis* in LXXXII preliminary to decarboxylation results in preferential hydrolytic cleavage at the acyl-to-malonate bond. The problem was solved by several devices permitting removal of the ester alkyl groups by reactions other than hydrolysis.

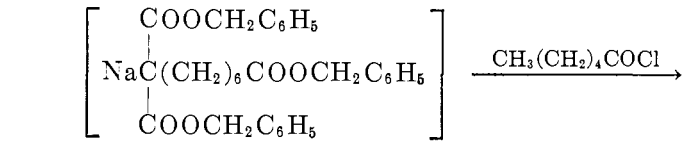
One way to expose the acid groups in LXXXII for decarboxylation would be to have R′ = benzyl and to break the benzyl-to-oxygen bond by hydrogenolysis. Formulations LXXXIII to LXXXVII for the synthesis of tetradecanoic acid illustrate how this possibility was realized (11). Alkylation of malonic ester with 7-bromoheptanoic ester (LXXXIII) gave the expected monosubstituted malonic ester (LXXXIV). The benzyl groups were introduced by ester interchange.

$$Br(CH_2)_6COOC_2H_5 \xrightarrow{NaCH(COOC_2H_5)_2}$$

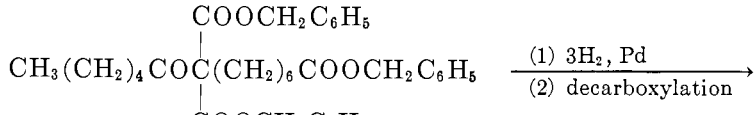
LXXXIII

$$(C_2H_5OOC)_2CH(CH_2)_6COOC_2H_5 \xrightarrow{C_6H_5CH_2ONa + C_6H_5CH_2OH}$$

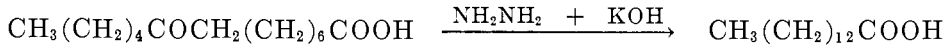
LXXXIV



LXXXV



LXXXVI

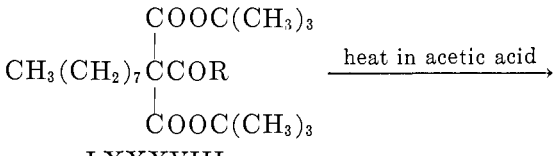


LXXXVII

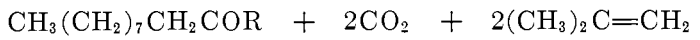
Tetradecanoic acid

Treatment of LXXXIV with one mole of sodium benzyloxide and two moles of benzyl alcohol gave the sodium derivative of the tribenzyl ester (LXXXV), which was directly acylated with hexanoyl chloride. Hydrogenolysis of acylmalonic ester LXXXVI exposed the carboxyl groups, two of which were lost readily by warming in alcohol. 9-Oxotetradecanoic acid obtained in this way in 70 per cent yield from triester LXXXIV was converted by Wolff–Kishner reduction to the final product (LXXXVII). Several other fatty acids have been prepared by the debenzylation procedure (8, 9, 11, 52, 221; also *cf.* Section III,H,4).

Two alternate procedures expose the carboxyl groups without hydrolysis *and* without hydrogenolysis. The procedures accordingly are applicable to molecules containing easily hydrogenated groups. Fonken and Johnson (128) utilized di-*tert*-butyl malonate in place of diethyl malonate in standard steps leading to acylmalonate LXXXVIII. Since the *tert*-butyl ester grouping decomposes to



LXXXVIII

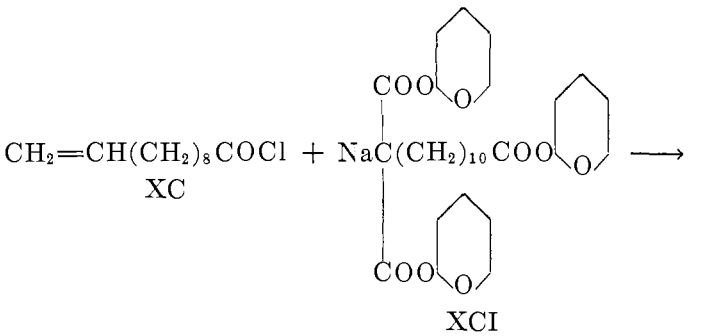


LXXXIX

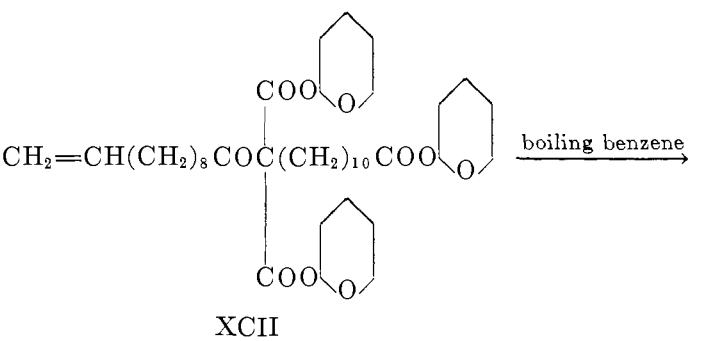
acid and isobutylene on warming in acetic acid containing some *p*-toluenesulfonic acid, such treatment of LXXXVIII, by exposing labile carboxylic acid groups, permits decarboxylation to LXXXIX. Although Fonken and Johnson did not prepare acids, their method should be adaptable to this end.

Tetrahydropyranyl esters are formed by allowing carboxylic acids to react with dihydropyran in the presence of a trace of sulfuric acid. Since heating reverses the process, the ditetrahydropyranyl malonate grouping should be deës-

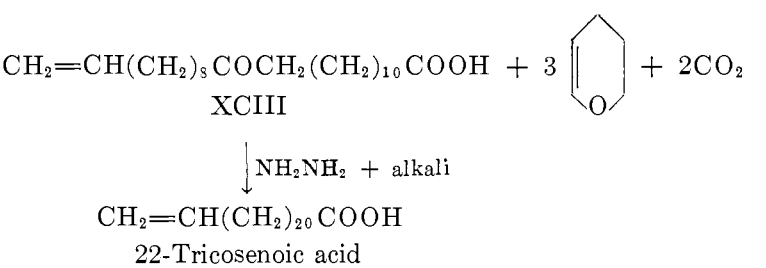
terified and then decarboxylated by heating. The use of this behavior in fatty acid work is illustrated in the following synthesis of 22-tricosenoic acid (53). Acylation of substituted malonic tetrahydropyranyl ester XCI (formed from the corresponding acid and dihydropyran) with acid chloride XC occurred normally to give acylmalonate XCII. Exposure of XCII to boiling benzene released dihydropyran and carbon dioxide to give a 75 per cent yield of the keto acid XCIII. Wolff–Kishner reduction afforded 22-tricosenoic acid. A variation makes



XC XCI



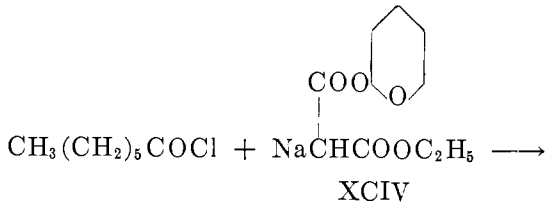
XCII



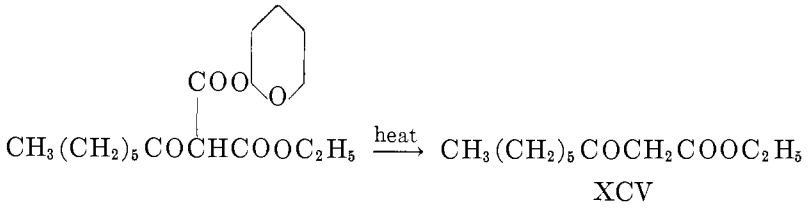
XCIII

22-Tricosenoic acid

use of ethyl tetrahydropyranyl malonate (XCIV), which when acylated—for example, with heptanoyl chloride—and then heated, loses only *one* carboxyl group. The product XCV accordingly is a β-keto ester. This variation, therefore, is an alternative to the acetoacetic ester acylation-deacetylation method for preparing β-keto esters (Section II,J,1). Other applications have been reported (53, 123, 230; also *cf.* Section III,H,3).



XCIV



XCV

K. SYNTHESIS ACCORDING TO AHMAD AND STRONG

Ahmad and Strong have described a sequence of reactions that has proved to be of considerable flexibility and general importance (6). A sodium acetylide is coupled with an α,ω-iodochloroalkane to give alkynyl chloride XCVI. This, in the nitrile synthesis, is converted to acetylenic acid XCVII. Half-hydrogenation gives the corresponding cis olefinic acid, which on isomerization over selenium

$$RC{\equiv}CH \xrightarrow[(2)\ I(CH_2)_nCl]{(1)\ NaNH_2\ in\ NH_3} RC{\equiv}C(CH_2)_nCl \xrightarrow[(2)\ hydrolysis]{(1)\ KCN}$$

XCVI

$$RC{\equiv}C(CH_2)_nCOOH \xrightarrow[Raney\ Ni]{H_2} RCH\overset{(cis)}{=}CH(CH_2)_nCOOH \xrightarrow{Se}$$

XCVII

$$RCH\overset{(trans)}{=}CH(CH_2)_nCOOH$$

gives the trans acid. Variations are possible. For example, R in the above formulas can be H, so that the alkynyl chloride XCVI would be a monosubstituted acetylene. Alkylation at the acetylenic hydrogen via the sodium derivative (or via the Grignard derivative with relatively active alkylating agents (280)) gives the disubstituted acetylene XCVI, in which R is alkyl (*cf.* 31, 140, 142, 280). Application of the malonic ester synthesis to XCVI extends the chain by two carbon atoms instead of one (*cf.* 113, 142, 201, 235). Sodium acetylide with alkynyl chloride XCVI gives a diyne which can be transformed further (233). The α,ω-iodochloroalkane precursor to XCVI can be replaced with the corresponding α,ω-bromochloroalkane (*cf.* 31, 233). Also, alkylation of the acetylenic lithium derivative in dioxane instead of the sodium derivative in liquid ammonia may offer advantages (201). In at least one case, the final trans acid product was obtained directly from the acetylenic acid by reduction with sodium and liquid ammonia (164).

The Ahmad and Strong method has been used for the preparation of octadecenoic acids (5, 132, 167) and other unsaturated linear fatty acids (164, 252, 280, 298), including palmitoleic acid (252), gadoleic acid (*cis*-9-eicosenoic acid) (252), petroselenic acid (*cis*-6-octadecenoic acid) (201), linoleic acid (142, 235), and linolenic acid (112; *cf.* Section III,B). In all cases the corresponding acetylenic acids—for example, tariric acid (6-octadecynoic acid) (201)—are made available. Branched-chain fatty acids result from branched-chain starting materials, and saturated acids can be obtained by complete hydrogenation at the acetylenic acid stage or at some other stage (163, 192).

Ricinoleic acid has been synthesized by an adaptation of the Ahmad and Strong procedure (113; *cf.* Section III,H,1), as has eleostearic acid (Section III,I).

L. GLASER COUPLING OF ACETYLENES (51; ALSO 232, P. 127)

A reaction by which two molecules of monosubstituted acetylene are oxidatively combined to form a conjugated diyne, i.e., XCVIII to XCIX, is known as Glaser coupling (145). Such oxidative coupling of two *different* acetylenes

$$\underset{\text{XCVIII}}{2RC{\equiv}CH} \xrightarrow{[O]} \underset{\text{XCIX}}{RC{\equiv}CC{\equiv}CR}$$

gives three possible products. When one of the reactants is an ω-acetylenic ester (C) and the other is an alkylacetylene, one of the three products will be a diacetylenic monocarboxylic ester (CI). Since effective separation of the three

$$CH_3CH_2CH_2C{\equiv}CH + \underset{\text{C}}{HC{\equiv}CCH_2CH_2COOCH_3} \xrightarrow{[O]} \underset{\text{CI}}{CH_3CH_2CH_2C{\equiv}CC{\equiv}CCH_2CH_2COOCH_3}$$

products is possible, mixed Glaser coupling provides a general method for the synthesis of diacetylenic acids.

Glaser coupling can be performed in any one of several ways; all, however, call for mild reaction conditions. In most of the couplings described below the oxidizing agent is oxygen, and the medium is water or aqueous methanol containing cuprous chloride, excess ammonium chloride, and either ammonia or hydrochloric acid. The mild reaction conditions permit the formation of coupling products of considerable complexity and sensitivity.

Mixed Glaser coupling has been used in syntheses of polyacetylenic esters from *Compositae*, for example, tetrahydromatricaria ester (CI) (96; also *cf.* 7, 43, 60, 95, 261), as well as for the synthesis of other more or less highly unsaturated, naturally occurring fatty acids (*cf.* Sections III,D,3, 4, and 5).

Hydroxy as well as ketone groups can be present in Glaser reactants. Examples are available in the synthesis of oenantheton (CII) (46) and cicutol (CIII) (47). Oxidation of a primary hydroxyl group in the cross-coupled product to

$$CH_3CH_2CH_2COCH_2CH_2(CH{=}CH)_2C{\equiv}CH + HC{\equiv}CCH{=}CHCH_3 \xrightarrow{[O]} CH_3CH_2CH_2COCH_2CH_2(CH{=}CH)_2(C{\equiv}C)_2CH{=}CHCH_3$$

CII

Oenantheton

$$CH_3CH_2CH_2CH_2(CH{=}CH)_3C{\equiv}CH + HC{\equiv}C(CH_2)_3OH \xrightarrow{[O]} CH_3(CH_2)_3(CH{=}CH)_3(C{\equiv}C)_2(CH_2)_3OH$$

CIII

Cicutol

carboxyl without disruption of the molecule is possible (60, 61). For example, the trans,trans form of matricarionol (CIV), obtained by the Glaser coupling of pentenyne and hydroxypentenyne, can be converted to *trans,trans*-matricaria acid (CV).

$$CH_3CH{=}CHC{\equiv}CH + HC{\equiv}CCH{=}CHCH_2OH \rightarrow CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCH_2OH \xrightarrow{CrO_3} CH_3CH{=}CH(C{\equiv}C)_2CH{=}CHCOOH$$

CIV

CV

M. MIXED KOLBE ELECTROLYSIS

Anodic oxidation of a mixture of two acids, RCOOH and R′COOH, gives three products: RR, R′R′, and the cross product RR′. Where one of the two reactants is the half-ester (CVI) of a dibasic acid, the cross product (CVII) is an ester of

$$RCOOH + HOOC(CH_2)_nCOOCH_3 \xrightarrow{[O]} R(CH_2)_nCOOCH_3 + \cdots$$

CVI CVII

a monobasic fatty acid. Because separation of the cross product poses no insurmountable difficulty, and because the cross product in most cases can be obtained in acceptable yield, this kind of mixed Kolbe electrolysis has been found eminently suitable for the synthesis of many and diverse fatty acids. Because a 1952 review is available (288), only an abbreviated account of the method is presented below.

Most published directions call for glass vessels, platinum electrodes, and methanol containing enough sodium methoxide to neutralize a small portion of the total acids (48). Generally the methyl or ethyl half-ester is used, although some advantage has been found in the benzyl half-ester (200). A practical device for sparing the more valuable of the two reactants is to use a mixture containing three to four molar amounts of the less valuable acid for every mole of the more

valuable acid. Conversion of the less expendable acid to the cross product can be materially improved in this way.

Saturated straight-chain acids react without difficulty with half-esters of saturated dibasic acids (146). Reaction with malonic half-ester, although not extensively exploited, is tantamount to homologation, and as such is an alternate to such processes as the Arndt–Eistert reaction. Branching in either reactant at the α-position tends to lower the yield; consequently, not many examples of such combinations have been reported (18, 20). Substituents such as alkyl, hydroxyl, or ketone located farther from the interacting centers create no special problems. 10-Fluorodecanoic acid and methyl hydrogen sebacate give methyl 18-fluorostearate, although in low yield (222a). Unsaturation, either ethylenic or acetylenic, no closer than the β-position causes no difficulty. Since asymmetry at positions other than alpha as well as ethylenic geometry is preserved, the mixed Kolbe method is useful for stereospecific synthesis and for establishing relationship—both optical and geometrical—between high-molecular-weight products and low-molecular-weight starting materials. Optically active methyl hydrogen 3-methylglutarate has been especially useful in inserting *C*-methyl in a single optical configuration. Optically active methyl hydrogen 3-acetoxyglutarate and 3-acetoxy-3-carbethoxypropionic acid may prove of equal value in introducing optically active hydroxyl groups (see Section III,H,5).

Many branched-chain acids have been prepared by mixed Kolbe electrolysis. For example, in connection with work on the wool fat acids, 12-methyltridec-

$$(CH_3)_2CHCH_2CH_2COOH + HOOC(CH_2)_8COOC_2H_5 \rightarrow (CH_3)_2CHCH_2CH_2(CH_2)_8COOC_2H_5$$

CVIII

Ethyl 12-methyltridecanoate

anoic ester (CVIII) was obtained by the anodic coupling of 4-methylpentanoic acid and ethyl hydrogen sebacate (163). A series of optically active "anteiso" acids was built up from dextrorotatory 4-methylhexanoic acid (CIX) by using the cross product from one mixed Kolbe electrolysis as the monobasic reactant in a subsequent mixed electrolysis (205). One stage, the combination of 4-methyl-

$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2COOH + HOOC(CH_2)_8COOCH_3 \rightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2(CH_2)_8COOCH_3$$

CIX

CX

Methyl 12-methyltetradecanoate

hexanoic acid with methyl hydrogen sebacate to give methyl 12-methyltetradecanoate (CX), is formulated above. Further examples of the synthesis of

branched-chain and also cyclic acids by mixed Kolbe electrolysis will be found in Sections III,E, III,F, and III,G (also *cf.* 19, 87, 183, 196, 199, 207, 208, 210, 211, 212, 268, and 296).

Kolbe electrolysis of ethylenic or acetylenic acids occurs normally when the unsaturation is separated by at least two carbon atoms from the carboxyl group. Formation of 6-pentadecynoic acid (CXII) from valeric acid and acetylenic half-ester CXI (31), of behenolic acid (CXIII) from stearolic acid and methyl hydrogen adipate (31), and of nervonic acid (CXIV) from oleic acid and methyl hydrogen suberate (49) will illustrate the method (also *cf.* 29, 30, 48, 50). The last conversion clearly establishes cis geometry in nervonic acid.

$$CH_3(CH_2)_3COOH + HOOC(CH_2)_4C{\equiv}C(CH_2)_4COOCH_3 \xrightarrow[(2)\ \text{saponification}]{(1)\ \text{electrolysis}} CH_3(CH_2)_7C{\equiv}C(CH_2)_4COOH$$

CXI — CXII — 6-Pentadecynoic acid

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_7COOH + HOOC(CH_2)_4COOCH_3 \xrightarrow[(2)\ \text{saponification}]{(1)\ \text{electrolysis}} CH_3(CH_2)_7C{\equiv}C(CH_2)_{11}COOH$$

Stearolic acid — CXIII — Behenolic acid

$$CH_3(CH_2)_7\overset{(cis)}{CH{=}CH}(CH_2)_7COOH + HOOC(CH_2)_6COOCH_3 \xrightarrow[(2)\ \text{saponification}]{(1)\ \text{electrolysis}} CH_3(CH_2)_7\overset{(cis)}{CH{=}CH}(CH_2)_{13}COOH$$

Oleic acid — CXIV — Nervonic acid

Further flexibility is attained by utilizing a vicinal dihydroxy acid as one of the acids undergoing electrolysis, and by converting the resulting dihydroxy product to an ethylenic acid by standard methods (Section II,O,5). *trans*-Vaccenic acid was obtained in this way from hydroxylated palmitoleic acid (i.e., *threo*-9,10-dihydroxypalmitic acid) and methyl hydrogen succinate (50; see Section III,A; also *cf.* 48, 200).

N. WITTIG–GEISSLER REACTION

Wittig and Geissler (292) observed that benzophenone with methyltriphenylphosphonium iodide (CXV) that had been allowed to react with phenyllithium

gave rise to 1,1-diphenylethylene (CXVII). The species CXVI reacting with the benzophenone may be described either as an alkylidene-triphenylphosphine

$$(C_6H_5)_3P \xrightarrow{CH_3I} \underset{\text{CXV}}{(C_6H_5)_3\overset{+}{P}CH_3\ \overset{-}{I}} \xrightarrow{C_6H_5Li}$$

$$\left[\begin{array}{c}(C_6H_5)_3P{=}CH_2 \\ \updownarrow \\ (C_6H_5)_3\overset{+}{P}{-}\overset{-}{C}H_2\end{array}\right]_{\text{CXVI}} \xrightarrow{(C_6H_5)_2CO} \underset{\text{CXVII}}{(C_6H_5)_2C{=}CH_2} + (C_6H_5)_3PO$$

or as an ylid. The process has been found to be general. The advantage in being able to convert the carbonyl double bond in a single mild step to an ethylenic

$$\underset{\text{CXVIII}}{RCHO} + (C_6H_5)_3P{=}CHR' \rightarrow \underset{\text{CXIX}}{RCH{=}CHR'}$$

double bond, i.e., CXVIII to CXIX, is great. A disadvantage is the appearance of the product XCIX in both cis and trans forms. Although the Wittig–Geissler reaction has been extensively exploited (*cf.* 42, 44, 46, 47, 170, 171, 282, 293, 294, 295), it has not been applied directly to the synthesis of fatty acids. Nevertheless, the potentialities of the reaction for such synthesis warrant its inclusion here.

O. ETHYLENIC UNSATURATION

1. Unsaturation (α,β- and other) by elimination of hydrogen bromide

Elimination of hydrogen bromide from an alkyl bromide grouping generates a double bond. Since α-bromo acids can be obtained by standard methods, the dehydrobromination is of special interest in connection with the preparation of α,β-unsaturated acids. The method has been carefully studied, especially in connection with the "phthioic" acids (Section III,F).

The Hell–Volhard–Zelinsky bromination of acids is still the favorite way of introducing bromine into the α-position. A catalytic amount of red phosphorus can be used; however, a larger amount—or, better, one mole of phosphorus tribromide—leads to the α-bromo acid bromide, which is conveniently and directly esterified with methanol. Thionyl chloride can be used in a separate reaction before bromination to convert the acid to the acid chloride, or both steps can be combined into one by performing the bromination in thionyl chloride as solvent (249). α-Methyl acids furnish 2-bromo-2-methyl acids without difficulty. *N*-Bromosuccinimide has been used for α-bromination but is not recommended for general application (*cf.* 73).

Dehydrobromination occurs with various basic reagents with, however, varying degrees of effectiveness. For example, in the dehydrobromination of methyl 2-bromododecanoate (CXX) (71) potassium hydroxide gives mainly 2-hydroxy-

dodecanoic acid. Potassium methoxide in methanol gives mainly the 2-methoxy ester, but potassium *tert*-butoxide in *tert*-butyl alcohol gives methyl 2-dodecenoate (CXXI) in good yield. However, the *tert*-butoxide presents complications, especially in the dehydrobromination of branched acids. Hot quinoline or pyridine is recommended as the reagent of choice for the elimination of hydrogen

$$CH_3(CH_2)_{10}COOH \xrightarrow[(2)\ \text{esterification}]{(1)\ Br_2} CH_3(CH_2)_9CHBrCOOCH_3 \longrightarrow$$

CXX

$$CH_3(CH_2)_8CH{=}CHCOOCH_3$$

CXXI

Methyl 2-dodecenoate

bromide, and many alkanoic acids have been converted to 2-alkenoic acids by this bromination-dehydrobromination method (*cf. inter alia* 27, 28, 69, 70, 73, 77, 177, 215).

In connection with this preparation of 2-alkenoic acids, the possibility of α,β–β,γ tautomerism has been reëxamined. The conclusions fall in line with those reached earlier by Linstead and coworkers (144). Thus, it is generally conceded that α,β-unsaturated *acids* are relatively resistant to equilibration with alkali, and that, in any case, the α,β-position is favored when there is no substituent close to the double bond or when there is an α-methyl substituent on the double bond. Supporting illustrations would include: the absence of isomerization in 2-octadecenoic acid on relatively short exposure to boiling 10 per cent alcoholic potassium hydroxide (215); the formation of no β,γ-isomer in the dehydrohalogenation of 2-iodoöctadecanoic acid by alcoholic potassium hydroxide (176, 215); the isolation of α,β-unsaturated acid in good yield (74 per cent) on treatment of 2-bromododecanoic acid with potassium *tert*-butoxide in *tert*-butyl alcohol (71); the insensitivity of 2,5,9-trimethyl-2-decenoic acid to alcoholic potassium hydroxide (177); the absence of change in optical rotation or in ultraviolet absorption after an alcoholic potassium hydroxide solution of optically active 2,4,8-trimethyl-2-nonenoic acid is boiled for 5 hr. (177; *cf.* 28); the similar absence of change in the optical rotation of optically active 2,4-dimethyl-2-dodecenoic acid in hot alcoholic alkali (69); and the uncomplicated isolation of α,β-unsaturated products upon the dehydrobromination of a number of long-chain branched acids by quinoline or pyridine (*cf.* 27, 28, 69, 77, 177).

Stronger alkali and longer exposure may result in isomerization (*cf.* 115, 215). The isolation of mixtures of α,β- and β,γ-unsaturated acids upon the saponification of either α,β- or β,γ-unsaturated *esters* has been attributed to isomerization *before* saponification (71, 83; also 80).

Where evidence is available it indicates that 2-alkenoic acids obtained on dehydrohalogenation have the double bond in the trans configuration (71, 215).

Halogen at positions other than alpha have been removed as hydrogen halide (83, 112, 113, 118, 126, 259). Generally, such halogen has been introduced by reaction of the corresponding alcohol with thionyl chloride, phosphorus oxychloride, phosphorus tribromide, etc. However, allylic bromination of the methyl esters of elaidic (204), oleic (204, 216), *cis*-6-octadecenoic (216), *cis*-13-docosenoic (216), 10-undecenoic (134), 12-tridecenoic (134), stearolic (216), and 13-docosynoic (216) acids with *N*-bromosuccinimide is also possible. Dehydrobromination of the bromination product from methyl elaidate with hot collidine gave a mixture from which *trans*-8,*trans*-10-octadecadienoic acid could be isolated (204). Thermal dehydrobromination gave conjugated dienes or ene-ynes (216).

2. α,β-Unsaturation by elimination of water

Dehydration of β-hydroxy esters (Section III,H,5), which are available as Reformatsky condensation products or as reduction products from β-keto esters, leads to α,β(and β,γ)-unsaturated esters. Some dehydration conditions could and probably do result in preliminary conversion of β-hydroxy to β-chloro, so that in point of fact the double bond is formed by dehydrochlorination. However, for convenience these processes will be treated here as dehydrations as long as the halogen compound is not actually isolated. Some examples are given below (also *cf.* 88, 208, 209, 242).

(*a*) $CH_3(CH_2)_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOC_2H_5 \xrightarrow[\text{in pyridine}]{SOCl_2}$

$$CH_3(CH_2)_5CH{=}CHCOOC_2H_5 \quad (83)$$

(*b*) $CH_3(CH_2)_4C{\equiv}C\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOC_2H_5 \xrightarrow[\text{hot pyridine}]{POCl_3 \text{ in}}$

$$CH_3(CH_2)_4C{\equiv}CCH{=}CHCOOC_2H_5 \quad (104)$$

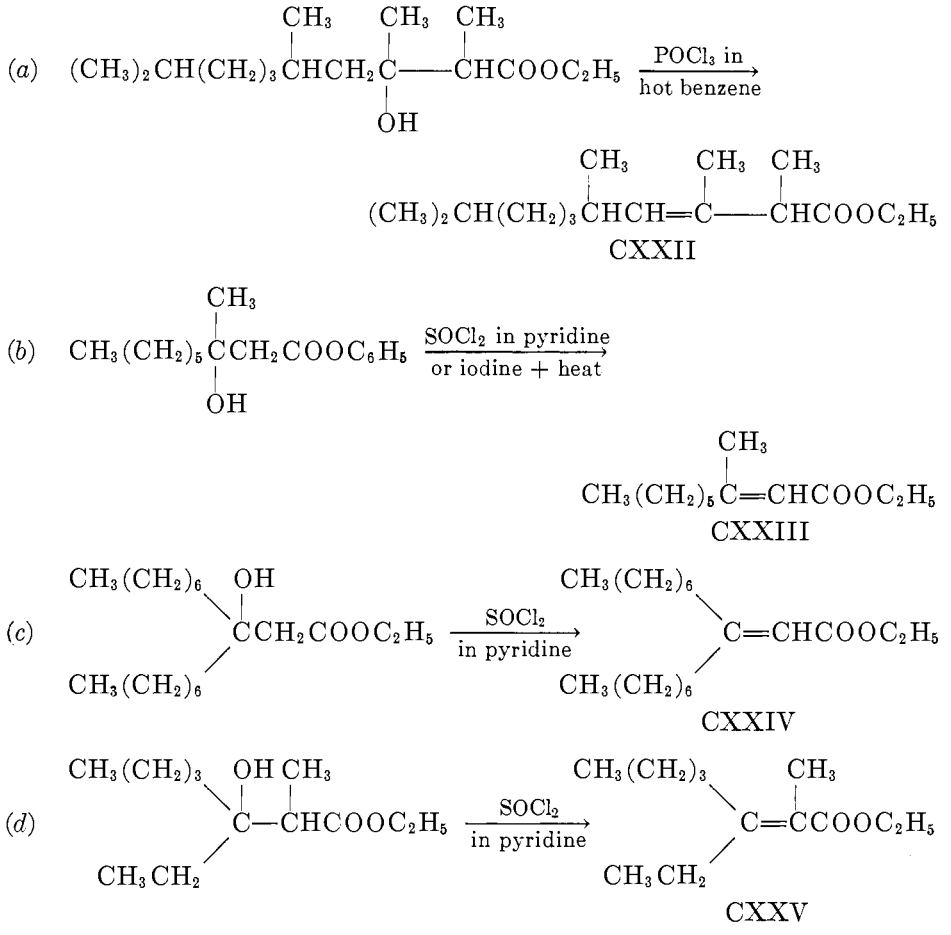
(*c*) $CH_3(CH_2)_6\underset{\displaystyle OH}{\underset{|}{C}}HCHCOOCH_3 \xrightarrow{KOH}$

$$\qquad\qquad\qquad\qquad\qquad\qquad\quad (CH_2)_5CH_3$$

$$CH_3(CH_2)_6\underset{\displaystyle OH}{\underset{|}{C}}HCHCOOH \xrightarrow[\text{some } KHSO_4]{(CH_3CO)_2O +} CH_3(CH_2)_6CH{=}\underset{\displaystyle (CH_2)_5CH_3}{\underset{|}{C}}COOH$$

(191; also *cf.* 227)

In some cases more or less β,γ-unsaturation is observed, as follows:



Only a small amount of the α,β-unsaturated isomer of CXXII was obtained (177). The α,β-unsaturated ester CXXIII was obtained mixed with two parts of the β,γ-unsaturated isomer (83). Esters CXXIV and CXXV were obtained as 58 per cent and 42 per cent mixtures with the respective β,γ-unsaturated esters (80).

β-Hydroxy esters are difficult to dehydrate with alkali. However, when the hydroxyl group is converted to ester, e.g., to acetate, benzoate, phosphate, methylsulfonate, etc., treatment with alkali does develop the α,β-unsaturation (197).

3. α,β-Unsaturated acids from aldehydes and ketones

Aldehydes dissolved in pyridine containing some piperidine are condensed smoothly with malonic acid to give α,β-unsaturated acids. For example, hexadecanal (CXXVI) in this (Doebner) process gives 2-octadecenoic acid (176).

The major disadvantage lies in the requirement of a long-chain aldehyde. The advantages include mild reaction conditions and stereospecific formation of trans α,β-unsaturation. The yields vary widely (*cf.* 71, 100, 101, 104, 114, 174, 175, 203a). Conversion of RCH_2COOH to RCH=CHCOOH is possible according to

$$\underset{\text{CXXVI}}{CH_3(CH_2)_{14}CHO} + CH_2(COOH)_2 \xrightarrow{\text{pyridine}} \underset{\text{2-Octadecenoic acid}}{CH_3(CH_2)_{14}CH{=}CHCOOH}$$

formulations CXXVII to CXXVIII (190). Here an even-numbered and hence readily available fatty acid such as palmitic acid is degraded by α-bromination

$$\underset{\text{CXXVII}}{CH_3(CH_2)_{13}CHBrCOOH} \xrightarrow{KOH} CH_3(CH_2)_{13}CHOHCOOH \xrightarrow{(CH_3COO)_4Pb}$$

$$CH_3(CH_2)_{13}CHO \xrightarrow{CH_2(COOH)_2} \underset{\text{2-Heptadecenoic acid}}{\underset{\text{CXXVIII}}{CH_3(CH_2)_{13}CH{=}CHCOOH}}$$

(CXXVII) and alkaline hydrolysis to the 2-hydroxy acid, which with lead tetraacetate gives the odd-numbered fatty aldehyde. Doebner condensation completes the process to furnish the odd-numbered α,β-unsaturated acid (CXXVIII).

Condensation of a carbonyl compound, e.g., 2-octanone, with cyanoacetic ester to give an α,β-unsaturated cyano ester, e.g., CXXIX, has not been utilized to any great extent in the synthesis of fatty acids (9, 118).

$$CH_3(CH_2)_5\overset{\displaystyle CH_3}{\overset{|}{C}}{=}O + \overset{\displaystyle CN}{\overset{|}{C}}H_2COOC_2H_5 \longrightarrow \underset{\text{CXXIX}}{CH_3(CH_2)_5\overset{\displaystyle CH_3}{\overset{|}{C}}{=}\overset{\displaystyle CN}{\overset{|}{C}}COOC_2H_5}$$

Reaction of the triphenylphosphine derivative CXXX with an aliphatic aldehyde, although not reported, should give an α,β-unsaturated ester (CXXXI) without difficulty (293; also *cf.* Section II,N).

$$RCHO + \underset{\text{CXXX}}{(C_6H_5)_3P{=}CHCOOC_2H_5} \longrightarrow \underset{\text{CXXXI}}{RCH{=}CHCOOC_2H_5}$$

Addition of ethoxyacetylene to ketones, followed by treatment with aqueous sulfuric acid, generates an α,β-unsaturated ester (232, p. 82; also *cf.* Section II,C).

4. α,β-Unsaturated acids from acetylenic or ethylenic compounds

Oxidation of an allyl alcohol or an α,β-unsaturated aldehyde leads to the corresponding α,β-unsaturated acid (Section II,A). Methods for preparing α,β-unsaturated aldehydes are, accordingly, pertinent (Section II,B). Carboxylation of metal acetylides followed by half-hydrogenation to an α,β-unsaturated acid is a standard process (Section II,A and II,O,6). Carbonation of vinyllithium or of vinyl Grignard reagents gives the α,β-unsaturated acid directly (Section II,A).

Acetylenes with nickel carbonyl give α,β-unsaturated acids (179, 237). The next three sections (O,5, O,6, and O,7) should be consulted for further information on the preparation of ethylenic acids from acetylenic or ethylenic compounds.

5. Stereospecific introduction and interconversions of ethylenic unsaturation (106)

Control of the cis and trans nature of ethylenic unsaturation is always desirable and sometimes indispensable for the synthesis of homogeneous unsaturated acids. Some aspects of pertinent stereospecific reactions are discussed below.

The conditions of many of the chain extensions and other reactions used in fatty acid synthesis often have little if any effect on the geometry of a remote double bond. Accordingly such methods, when appropriately applied, offer stereospecific pathways to unsaturated acids. As far as methods for the stereospecific generation of olefinic bonds are concerned, half-hydrogenation of a triple to a cis double bond has received by far the most extensive application (Section II,O,6). The degree of stereospecificity in reduction of the triple to the trans double bond by sodium in liquid ammonia is high, but the presence of the carboxyl group complicates the process (Section II,O,7). Reduction of γ-substituted propargyl alcohols to the trans allyl alcohol (232, p. 30) by lithium aluminum hydride should be kept in mind as potentially useful in the synthesis of fatty acids.

Trans α,β-ethylenic acids are formed efficiently and stereospecifically in the Doebner combination of aldehydes and malonic acid (Section II,O,3; also 100, 101, 104, 106, 109, 114). α,β-Unsaturated aldehydes in contact with 2 *N* sulfuric acid equilibrate so as to give almost entirely the trans form (*cf.* 100, 104, 114, 236, 263). Formulas CXXXII to CXXXIII show a useful sequence in which this process is used. Ethyl orthoformate with acetylenic Grignard reagent CXXXII gives the acetal, which on half-hydrogenation leads to the cis ethylenic acetal. Steam distillation from aqueous acid not only hydrolyzes the acetal func-

$$\underset{\text{CXXXII}}{RC{\equiv}CMgBr} \xrightarrow{HC(OC_2H_5)_3} RC{\equiv}CCH(OC_2H_5)_2 \xrightarrow[\text{catalyst}]{H_2}$$

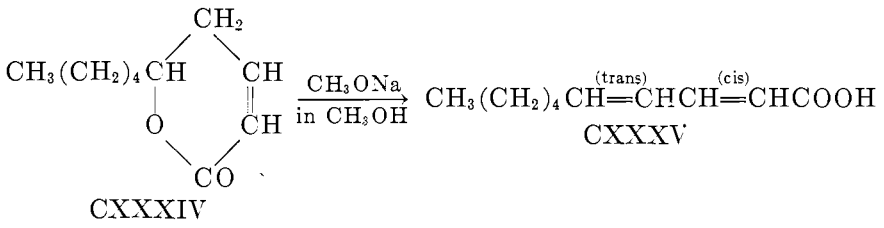
$$\overset{(cis)}{RCH{=}CHCH(OC_2H_5)_2} \xrightarrow{H_2O(H^+)} \underset{\text{CXXXIII}}{\overset{(trans)}{RCH{=}CHCHO}}$$

tion but also isomerizes the double bond to give trans aldehyde CXXXIII.

Powdered sodium acting on either *cis*- or *trans*-2-alkyl-3-chloro(or bromo)-tetrahydropyran gives a trans double-bonded product in a highly stereospecific manner (Section II,F; also *cf.* 55, 107, 108, 110, 111).

Methoxide ring openings of lactones such as CXXXIV give, in a stereospecific manner, a new trans bond, as in *cis*-2,*trans*-4-decadienoic acid (CXXXV) (104, 125).

A large body of information on stereospecific introduction, as well as interconversion, of ethylenic unsaturation is available in connection with work on the carotenoids and on vitamin A (*cf.* Section III,G). The processes developed



CXXXIV CXXXV

and used in this field are often of direct applicability to problems connected with fatty acids.

Geometrical equilibration of a double bond (with selenium, iodine, or other reagents) followed by isolation of one of the geometrical forms has been used in the synthesis of fatty acids. An alternate method of inverting the configuration of a double bond proceeds through three successive reactions of chlorination, monodehydrochlorination, and removal of the remaining chlorine by reduction with sodium and liquid ammonia (160). The process may be illustrated by the conversion of *cis*-3-hexene to *trans*-3-hexene. Chlorination of *cis*-3-hexene (CXXXVI) gave *threo*-3,4-dichlorohexane. Potassium hydroxide in propyl alcohol removed one mole of hydrogen chloride and gave vinyl chloride CXXXVII

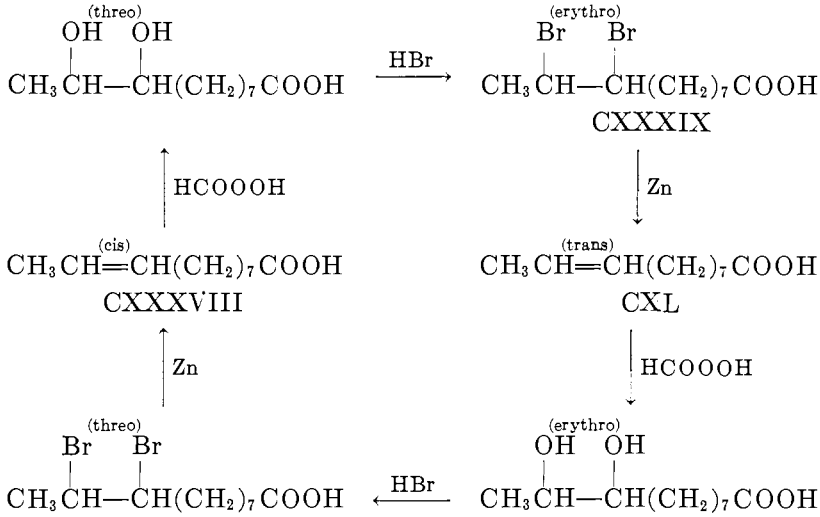
$$\underset{\text{CXXXVI}}{CH_3CH_2\overset{(cis)}{CH{=}CH}CH_2CH_3} \xrightarrow{Cl_2} CH_3CH_2\overset{(threo)}{CHCl{-}CH}ClCH_2CH_3 \xrightarrow[\text{propyl alcohol}]{\text{KOH in}}$$

$$\underset{\text{CXXXVII}}{CH_3CH_2\overset{(trans)}{CH{=}C}ClCH_2CH_3} \xrightarrow{\text{Na in } NH_3} CH_3CH_2\overset{(trans)}{CH{=}CH}CH_2CH_3$$

in the trans configuration. Reduction with sodium in liquid ammonia occurred with retention of configuration to give the desired trans olefin. An analogous sequence was used in changing trans olefins to cis olefins. The degree of stereospecificity in the addition of chlorine was estimated as better than 98 per cent; the degree of stereospecificity from the dichloro compound to the olefin was better than 95 per cent. The method has been applied to fatty acids, but as yet only in a preliminary fashion.

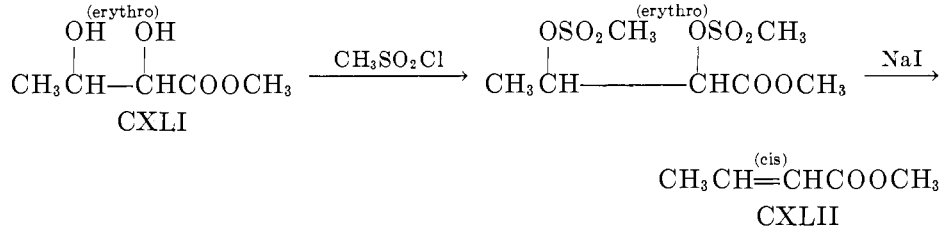
Another stereospecific interconversion of one geometric form to the other makes use of a different set of three reactions: viz., olefin hydroxylation, conversion to the dibromide, and regeneration of olefin by debromination with zinc. Under optimum conditions the stereospecificity is excellent; however, deviation from optimum conditions results in mixtures. A good example of the method may be found in the conversion of *cis*-9-undecenoic acid (CXXXVIII) to *trans*-9-undecenoic acid (CXL) and vice versa (10). Hydroxylation of *cis*-9-undecenoic acid (CXXXVIII) with per acids, e.g., performic acid, gave *threo*-9,10-dihydroxyundecanoic acid. Hydrogen bromide in glacial acetic acid containing some sulfuric acid converted the threo glycol to the erythro dibromide (CXXXIX), and zinc in ethanol converted the erythro dibromide to *trans*-9-undecenoic acid (CXL). The reverse process, that is, hydroxylation of the trans acid to the erythro glycol, bromination to the threo dibromide, and debromination with zinc to

cis-9-undecenoic acid (CXXXVIII) was also possible. The hydroxylation with per acid is completely stereospecific. The hydrobromination and debromination products are obtained homogeneous when proper reaction conditions are used.



Reports of several other conversions making use of these three steps have appeared (*cf.* 29, 215; also see Sections II,M, III,A, and III,H,4).

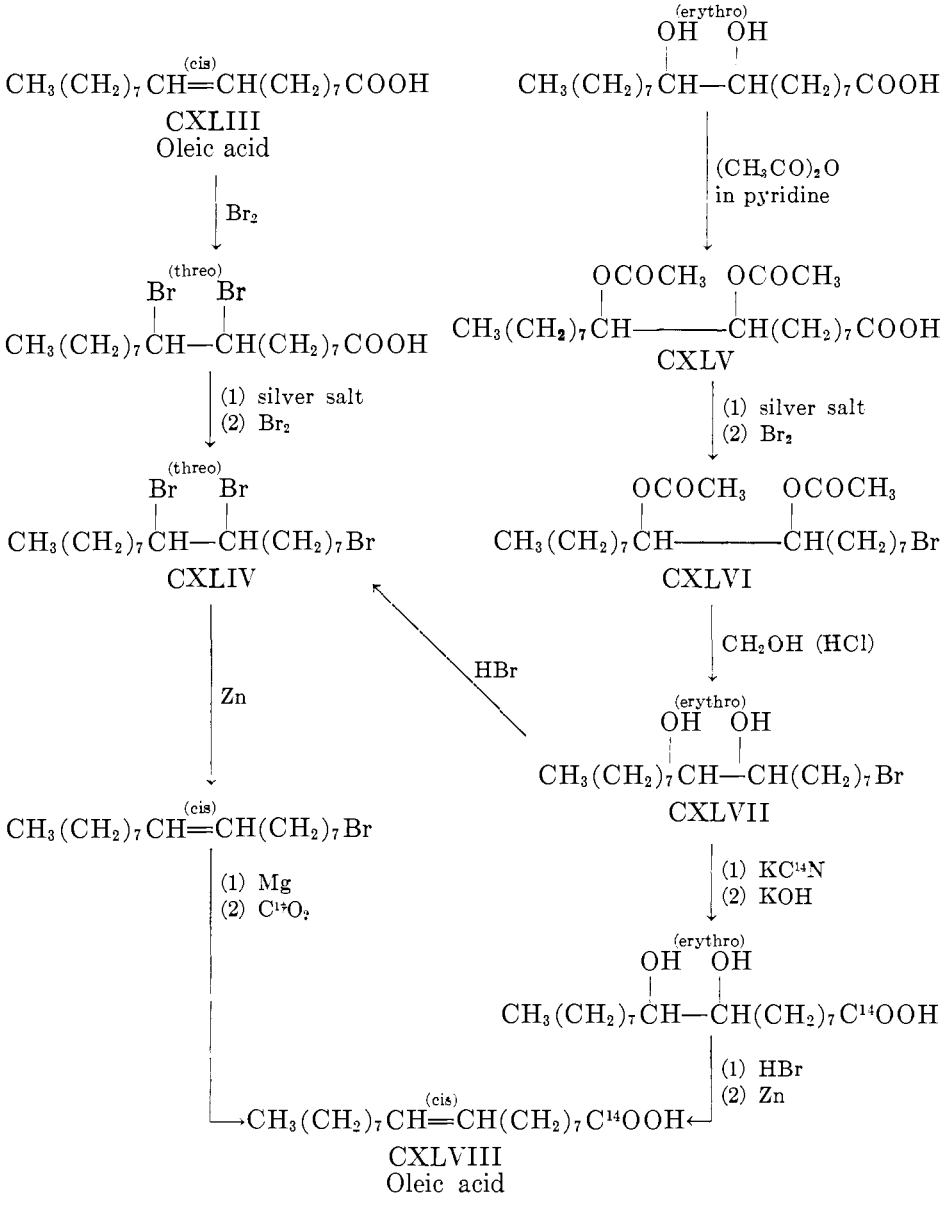
A variation of interest in that exposure of the dihydroxy acid to hydrobromination conditions is obviated, substitutes dimethanesulfonation followed by sodium iodide for the hydrobromination-debromination steps (198). For exam-



ple, erythro compound CXLI with methanesulfonyl chloride was converted to the erythro dimethanesulfonate. Sodium iodide eliminated the two methanesulfonate groups to give cis compound CXLII. Whether or not this process is of general applicability is not known as yet.

Vicinal glycols and dibromides have been made use of in the preparation of isotopically labeled unsaturated fatty acids. For example, carboxyl-labeled oleic acid was prepared by degrading *erythro*-9,10-diacetoxystearic acid (CXLV) by the silver salt–bromine decarboxylation to bromide CXLVI. Ester interchange in methanolic hydrogen chloride gave the erythro dihydroxyalkyl bromide CXLVII, which by nitrile synthesis with $KC^{14}N$ gave carboxyl-labeled 9,10-dihydroxystearic acid. Regeneration of the double bond by hydrobromination followed by debromination with zinc furnished the desired oleic acid (CXLVIII)

(37). Use of $KC^{13}N$ gave C^{13}-labeled oleic acid. An alternate scheme, adapted to the use of $C^{14}O_2$ instead of $KC^{14}N$, started with a stereospecific bromination of oleic acid (CXLIII) to *threo*-9,10-dibromostearic acid. Degradation of the silver



salt with bromine gave the threo tribromide CXLIV. Debromination with zinc, followed by Grignardation and carbonation, completed the process (166). The best features of both routes can be combined by working with the solid crystal-

line compounds from CXLV to CXLVII, and then converting dihydroxyalkyl bromide CXLVII to tribromide CXLIV. This permits the use of $C^{14}O_2$ instead of $KC^{14}N$ and the introduction of activity as late as possible (135).

A synthesis of carboxyl-labeled linoleic acid (CXLIX) makes use of stereospecific bromination and debromination with zinc (165; *cf.* Section III,B). A

$$CH_3(CH_2)_4CH\overset{(cis)}{=}CHCH_2CH\overset{(cis)}{=}CH(CH_2)_7C^{14}OOH$$

CXLIX
Linoleic acid

$$CH_3(CH_2)_4CH\overset{(cis)}{=}CHCH_2CH\overset{(cis)}{=}CH(CH_2)_6COOH$$

CL
Norlinoleic acid

synthesis of norlinoleic acid (CL) proceeds in part through common intermediates (38; *cf.* Section III,B).

6. Half-hydrogenation of acetylenic unsaturation (125a)

Catalytic half-hydrogenation of a triple bond is probably the most important general method of introducing a cis double bond. Ideal conditions for half-hydrogenation would (*a*) bring hydrogen absorption to a complete stop when one mole of hydrogen had been taken up, (*b*) give olefinic product to the exclusion of unreacted starting material and saturated material, and (*c*) furnish cis olefin to the exclusion of trans. The second feature is generally discussed under the term selectivity; the third under the term stereospecificity. Complete selectivity and complete stereospecificity are seldom if ever attained, although under proper hydrogenation conditions they may be closely approximated.

The relation of catalyst to selectivity and stereospecificity has been extensively studied. Other reaction parameters—for example, solvent or temperature—have not been as carefully studied. Systematic investigation along these lines may be rewarding. Of the possible catalysts for half-hydrogenation, platinum is clearly unsatisfactory, both selectivity and stereospecificity being low. Raney nickel or palladium in various modifications is the catalyst most frequently used.

(a) Half-hydrogenation over Raney nickel

Raney nickel is a useful but by no means an ideal catalyst for converting an acetylene to a cis olefin. The surprising report that hydrogenation of stearolic acid over Raney nickel (W-6) catalyst gave the *trans*-elaidic acid (2) is almost certainly in error (287). Some of the pertinent results on catalysis with Raney nickel are briefly summarized below.

Addition of one mole of hydrogen to 5-octynoic acid over W-5 Raney catalyst yielded (practically 100 per cent) what was regarded as essentially homogeneous *cis*-5-octenoic acid (164).

In the reduction of octadecynes to octadecenes, freshly prepared Raney nickel was found not to be particularly selective with monoacetylenes but appreciably more selective with disubstituted acetylenes. In the latter case the rates of hy-

drogenation before and after absorption of one mole of hydrogen differed considerably. Aged (nonpyrophoric) Raney nickel also showed large differences in the two hydrogenation rates. Raney nickel containing 10 per cent copper was found to give a fast, selective, and stereospecific reduction of octadecynes (124).

The mixtures produced when pentynes, hexynes, or octynes were hydrogenated over Raney nickel to the point at which 0.3–0.5 mole of hydrogen was absorbed gave, on fractionation, cis olefins pure to an extent of 90 per cent or better (160).

In a careful study of the hydrogenation of methyl stearolate, the catalyst used was Raney nickel which had been washed and digested to remove all or most of the free alkali and the aluminum. When exactly one mole of hydrogen had been introduced, the product consisted of methyl oleate (88.5 per cent), methyl elaidate (5.6 per cent), methyl stearate (3.7 per cent), and recovered methyl stearolate (2.1 per cent). Deuteration of methyl stearolate under similar conditions gave similar results. The alkali-free and aluminum-free catalyst gave a rate of hydrogenation of methyl stearolate after one mole had been adsorbed that was almost negligible. With 9-octadecyne, deuteration over this catalyst stopped completely at the one-mole mark and furnished *cis*-dideuterated-9-octadecene in a clean-cut manner (186).

Far less satisfactory was the behavior of a conjugated diacetylene, dimethyl 10,12-docosadiynedioate, in hydrogenation with Raney nickel at 100°C. (240). No discontinuity in rate of hydrogenation was noted until almost four moles of hydrogen had been absorbed. Analysis of the reaction mixture at intervals showed that at no time was there a significant accumulation of the conjugated ene-yne or the conjugated diene. At 25 per cent of complete hydrogenation (one mole of hydrogen absorbed) the monoacetylene, that is, dimethyl 10-docosynedioate, was present in appreciable amounts. At 75 per cent of complete hydrogenation (three moles of hydrogen absorbed) 83 per cent of the mixture was dimethyl 10-docosenedioate, of which about half was cis and half trans. This unusual behavior with respect to selectivity and stereospecificity may be the result of the 100° temperature, or less likely the effect of the conjugated diyne.

(b) Half-hydrogenation over palladium

Palladium has been used in combination with charcoal, starch, polyvinyl alcohol, calcium carbonate, barium sulfate, etc. Palladium in one or more of these forms is most widely accepted as the catalyst of choice for the hydrogenation of an acetylene to a cis olefin. However, the following brief summaries of some pertinent reports show that palladium still falls short of being the perfect catalyst.

Palladium on starch with either 1-octyne or 9-octadecyne permitted only very slow absorption of hydrogen and was only slightly specific (124). When one mole of hydrogen was added to 2-dodecynedioic acid over the same catalyst, as well as over palladium on polyvinyl alcohol, calcium carbonate, or barium sulfate, the desired *cis*-2-dodecenedioic acid was invariably accompanied by some of the overhydrogenation product, dodecanedioic acid. No trace of *trans*-2-dodecenedioic acid was observed (189). In the hydrogenation of another dibasic acid, 9-octadecynedioic acid, over 10 per cent palladium on charcoal catalyst in meth-

anol as solvent, there was no sharp break in the hydrogenation curve, and a mixture of products was obtained at the half-hydrogenation point. However, when acid slightly less pure than the analytical material (m.p. 95–99°C. instead of 99–100°C.) was hydrogenated, absorption stopped automatically at the one-mole mark, and pure *cis*-9-octadecenedioic acid was obtained in over 90 per cent yield (140).

Hydrogenation of 2,8-dodecadiynoic acid (233), 2,6-nonadiyn-1-ol, or the acetal of 2,6-nonadiynal to the two-mole mark over palladium on calcium carbonate catalyst in ethyl acetate gave cis products, which were probably contaminated with small amounts of trans ethylenic material as well as with materials formed by overhydrogenation or nonhydrogenation of the acetylenic links (263). The rate of hydrogenation of 3-hexyn-1-ol over 5 per cent palladium on calcium carbonate catalyst in methyl acetate fell to an almost negligible value after 0.99 mole of hydrogen had been absorbed. The product was *cis*-3-hexen-1-ol contaminated with some of the *trans* isomer (264).

Some overhydrogenation was observed when palladium on barium sulfate catalyzed the absorption of one mole of hydrogen by 10-undecynoic acid (105). 9-Undecynoic acid, on absorption of 1.08 mole of hydrogen over a 5 per cent palladium on calcium carbonate catalyst in ethyl acetate, gave a product containing 92 per cent of *cis*-9-undecenoic acid. Very little if any trans product was formed, the impurities presumably consisting of starting material and undecanoic acid (10). The same catalyst with stearolic acid showed lack of both selectivity and stereospecificity (31).

The use of 5 per cent palladium on charcoal in ethanol–pyridine (4:1) as solvent has been recommended for the half-hydrogenation of 11-octadecynoic acid to *cis*-vaccenic acid. A small amount (ca. 0.1 per cent) of stearic acid was separated from the recrystallized product (88 per cent yield) (162). The beneficial effect of hydrogenation in the presence of organic base was further pointed up in the half-hydrogenation of 17-ethynyl steroids in pyridine (157), and in the half-hydrogenation of a butynylcyclopentenolone in ethyl acetate containing some quinoline (246)—both over palladium on calcium carbonate.

A palladium catalyst, prepared and used according to a recipe given by Lindlar (194), has given outstanding results. The Lindlar catalyst is 5 per cent palladium on calcium carbonate on which a small percentage of lead has been deposited. Quinoline in small proportion in the hydrogenation mixture was found to enhance selectivity and stereospecificity. In many, but not all, applications hydrogenation stopped spontaneously after the absorption of one mole of hydrogen. Some examples of the use of the Lindlar catalyst for the controlled introduction of cis unsaturation in fatty acids are given below.

Hydrogenation of stearolic acid with the Lindlar catalyst in ethyl acetate containing quinoline until no more hydrogen was absorbed gave a product in which no acetylene could be detected and in which less than 2 per cent was the saturated stearic acid (105). With the usual proportion of quinoline approximately 5 per cent of the *trans*-elaidic acid was obtained, but with slightly more than the usual proportion of quinoline this figure was reduced to 1–2 per cent (30, 31).

No stearolic and no stearic acid could be detected when the hydrogenation was interrupted at the one-mole mark; oleic acid was obtained in 74 per cent yield (after crystallization). The Lindlar catalyst gave excellent results also in the hydrogenation of 13-docosynoic acid to *cis*-13-docosenoic acid (30, 31).

Half-hydrogenation of ricinstearolic acid to ricinoleic acid over the Lindlar catalyst proceeded selectively and stereospecifically even in the absence of quinoline (113).

The selectivity with terminally unsaturated 10-undecynoic acid leaves something to be desired. Hydrogenation with the Lindlar catalyst (plus quinoline) in ethyl acetate stopped after a little more than one mole of hydrogen had been absorbed. Although no acetylenic starting material was found, 9 per cent of the saturated undecanoic acid was detected. Interruption of the hydrogenation just before hydrogenation stopped of its own accord gave some of the saturated acid as well as some acetylenic starting material (105).

Hydrogenation of methyl *trans*-2-decen-4-ynoate showed no sharp decrease in the rate of hydrogenation after one mole of hydrogen was absorbed (104). Although a mixture was obtained (selectivity low), the new double bond appeared only in the cis configuration. Absorption of two moles of hydrogen over the Lindlar catalyst by methyl 2,4-decadiynoate gave methyl *cis*-2,*cis*-4-decadienoate as the major isolated product. However, the purity of this product has been questioned (7). Other materials, the results of over- and underhydrogenation, were also obtained. Little if any trans ethylenic bond was developed (104).

Addition of two moles of hydrogen to methyl 10,12-octadecadiynoate over the Lindlar catalyst (plus quinoline) followed by fractional crystallization of the products afforded methyl *cis*-10,*cis*-12-octadecadienoate (7).

Hydrogenation of *trans*-11-octadecen-9-ynoic acid (ximenynic acid) in alcohol in the presence of the Lindlar catalyst showed no break in the hydrogenation curve after absorption of one mole of hydrogen. When the process was interrupted at the one-mole mark, *cis*-9,*trans*-11-octadecadienoic acid was obtained (149).

Introduction of one mole of hydrogen over the Lindlar catalyst to the methyl ester of *trans*-3-tridecen-5-ynoic acid gave the corresponding ester of *trans*-3,*cis*-5-tridecadienoic acid in 90 per cent yield (92).

7. Chemical reduction of acetylenic unsaturation

A method for reducing triple bonds to trans double bonds by treatment with sodium in liquid ammonia, although highly selective and stereospecific (*cf. inter alia* 101, 156, 264), has found little application in the synthesis of fatty acids. 5-Octynoic acid has been converted in this way to *trans*-5-octenoic acid in 85 per cent yield (164). However, attempted reduction of octadecynoic acids or of 6-dodecynedioic acid (29) failed. Possibly insolubility of the sodium salts of the longer acids blocked the reaction. The reduction of octadecynes to *trans*-octadecenes, which failed at −35°C. but proceeded apparently with little difficulty at room temperature (124), suggests that higher temperatures should be tried in the reduction of the acetylenic acids.

The stereospecific reduction of a propargyl alcohol to a trans allyl alcohol by lithium aluminum hydride has not yet been applied to any considerable extent to the synthesis of fatty acids (232, p. 30).

The invalidity of the commonly accepted rule that "chemical" reduction of acetylenes gives the trans olefin has been emphasized by Rabinovitch and Looney (231). Besides the earlier observation (243) that titanous chloride and zinc in acetic acid–hydrochloric acid convert stearolic acid to oleic acid, several new cis reductions were discovered. For example, the zinc–copper couple in 95 per cent acetic acid converted tolane to *cis*-stilbene, zinc dust in alcoholic hydrogen chloride converted dideuteroacetylene to *cis*-dideuteroethylene, and the zinc–copper couple in 1*N* hydrochloric acid converted 1-deuteropropyne to the *cis*-deuteropropene. The possibility that "chemical" half-reductions giving rise to cis products are, in fact, catalytic hydrogenations has been considered.

P. ACETYLENIC UNSATURATION (173, 232)

Most syntheses of acetylenic acids proceed by the manipulation of fragments already containing the triple bond. However, some syntheses develop acetylenic unsaturation by bromination of the proper ethylene and then dehydrobromination. The dehydrobromination is effected either with potassium hydroxide or with sodium amide. Potassium hydroxide was used, for example, to convert ricinoleic acid dibromide to ricinstearolic acid (113, 147). Ethanolic potassium hydroxide converts the dibromide of 22-tricosenoic acid to 22-tricosynoic acid (271); concentrated aqueous potassium hydroxide at 150°C. converts undecylenic acid dibromide to 10-undecynoic acid (240). Potassium hydroxide at somewhat higher temperatures isomerized the latter two products to 21-tricosynoic acid and 9-undecynoic acid, respectively (10). In the same way, alkali isomerized 6,12-tridecadiynoic acid to 6,11-tridecadiynoic acid (31).

Sodium amide in liquid ammonia has been preferred by some workers for dehydrobromination because this particular kind of isomerization is not observed, and because in some cases the yields are higher. 10-Undecynoic acid (189), stearolic acid (187), and 6-octadecynoic acid (187), as well as a number of fatty acid intermediates (101, 114, 234, 263), have been prepared with sodium amide. Linoleic acid tetrabromide with sodium amide does not give 9,12-octadecadiynoic acid (187).

A study of the dehydrobromination of vicinal dibromoalkanes has shown that sodium amide under the proper conditions converts 1,2-dibromoalkanes to 1-alkynes and 2,3-dibromoalkanes to 2-alkynes with no sign of bond migration in either case. On the other hand, dehydrobromination of 3,4-dibromo and other internal vicinal dibromides by means of sodium amide occurs with bond migration (206). The homogeneity of such dehydrobromination products as ricinstearolic acid or stearolic acid, accordingly, should be carefully checked.

Q. INTRODUCTION OF BRANCHING

The presence of branched chains in several groups of natural fatty acids has stimulated considerable synthetic work on branched-chain acids (*cf.* 121). Such

groups would include, on the one hand, the acids in wool wax (283; also 152, 153) terminating in the isopropyl group ("iso" series) or in the secondary butyl group ("anteiso" series) (14, 163, 205, 221) and, on the other hand, the branched-chain acids from various bacteria (23).

Simply by making use of properly branched starting materials, most of the general methods discussed before lend themselves without modification to the introduction of branching in fatty acids. Examples and references will be found scattered throughout this paper; the sections on tuberculostearic acid (III,E), "phthioic" acid (III,F), and "mycolic" acids (III,H,3) are, of course, directly pertinent. Only a sampling is given (Section III,G) of the extensive work on the branched-chain isoprenoid compounds.

Mention may be made of methods which are of utility in developing a branch at the point of juncture of two fragments. Such methods include the Reformatsky process with α-bromopropionic ester (e.g., 59, 80; also see Section III,H,5), the Reformatsky process with ketones (e.g., 59, 83), the malonic ester process with monoalkylated malonic esters (e.g., 76), and addition of organometals to ketones (e.g., 180, 192). Methyl hydrogen 3-methylglutarate, in both the racemic and the optically active forms, has been of great service in incorporating a branched methyl group by any one of several methods (*cf. inter alia* 203, 268, 269).

Some systematic syntheses of series of branched-chain acids deserve mention. All the monomethylstearic acids (291; also 74, 78, 85) as well as all the monomethylpalmitic acids (290) have been prepared. The 3-, 4-, 5-, 6-, and 7-monomethyldecanoic acids have been synthesized (225). Stearic acids substituted in the α-position with the entire series of normal alkyl groups from methyl to dodecyl are available (289), as is a series of 2-alkyl-3-methylnonanoic acids (120). Five long-chain acids terminating in the *tert*-butyl group have been described (259).

The contributions of Cason and his associates to the field of the synthesis and properties of branched-chain acids deserve special mention.

III. Syntheses of Specific Acids

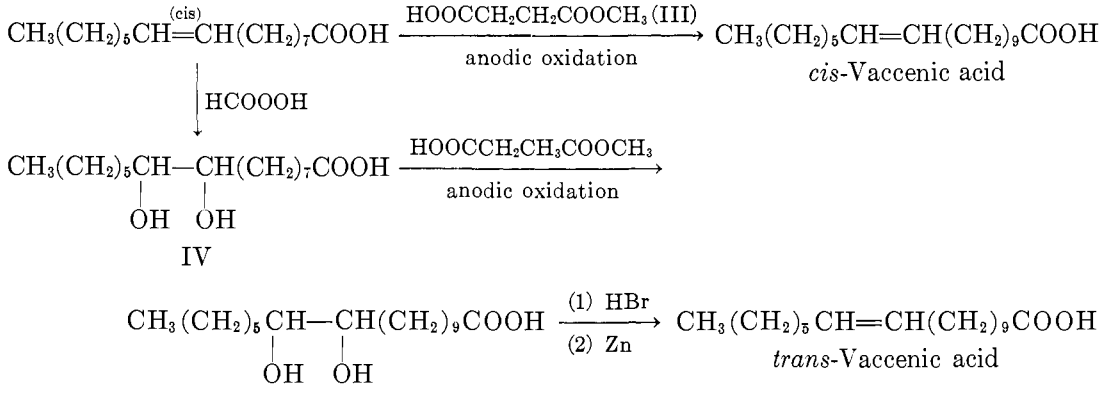
A. VACCENIC ACID

trans-Vaccenic acid, i.e., *trans*-11-octadecenoic acid, has been isolated from butter as well as from sheep and ox body fats. *cis*-Vaccenic acid is the principal unsaturated acid in the fats from *Lactobacillus arabinosus* and *Lactobacillus casei*. The cis acid also occurs in fat from horse brain. The original synthesis by Ahmad, Bumpus, and Strong (5) has been repeated several times (132, 167; also *cf.* 162). Alternate syntheses starting from undecylenic acid (126, 134) and from palmi-

$$\underset{\text{Palmitoleic acid}}{\underset{\text{I}}{CH_3(CH_2)_5\overset{(cis)}{CH{=}CH}(CH_2)_7COOH}} \xrightarrow[\text{(3) HBr}]{\text{(1) esterification; (2) Na and alcohol}} \xrightarrow[\text{(4) } NaCH(COOC_2H_5)_2\text{, etc.}]{} CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$$

II

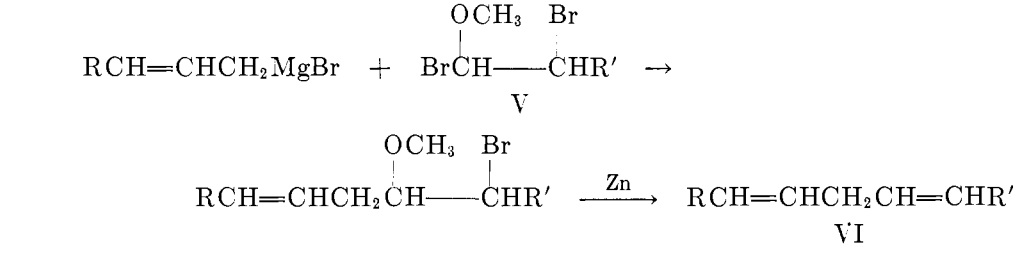
toleic acid have been reported. One synthesis (285) adds two carbon atoms to the carboxylic end of the sixteen-carbon palmitoleic acid (I) by Bouveault–Blanc reduction to alcohol, formation of bromide, and application of the malonate process. Although this four-step process gave a mixture of the *cis*- and *trans*-vaccenic acids (II), another scheme, by combining palmitoleic acid and methyl



hydrogen succinate (III) in mixed Kolbe oxidation, gave pure *cis*-vaccenic acid in one step. *trans*-Vaccenic acid was obtained by cross Kolbe coupling of hydroxylated palmitoleic acid (IV) and methyl hydrogen succinate, and by regenerating the double bond by stereospecific hydrobromination and debromination (see Section II,O,5) (50).

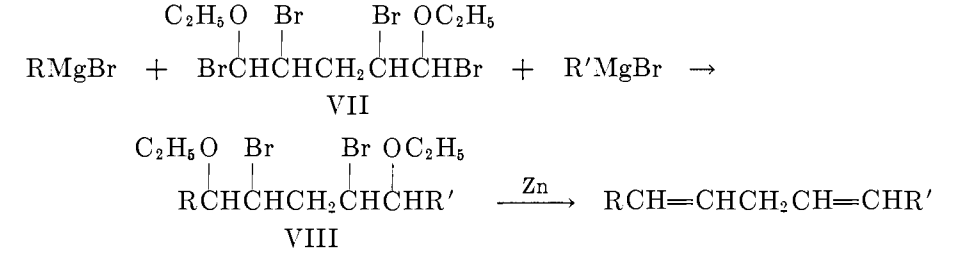
B. LINOLEIC AND LINOLENIC ACIDS (SKIPPED UNSATURATION)

Linoleic and linolenic acids (*cis*-9,*cis*-12-octadecadienoic acid and *cis*-9,*cis*-12,*cis*-15-octadecatrienoic acid, respectively), together with other naturally occurring polyunsaturated fatty acids, contain ethylenic double bonds separated by a single methylene group. The main feature in the syntheses of these acids is construction of such "methylene interrupted" or "skipped" (136) unsaturation systems. In two earlier syntheses of linoleic acid, the skipped diene system was developed by adaptation of the method of Boord and Swallen (260). In one synthesis (219) a substituted allylmagnesium bromide was coupled with an α,β-dibromo ether (V), and the resulting monoethylenic bromo ether converted to

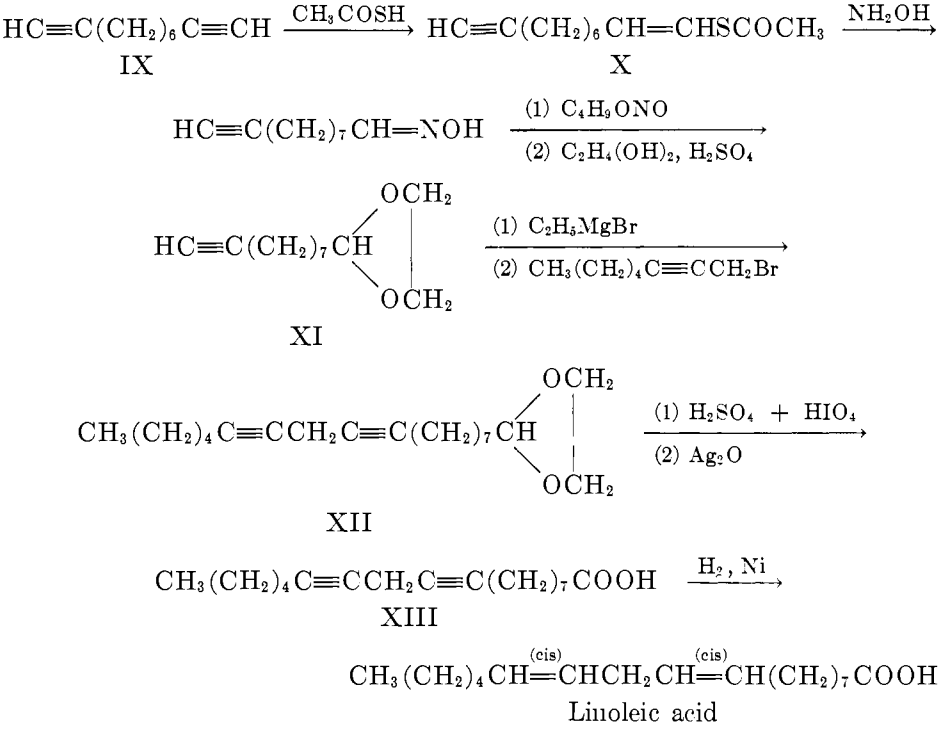


the skipped diyne (VI) with zinc. In the second synthesis (34; also *cf.* 151) two different Grignard reagents were coupled with a bis(α,β-dibromo ether) (VII).

Skipped unsaturation was developed in the *mixed* coupled product (VIII), again by reaction with zinc. Later it was found more convenient to build skipped cis diene systems by half-hydrogenating the corresponding skipped diynes, which



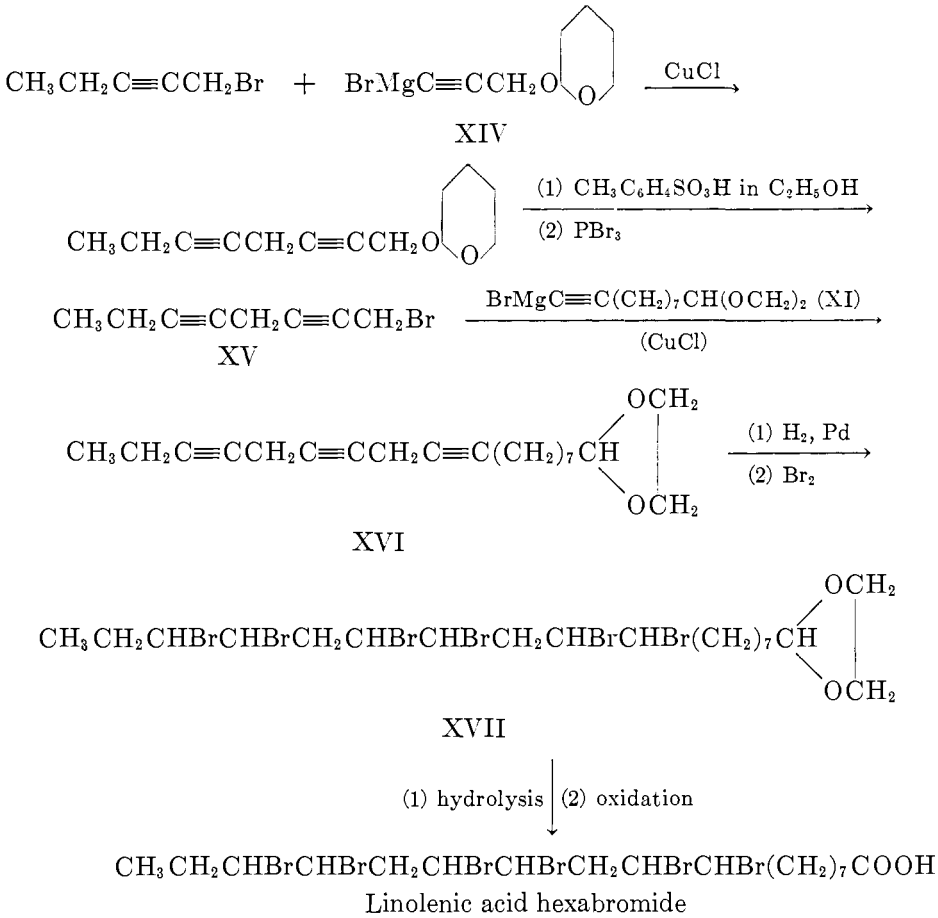
in turn could be formed satisfactorily by coupling acetylenic Grignard derivatives either with propargyl bromides (136, 139; also *cf.* 138) or with propargyl methanesulfonates. One of the two syntheses of linoleic acid (142, 235, 287; also *cf.* 280) is outlined below (287). 1,9-Decadiyne (IX), from 1,6-dibromohexane



and sodium acetylide, was combined with thioacetic acid to form the vinyl thioacetate derivative X. Hydroxylamine hydrochloride converted the thioacetate to the oxime of 9-decynal. This oxime with nitrous acid gave an aldehyde which with ethylene glycol gave the cyclic acetal XI. 1-Bromo-2-octyne with the Grignard derivative of XI and in the presence of cuprous copper gave the

eighteen-carbon skipped diyne compound XII. Silver oxide oxidation of the aldehyde, after removal of the protecting acetal group, gave 9,12-octadecadiynoic acid (XIII), which on half-hydrogenation afforded linoleic acid.

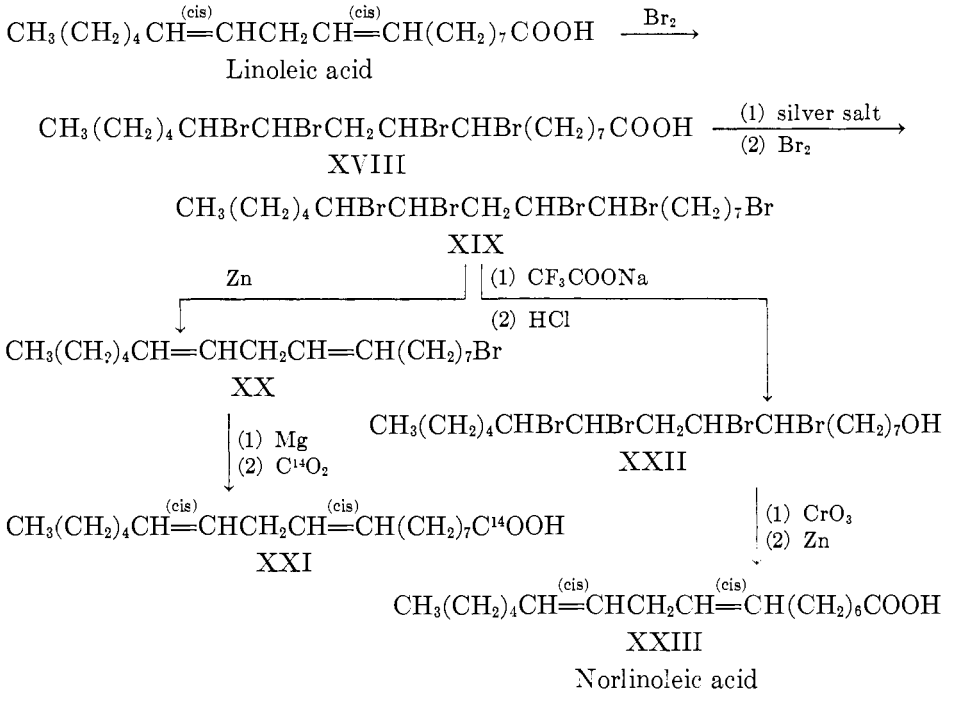
In a synthesis of linolenic acid (218), the skipped triene system was formed in an analogous manner by half-hydrogenation of the corresponding skipped triyne (*cf.* 137). The synthesis (218) proceeds by coupling 1-bromo-2-pentyne



with the acetylenic Grignard derivative XIV. Removal of the protecting tetrahydropyranyl group by treatment with alcohol containing *p*-toluenesulfonic acid was followed by conversion of the alcohol to bromide XV with phosphorus tribromide. The Grignard derivative of the acetylenic acetal XI, prepared in this work from 9-decynoic acid, was then coupled with propargyl bromide (XV) to give the eighteen-carbon skipped triyne compound XVI. Half-hydrogenation was followed by addition of bromine to give XVII. Hydrolysis of the acetal and oxidation of the exposed aldehyde grouping gave linolenic acid hexabromide, from which, by debromination with zinc, linolenic acid itself had previously been obtained.

Linoleic acid (XXI) labeled with carbon-14 in the carboxyl group has been prepared by the degradation and reconstitution of natural linoleic acid (165). Decarboxylation of linoleic acid tetrabromide (XVIII) by the action of bromine on the silver salt gave pentabromide XIX, which with zinc gave the seventeen-carbon diunsaturated bromide XX. Carbonation of the Grignard derivative of the bromide with radioactive carbon dioxide afforded labeled linoleic acid (XXI).

The same pentabromide (XIX) was used in work on the synthesis of norlinoleic acid (XXIII).



The pentabromide was treated first with sodium trifluoroacetate and then with hydrochloric acid to effect selective conversion of primary bromide to primary alcohol, as in XXII. Oxidation gave the seventeen-carbon acid, which on debromination with zinc gave norlinoleic acid (XXIII) (38).

C. INSECTICIDAL FATTY ACID AMIDES

Herculin, an insecticidal principle from Southern prickly ash, is the isobutyl amide of a twelve-carbon unsaturated straight-chain acid. The original suggestion that herculin was *N*-isobutyl-2,8-dodecadienamide led to the synthesis of all four possible geometrically isomeric forms of XXIV, none of which, however, proved to be identical with herculin. Reinvestigation led to a revised structure (XXV) (102) and a new name, neoherculin, for the insecticidal material. The revised structure has not yet been corroborated by synthesis. In related work, synthesis of the four stereoisomers of *N*-isobutyl-2,6-decadienamide (XXVI) (101, 234) proved that this structure could not be correct for pellitorine, an in-

secticide from *Anacyclus pyrethrum*. Later it was shown that a major component of "pellitorine," which was not homogeneous, was the isobutyl amide of *trans*-2,*trans*-4-decadienoic acid (XXVII) (103). During the course of the work,

$$CH_3(CH_2)_2CH{=}CH(CH_2)_4CH{=}CHCONHCH_2CH(CH_3)_2$$

XXIV

N-Isobutyl-2,8-dodecadienamide

$$CH_3CH{=}CHCH{=}CHCH{=}CHCH_2CH_2CH{=}CHCONHCH_2CH(CH_3)_2$$

XXV

Neoherculin

$$CH_3CH_2CH_2CH{=}CHCH_2CH_2CH{=}CHCONHCH_2CH(CH_3)_2$$

XXVI

N-Isobutyl-2,6-decadienamide

$$CH_3(CH_2)_4CH{=}CHCH{=}CHCONHCH_2CH(CH_3)_2$$

XXVII

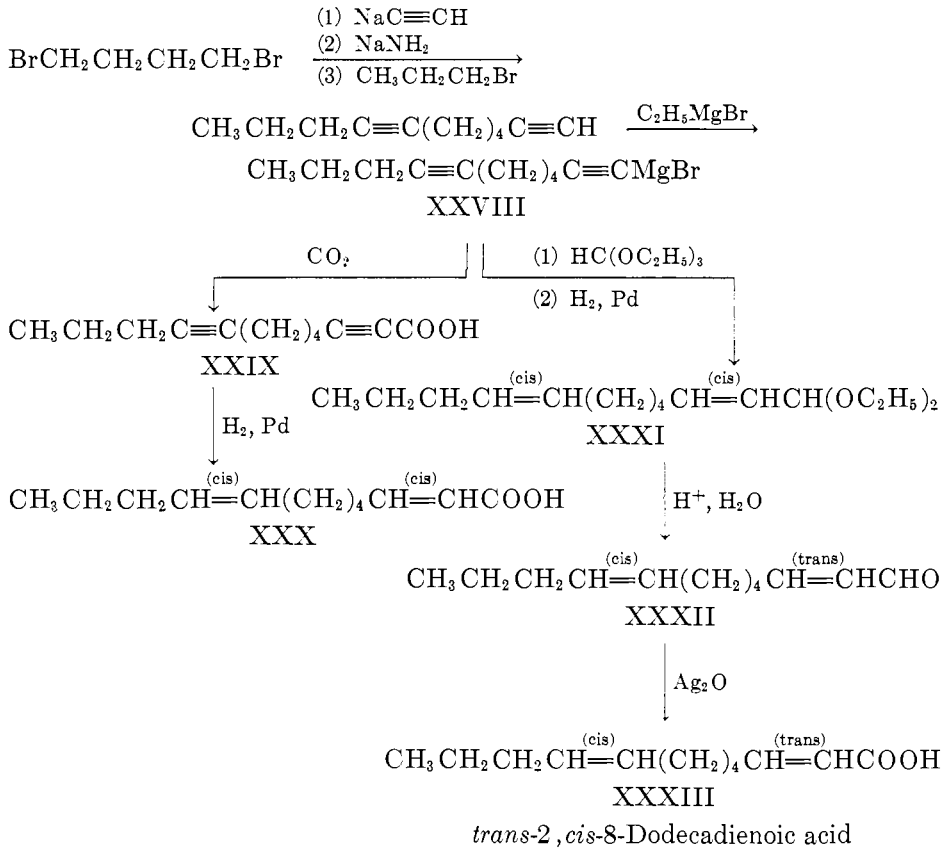
N-Isobutyl-2,4-decadienamide

all four geometrical isomers of 2,4-decadienoic acid (*cf.* Section III,J) were prepared (104, 174).

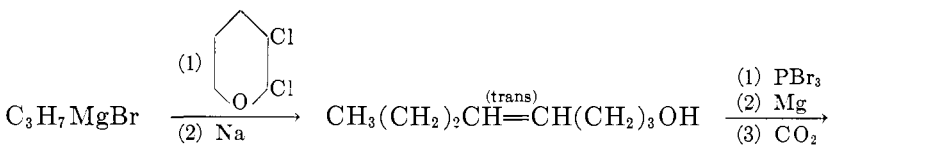
To illustrate some of the reactions employed for these syntheses and, more important, to show how geometry at the double bond is controlled, the steps in the preparation of the four 2,8-dodecadienoic acids are discussed below in some detail. The acids with $\Delta^{8,9}$ cis were prepared (233, 236) by way of 1,7-undecadiyne, which was prepared from 1,4-dibromobutane by combination with sodium acetylide and then monoalkylation of the resulting 1,7-octadiyne with propyl iodide. Carbonation of the Grignard derivative of 1,7-undecadiyne XXVIII gave 2,8-dodecadiynoic acid (XXIX), which on half-hydrogenation over palladium on calcium carbonate gave *cis*-2,*cis*-8-dodecadienoic acid (XXX). The same Grignard derivative (XXVIII) with ethyl orthoformate led to the expected acetal, which on half-hydrogenation gave the diolefinic (cis,cis) acetal XXXI. Steam distillation from aqueous oxalic acid not only exposed the free aldehyde but also isomerized the cis α,β double bond in a stereospecific manner to trans. Oxidation of *trans*-2,*cis*-8 aldehyde XXXII with silver nitrate in aqueous sodium hydroxide solution furnished the desired *trans*-2,*cis*-8-dodecadienoic acid (XXXIII).

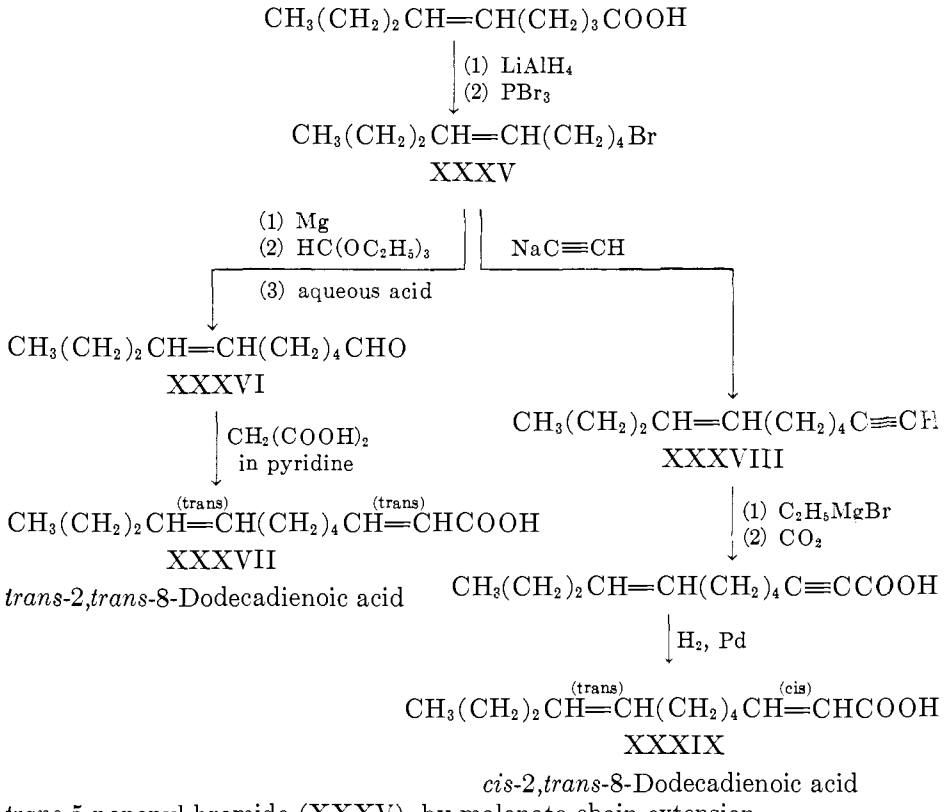
The acids with $\Delta^{8,9}$ trans were obtained (100) from *trans*-5-nonenyl bromide (XXXV). To get this material, the three-carbon chain of propylmagnesium bromide was extended by five carbon atoms by a standard procedure (Section II,F), involving coupling with 2,3-dichlorotetrahydropyran followed by treatment with powdered sodium. The *trans*-4-octen-1-ol (XXXIV) produced in this way in a stereospecific manner was converted by Grignardation and carbonation to *trans*-5-nonenoic acid, which after reduction with lithium aluminum hydride followed by treatment with phosphorus bromide gave the necessary bromide (XXXV). The trans,trans final product was reached by Grignardation,

reaction with ethyl orthoformate, and hydrolysis to give the intermediate aldehyde (XXXVI), which in the Doebner reaction then gave *trans*-2,*trans*-8-dodecadienoic acid (XXXVII). The fourth stereoisomer was obtained by extending the carbon chain of the bromide XXXV with sodium acetylide, carbonating the Grignard derivative of the monosubstituted acetylene XXXVIII, and half-hydrogenating the resulting acetylenic α,β-unsaturated acid to *cis*-2, *trans*-8-dodecadienoic acid (XXXIX).

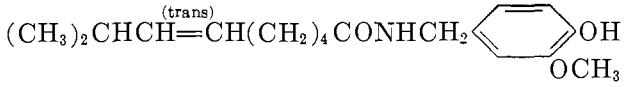


A new synthesis of capsaicin (XL), isolated from red pepper, has been reported (107). The synthesis of the corresponding acid proceeds from *trans*-1-bromo-6-methyl-4-heptene, prepared by reactions analogous to those used for





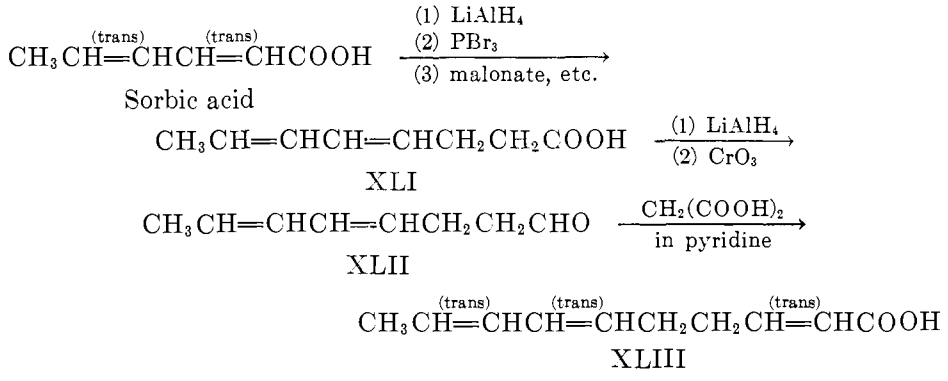
trans-5-nonenyl bromide (XXXV), by malonate chain extension.



XL

Capsaicin

Affinin, another insecticidal principle, has been prepared (175) by elaborating the six-carbon acid, sorbic acid, in a standard sequence to *trans*-4,*trans*-6-octa-



dienoic acid ((XLI), forming the corresponding aldehyde (XLII) by lithium aluminum hydride reduction to the alcohol followed by reoxidation by chromic oxide, and further extending the chain by application of the Doebner process. The isobutyl amide of the all-*trans*-2,6,8-decatrienoic acid (XLIII) so obtained was identical with affinin.

Synthesis of the isobutyl amides of *trans*-2,*trans*-4,*cis*-8-dodecatrienoic acid and of all-*trans*-2,4,8-dodecatrienoic acid by stereospecific methods similar to those described above has demonstrated that these amides are not the same as "sanshoöl I", an insecticide from *Zanthoxylum piperitum* D.C. (114).

D. ACETYLENIC ACIDS

1. Stearolic and tariric acids

Both simple (298) and complex acetylenic acids have been synthesized. For example, stearolic acid (9-octadecynoic acid), long known as the dehydrobromination product of oleic acid dibromide, has been prepared by crossed Kolbe syntheses from both 5-decynedioic acid (XLV: $n = 3$) and 6-dodecynedioic acid (XLV: $n = 4$). The former acid was prepared (31) by coupling the sodium de-

$$\underset{\text{XLIV}}{Cl(CH_2)_nC{\equiv}CH} \xrightarrow[(2)\ Br(CH_2)_nCl]{(1)\ NaNH_2} Cl(CH_2)_nC{\equiv}C(CH_2)_nCl \xrightarrow[(3)\ \text{saponification}]{(1)\ NaI,\ (2)\ KCN} \underset{\text{XLV}}{HOOC(CH_2)_nC{\equiv}C(CH_2)_nCOOH}$$

rivative of 5-chloro-1-pentyne (XLIV: $n = 3$) with 1-bromo-3-chloropropane, and inserting terminal carboxyl groups by way of a nitrile process. 6-Dodecynedioic acid (XLV: $n = 4$) was prepared from 6-chloro-1-hexyne and 1-bromo-4-chlorobutane by analogous reactions (29). Crossed Kolbe coupling of methyl hydrogen 5-decynedioate (XLVI) with hexanoic acid gave methyl 5-tetradecynoate; the same process with methyl hydrogen adipate and 5-tetradecynoic acid (XLVII) added four carbon atoms and furnished methyl stearolate (XLVIII) (31). Crossed Kolbe combination of methyl hydrogen 6-dodecynoate (XLIX)

$$\underset{\text{XLVI}}{HOOC(CH_2)_3C{\equiv}C(CH_2)_3COOCH_3} \xrightarrow[\text{anodic oxidation}]{CH_3(CH_2)_4COOH}$$

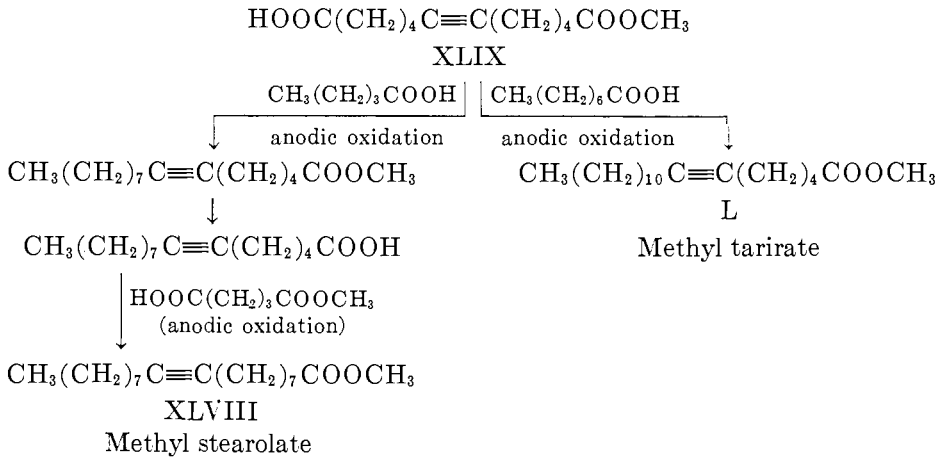
$$CH_3(CH_2)_4(CH_2)_3C{\equiv}C(CH_2)_3COOCH_3 \xrightarrow{\text{hydrolysis}}$$

$$\underset{\text{XLVII}}{CH_3(CH_2)_7C{\equiv}C(CH_2)_3COOH} \xrightarrow[\text{anodic oxidation}]{HOOC(CH_2)_4COOCH_3}$$

$$\underset{\text{XLVIII}}{CH_3(CH_2)_7C{\equiv}C(CH_2)_3(CH_2)_4COOCH_3}$$

Methyl stearolate

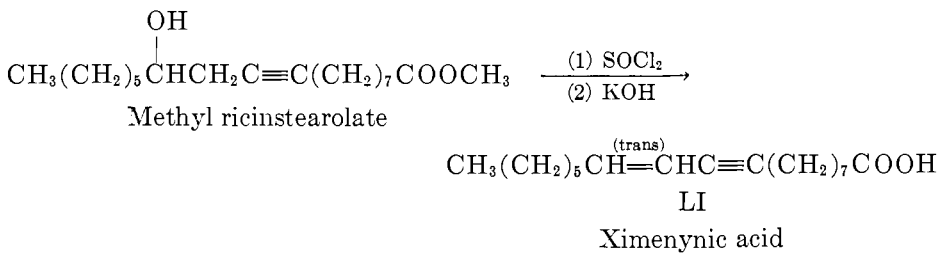
first with valeric acid and then with methyl hydrogen glutarate again furnished methyl stearolate (31). Crossed Kolbe combination of the same methyl hydrogen



dodecynoate (XLIX) with octanoic acid gave the methyl ester (L) of tariric acid (from *Picramnia Sow*) directly (29). Tariric acid was also synthesized in another investigation (201) by a sequence essentially that of Ahmad and Strong (Section II,K).

2. Ximenynic acid (santalbic acid)

Both santalbic acid from sandal oil and ximenynic acid from several species of *Ximenia* and *Santalaceae* have been shown to have the structure of *trans*-11-octadecen-9-ynoic acid (LI) (*cf.* 149). Since ricinstearolic acid, which has been synthesized (Section III,H,1), has been converted with thionyl chloride to the



corresponding chloro compound and then with alcoholic potassium hydroxide to ximenynic acid (113, 147), total synthesis of the latter may be claimed. Ximenynic acid or an isomer has also been obtained from methyl stearolate by brominating with *N*-bromosuccinimide on the 10- or the 8-position and heating to remove hydrogen bromide (216).

3. Erythrogenic acid (isanic acid)

Synthesis of erythrogenic acid (isanic acid), from the seed fat of *Onguekoa gore*, has been realized (39). The synthesis, in showing that the correct structure of erythrogenic acid is 17-octadecen-9,11-diynoic acid (LVII), disposed finally of

an alternate possibility: namely, 17-octadecen-9,15-diynoic acid. 9-Decynoic acid (LIV), one of the moieties needed in the final stage of the synthesis, was prepared from 10-undecynoic ester (LII) by Barbier–Wieland degradation. Selective oxidative cleavage of intermediate ene-yne LIII (obtained as the dehydration product from the phenyl Grignard adduct) at the ethylenic unsaturation is noteworthy. The second moiety, 1-octen-7-yne (LVI), was formed by alkylating sodium acetylide with 4-chloro-1-iodo-butane (LV), half-hydrogenating the product, 6-chloro-1-hexyne, to 6-chloro-1-hexene, and combining the latter with

$$\underset{\text{LII}}{HC{\equiv}C(CH_2)_8COOC_2H_5} \xrightarrow[\text{(2) heat to 220°C.}]{\text{(1) } C_6H_5MgBr} HC{\equiv}C(CH_2)_7CH{=}C(C_6H_5)_2 \xrightarrow{CrO_3} \underset{\text{9-Decynoic acid}}{\underset{\text{LIV}}{HC{\equiv}C(CH_2)_7COOH}}$$

$$\underset{\text{LV}}{I(CH_2)_4Cl} \xrightarrow{NaC{\equiv}CH} HC{\equiv}CH(CH_2)_4Cl \xrightarrow[H_2]{Pd\text{-}CaCO_3} CH_2{=}CH(CH_2)_4Cl \xrightarrow[\text{(2) } NaC{\equiv}CH]{\text{(1) NaI}} \underset{\text{LVI}}{CH_2{=}CH(CH_2)_4C{\equiv}CH}$$

sodium acetylide. Mixed Glaser coupling with 1-octen-7-yne (LVI) and 9-decynoic acid (LIV) gave the desired erythrogenic acid (LVII) as the cross product.

$$\underset{\substack{\text{LVI}\\ \text{1-Octen-7-yne}}}{CH_2{=}CH(CH_2)_4C{\equiv}CH} + \underset{\substack{\text{LIV}\\ \text{9-Decynoic acid}}}{HC{\equiv}C(CH_2)_7COOH} \rightarrow \underset{\substack{\text{LVII}\\ \text{Erythrogenic acid}}}{CH_2{=}CH(CH_2)_4C{\equiv}CC{\equiv}C(CH_2)_7COOH}$$

4. Acids from Compositae

The accompanying formulas (LVIII to LXI) show some of the polyacetylenic compounds from various species of *Compositae*. The *trans*-2,*cis*-8 stereoisomer, as well as matricaria ester itself (LVIII), which is *cis*-2,*cis*-8, has been isolated (262). Interestingly enough, the *trans*-2,*trans*-8 isomer of matricaria ester can be extracted from a wood-rotting fungus (62). These and other naturally occurring polyacetylenic compounds have been authoritatively reviewed recently (41).

Synthetic work in this field has drawn heavily on and has benefitted greatly from recent developments in acetylene chemistry (*cf. inter alia* 232). Synthesis of a number of these compounds as well as of other more or less closely related polyacetylenes (13, 43, 60, 61, 95, 96, 159, 257) has been realized. To illustrate

$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$

LVIII

Matricaria ester

$CH_3CH{=}CHC{\equiv}CC{\equiv}CCH_2CH_2COOCH_3$

LIX

α,β-Dihydromatricaria ester

$CH_3CH{=}CHC{\equiv}CC{\equiv}CC{\equiv}CCOOCH_3$

LX

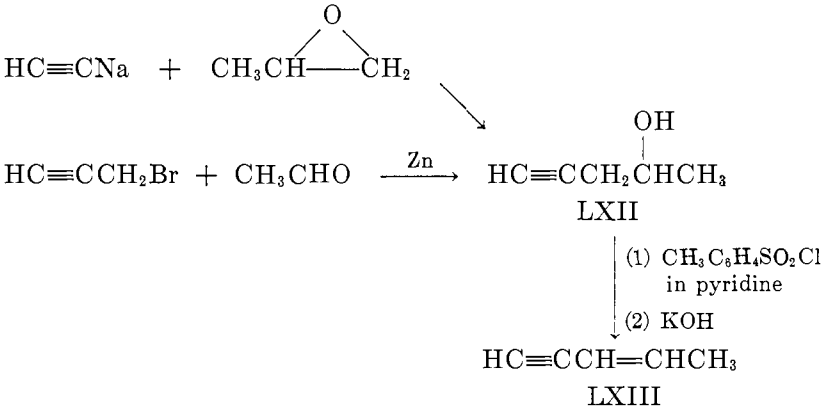
α,β-Dehydromatricaria ester

$CH_3CH_2CH_2C{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$

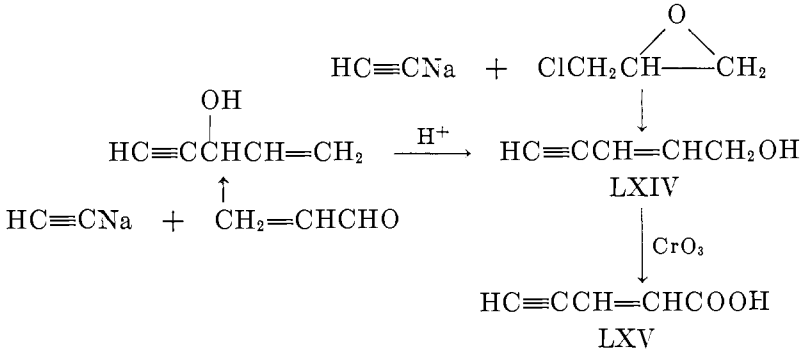
LXI

Lachnophyllum ester

some of the reactions involved, the synthesis of two forms of matricaria ester is given below (60). 3-Penten-1-yne (LXIII), one of the intermediates needed for the final stage of the synthesis, was prepared by the two-stage dehydration of 4-pentyn-2-ol (LXII). This alcohol was prepared from acetylene and propylene oxide or from the zinc condensation of propargyl bromide and acetalde-



hyde. The second penultimate moiety, *trans*-2-penten-4-ynoic acid (LXV) was



prepared by controlled chromic oxide oxidation of the corresponding alcohol (LXIV). This was obtained from sodium acetylide and epichlorohydrin or, by acid-catalyzed rearrangement, from the condensation product of sodium acetylide and acrolein (95, 261). Glaser coupling of the methyl ester of *trans*-2-penten-4-ynoic acid and 3-penten-1-yne, which was a mixture of cis and trans forms, gave

$$CH_3CH{=}CHC{\equiv}CH + HC{\equiv}CCH{=}CHCOOCH_3 \rightarrow CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCOOCH_3$$

LXVI

Matricaria ester

as the cross product a separable mixture of *trans*-2,*trans*-8- and *trans*-2,*cis*-8-matricaria ester (LXVI).

5. *Isomycomycin*

The structure of the antibiotic mycomycin (LXVII) has been elucidated (91). Although no synthesis of mycomycin has appeared, an elegant synthesis of iso-

$$HC{\equiv}CC{\equiv}CCH{=}C{=}CHCH{=}CHCH{=}CHCH_2COOH \xrightarrow{OH^-} CH_3(C{\equiv}C)_3(CH{=}CH)_2CH_2COOH$$

LXVII — Mycomycin

LXVIII — Isomycomycin

mycomycin (LXVIII), an isomerization product from mycomycin (90), has been completed (45) as follows: Lithium acetylide was added to pentadienal (LXIX) to give a secondary alcohol (LXX). Phosphorus tribromide converted alcohol LXX to primary bromide LXXI, which with cyanide in weakly acidic solution

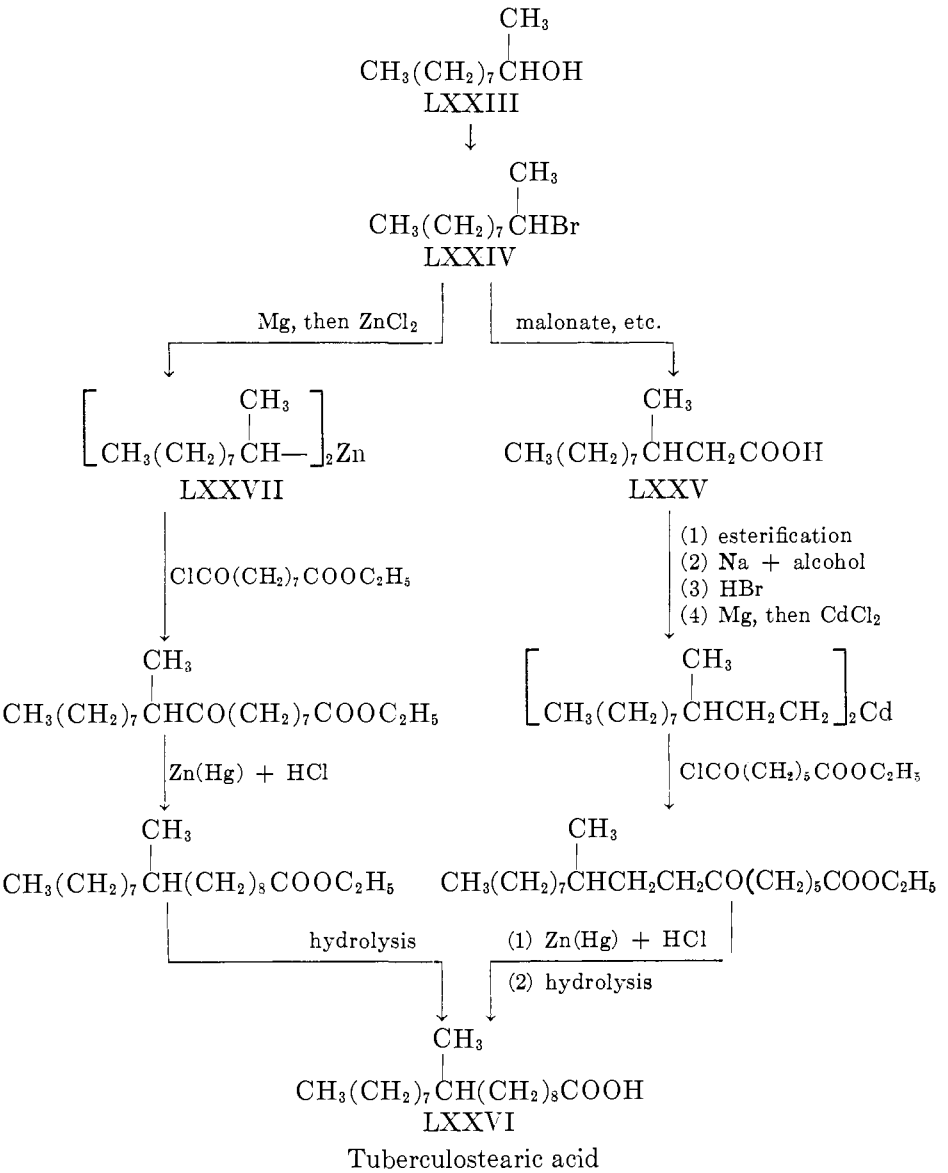
$$CH_2{=}CHCH{=}CHCHO \xrightarrow{LiC{\equiv}CH} HC{\equiv}CCHOHCH{=}CHCH{=}CH_2 \xrightarrow{PBr_3} HC{\equiv}CCH{=}CHCH{=}CHCH_2Br \xrightarrow{NaCN} HC{\equiv}CCH{=}CHCH{=}CHCH_2CN \xrightarrow[[O]]{CH_3C{\equiv}CC{\equiv}CH} CH_3C{\equiv}CC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH_2CN \xrightarrow[(2)\ \text{saponification}]{(1)\ CH_3OH\,(HCl)} CH_3(C{\equiv}C)_3(CH{=}CH)_2CH_2COOH$$

LIX — LXX — LXXI — LXXII — LXVIII — Isomycomycin

gave nitrile LXXII. Mixed Glaser coupling with 1,3-pentadiyne led to the nitrile of isomycomycin, and finally hydrolysis in two stages gave isomycomycin (LXVIII) itself. Other acids with a double bond conjugated to three triple bonds were synthesized by related reactions (45). Related model compounds—for example, methyl 3,5-tridecadienoate—have also been prepared (92).

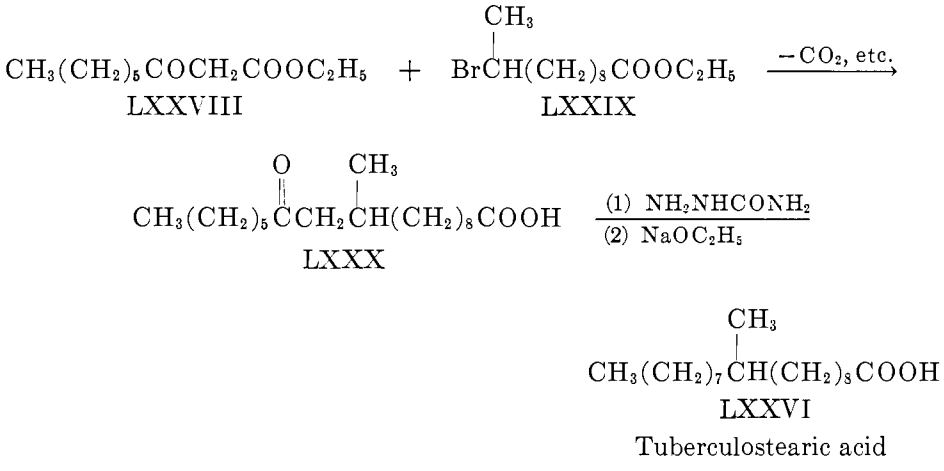
E. TUBERCULOSTEARIC ACID (23)

Several different syntheses of tuberculostearic acid (LXXVI) (10-methyloctadecanoic acid) (266), one of the fatty acids isolated from the tubercle bacillus



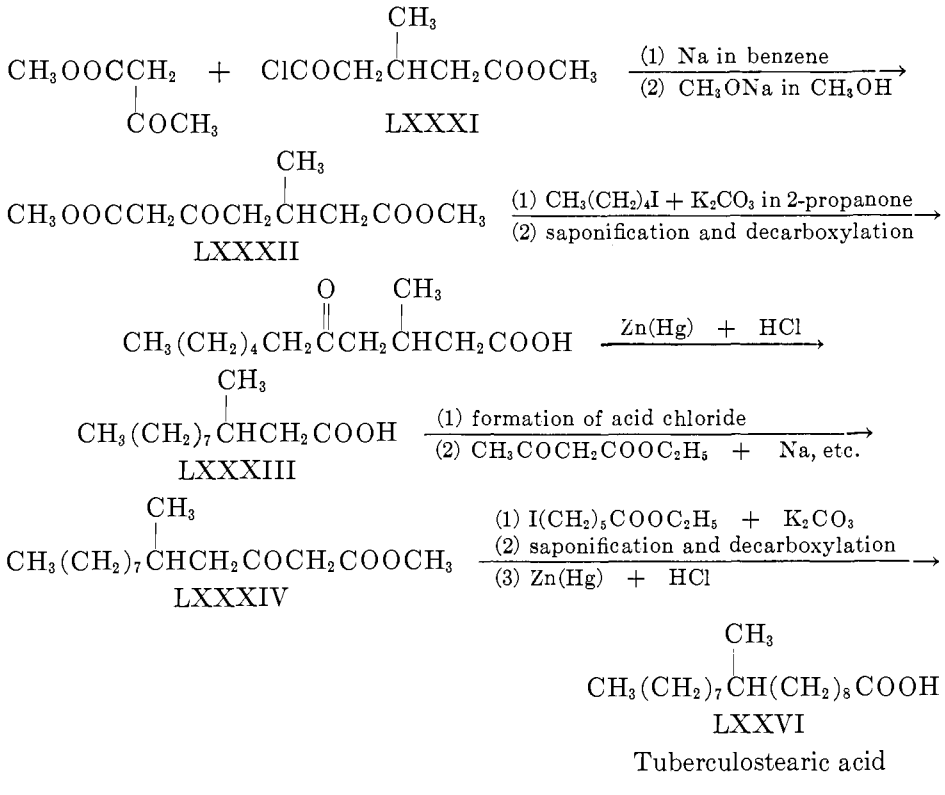
(12, 84), have been reported. In one of the early syntheses (229; also *cf.* 266) 2-decanol (LXXIII) was the starting point. Extension of the chain by bromination and combination with sodiomalonate gave 3-methylundecanoic acid (LXXV). Ethyl 3-methylundecanoate was reduced (Bouveault–Blanc) to the alcohol, and the corresponding bromide converted in the usual way to the organocadmium derivative. Coupling with the acid chloride of ethyl hydrogen heptanedioate followed by Clemmensen reduction and hydrolysis gave tuberculostearic acid (LXXVI). Resolution of the starting alcohol (LXXIII) and again of the intermediate 3-methylundecanoic acid led to the optically active forms. An alternate conversion of the same 2-bromodecane (LXXIV) to tuberculostearic acid proceeded by coupling organozinc derivative LXXVII with the acid chloride of ethyl hydrogen nonanedioate (247). Clemmensen reduction of the resulting keto ester followed by hydrolysis of the ester gave tuberculostearic acid.

Bromo ester LXXIX, the hydrogen bromide addition product from 10-undecenoic acid, has the same features, including the methyl branch, as the first eleven carbon atoms of tuberculostearic acid. The terminal eight-carbon chain was attached by alkylating the β-keto ester LXXVIII with the bromo ester. 12-Oxotuberculostearic acid (LXXX), formed after hydrolysis and decarboxylation, was converted to tuberculostearic acid (LXXVI) by Wolff–Kishner reduction (15).

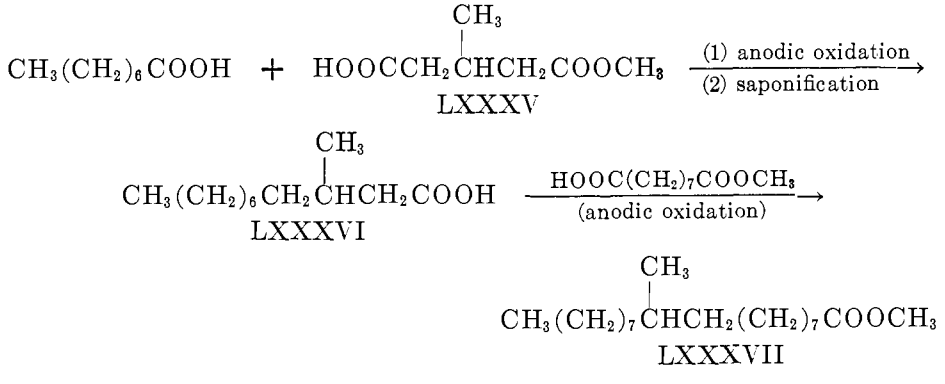


3-Methylglutaric acid was the starting point in two other syntheses of tuberculostearic acid. In one report (269) the acid chloride (LXXXI) of methyl hydrogen glutarate was combined with acetoacetic ester in a standard acylation-deacetylation procedure to yield β-keto ester LXXXII. Alkylation of this β-keto ester with pentyl iodide, followed by saponification and decarboxylation, afforded 5-oxo-3-methylundecanoic acid, which by Clemmensen reduction gave 3-methylundecanoic acid (LXXXIII). This acid was converted to tuberculostearic acid by a series involving acylation, alkylation, and Clemmensen reduction (*cf.* LXXXIII, LXXXIV, and LXXVI). D-, L-, and racemic tuberculo-

stearic acids were obtained in this work by starting, respectively, with the two optically active forms and with the racemic form of methyl hydrogen 3-methylglutarate.



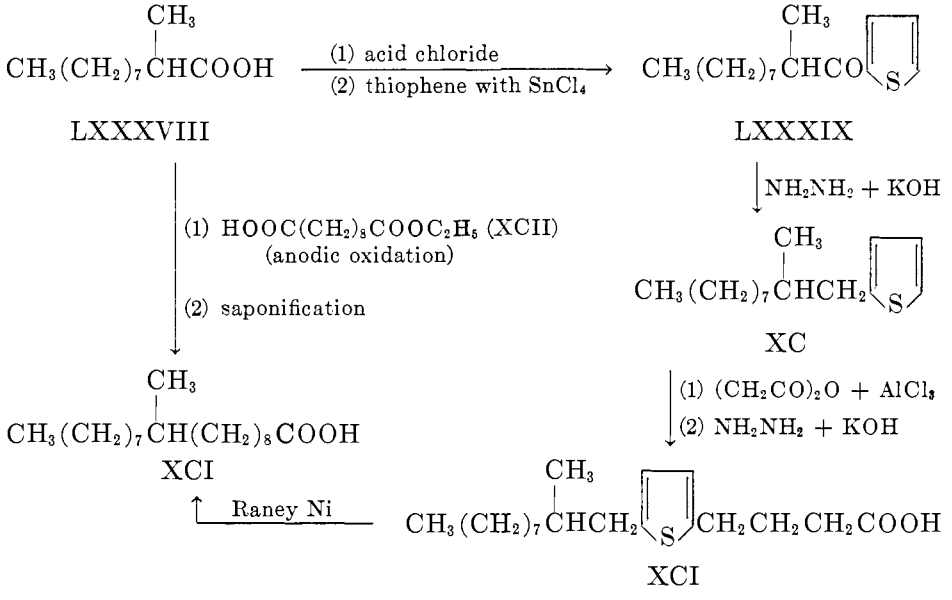
3-Methylglutaric acid could be elaborated to tuberculostearic acid in fewer steps by application of mixed Kolbe electrolyses (196). In the first stage octanoic



acid and methyl hydrogen 3-methylglutarate (LXXXV) were combined to form the cross product, 3-methylundecanoic methyl ester. The second stage com-

bined 3-methylundecanoic acid (LXXXVI) with methyl hydrogen nonanedioate to generate methyl tuberculostearate (LXXXVII). Here, too, the use of optically active methyl hydrogen 3-methylglutarate led to optically active tuberculostearic acid (196).

Comparison of the three paths by which seven carbon atoms were added to 3-methylundecanoic acid (LXXV, LXXXIII, and LXXXVI) in its conversion to tuberculostearic acid is interesting. With azelaic acid readily available, the simplest procedure is clearly the mixed Kolbe reaction. The advantages of the Kolbe method receive further emphasis in the comparison of two pathways by which 2-methyldecanoic acid (LXXXVIII) has been converted to tuberculostearic acid. In one report (278), Friedel–Crafts combination of 2-methyl-



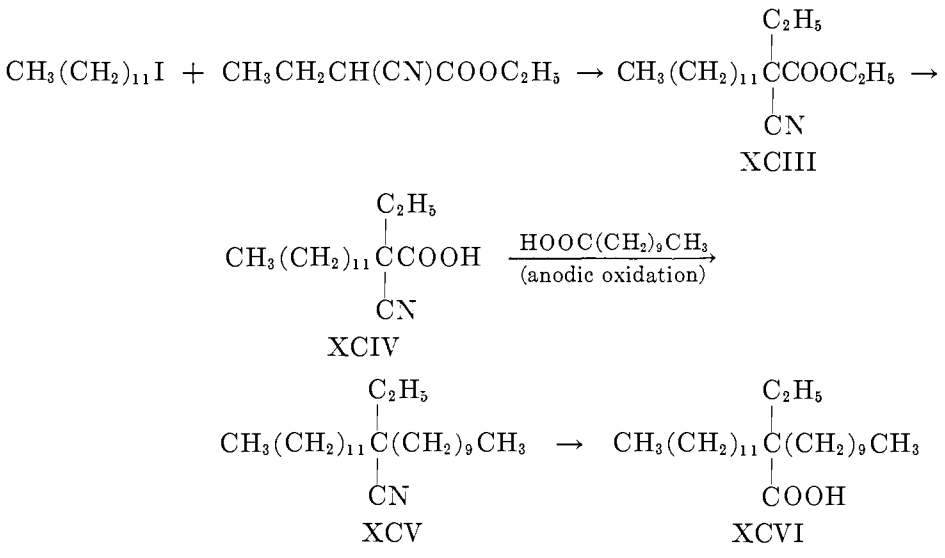
decanoyl chloride with thiophene gave the 2-acylthiophene LXXXIX, which by Wolff–Kishner reduction gave the 2-alkylthiophene XC. Friedel–Crafts reaction with succinic anhydride again followed by Wolff–Kishner reduction led to the disubstituted thiophene XCI. Treatment with excess Raney nickel removed sulfur and gave rise to tuberculostearic acid. This six-stage conversion is less convenient than mixed Kolbe coupling of 2-methyldecanoic acid with ethyl hydrogen sebacate (XCII) (20), which in a single stage led directly to methyl tuberculostearate.

F. "PHTHIOIC" ACID (23)

Phthioic acid is the name originally assigned to one of the fatty acids, $C_{26}H_{52}O_2$, from the tubercle bacillus (12, 267). Each of the several structures proposed was accepted seriously enough and survived long enough to stimulate considerable synthetic work. We find now, accordingly, that a large body of excellent syn-

thetic work, especially on branched-chain acids, owes its existence to *incorrect* structures for phthioic acid.

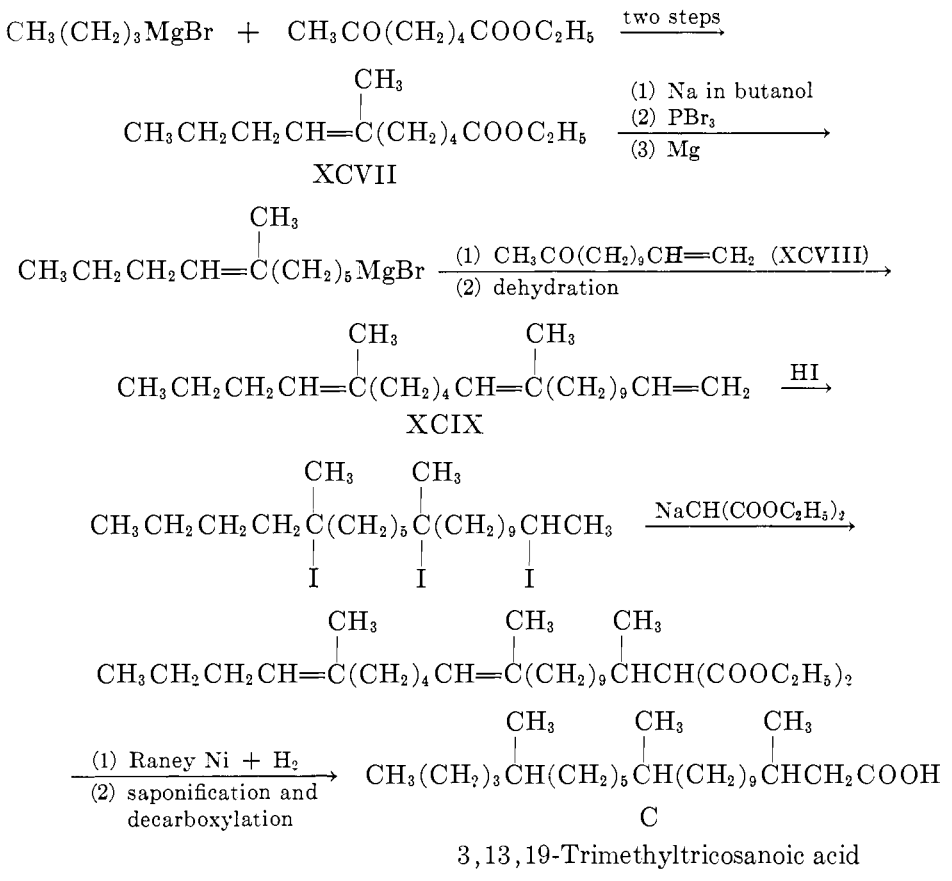
An early suggestion (248, 267) that phthioic acid was a polymethylated fatty acid was challenged on the basis of physical evidence seemingly supporting a bulky molecule, such as a trialkylacetic acid, rather than an extended molecule (270). Among the acids considered was ethyldecyldodecylacetic acid (XCVI), a synthesis of which is given below (18; also *cf.* 16, 17). Alkylation of ethyl-



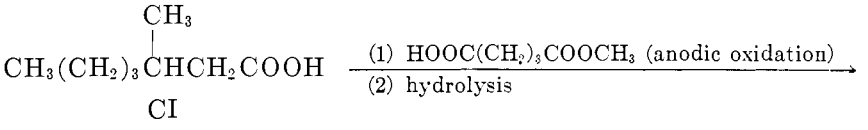
Ethyldecyldodecylacetic acid

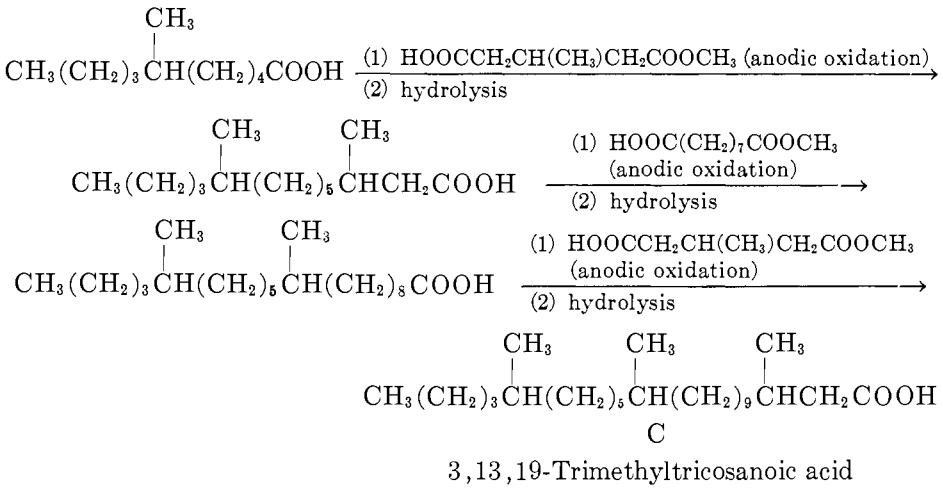
cyanoacetic ester with dodecyl iodide gave a disubstituted cyanoacetic ester (XCIII). The corresponding acid (XCIV), serving as an unusual partner in mixed anodic oxidation with undecanoic acid, gave a trisubstituted acetonitrile (XCV) as the cross product. Hydrolysis in two stages led to the desired ethyldecyldodecylacetic acid (XCVI). Other kinds of syntheses for trisubstituted acetic acids also were developed (e.g., compare 64 and 265). None of the synthetic acids proved to be the same as phthioic acid.

Eventually, continued degradative work led to the conclusion that the proposed trialkylacetic acid structure was untenable, and that phthioic acid was actually 3,13,19-trimethyltricosanoic acid (225). Considerable effort was expended, subsequently, in exploring synthetic approaches. Two syntheses are described below, the first of which may be taken as illustrative of the earlier *modus operandi* of Robinson, Polgar, and their associates (118; also *cf.* 225, 226). Butylmagnesium bromide was added to 6-oxoheptanoic ester, and the resulting tertiary alcohol dehydrated to unsaturated ester XCVII. Bouveault–Blanc reduction furnished the expected alcohol, which was converted to the Grignard derivative via the bromide. Addition of the Grignard derivative to 12-tridecen-2-one (XCVIII) followed by dehydration gave the triene XCIX. The triiodide, formed by addition of hydriodic acid, reacted with sodiomalonate to bring about



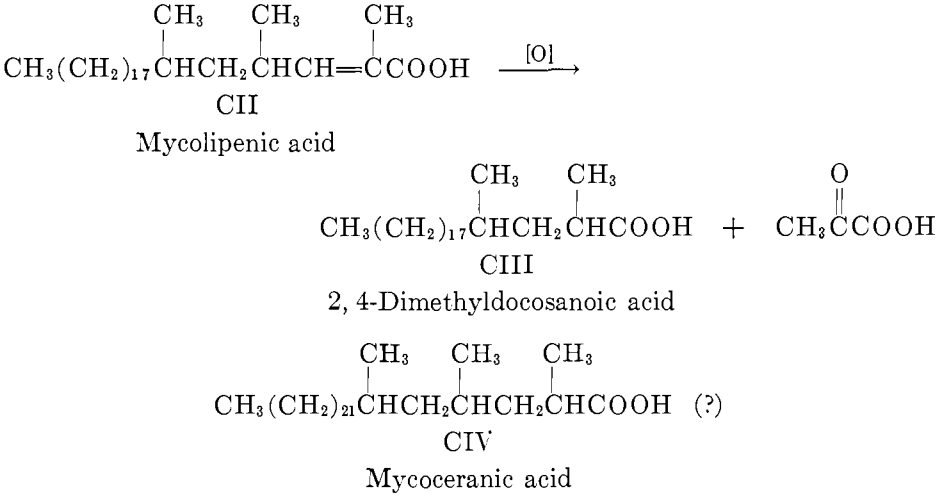
dehydrohalogenation at the two tertiary positions and alkylation of the malonate at the secondary position. The synthesis of 3,13,19-trimethyltricosanoic acid (C) was completed by hydrogenation of the ethylenic bonds, and by the usual saponification and decarboxylation treatment. Uncertainty as to the exact disposition of double bonds in the intermediates was of little consequence, since the final product was saturated. Lack of control of the stereochemistry at the branched positions, however, was more serious. Another method, proceeding by a cumulation of mixed Kolbe couplings, showed promise of overcoming this difficulty (199; also *cf.* 208, 211). By this scheme 3-methylheptanoic acid (CI) was coupled successively with methyl hydrogen glutarate, methyl hydrogen 3-methylglutarate, methyl hydrogen azelate, and again methyl hydrogen 3-methylglutarate to give finally 3,13,19-trimethyltricosanoic acid (C). Introduction of each center of asymmetry was both independent and controllable. This at-





tractive series of reactions, which made attainment of stereochemically homogeneous material feasible, was however not pursued further, for evidence began to accumulate that phthioic acid was not a single substance but a mixture of several substances, possibly of many (82, 84, 93).

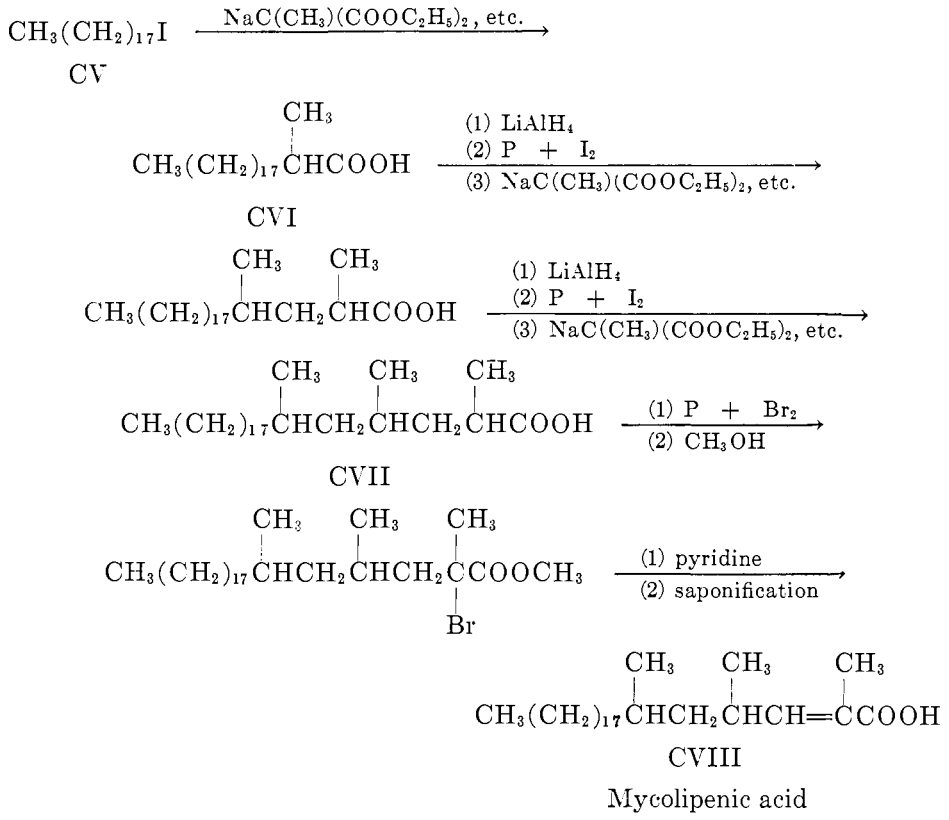
One group of investigators succeeded in isolating an *unsaturated* acid, which was named "mycolipenic acid" (93); another group isolated "C_{27}-phthienoic acid" (75), possibly (27) identical with mycolipenic acid. The assigned structure of mycolipenic acid (CII) rests on degradative evidence (94) and, in part, on synthesis. For example, oxidative cleavage at the double bond gave pyruvic acid as well as a new acid, 2,4-dimethyldocosanoic acid (CIII).



The structure of this last acid appears secure, inasmuch as a synthetic material proved to be identical with the degradation acid (130). "Mycoceranic acid"

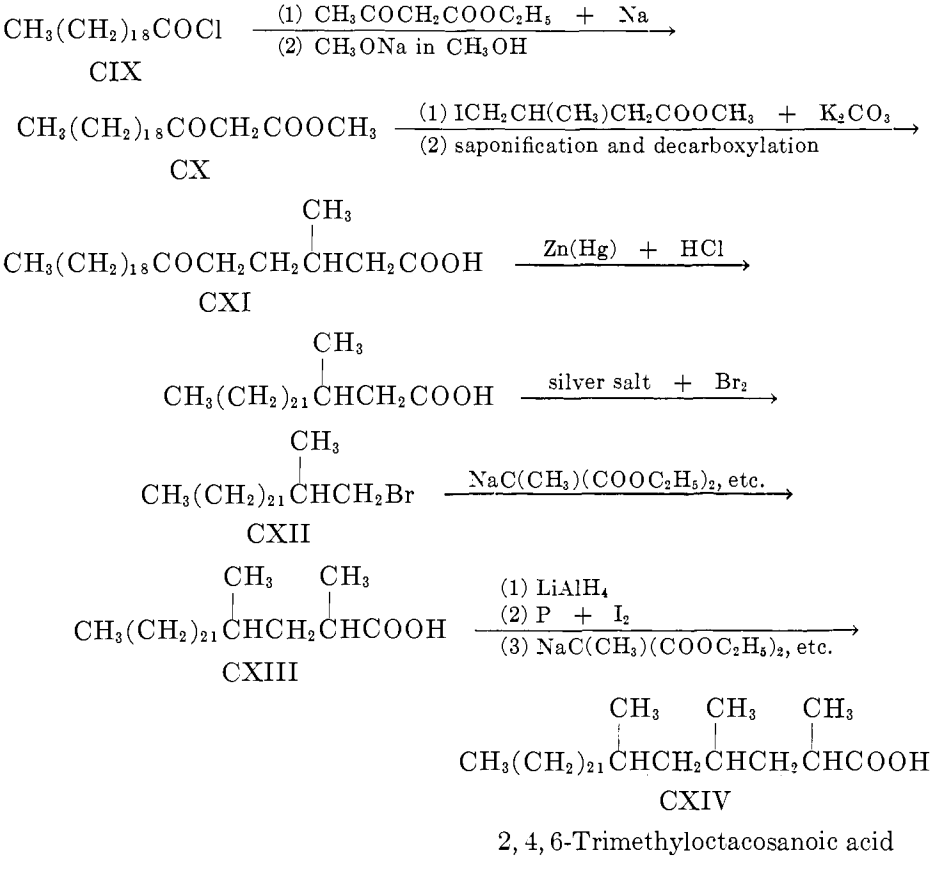
(CIV) (224), another tubercle bacillus acid, was assigned the provisional structure of 2,4,6-trimethyloctacosanoic acid on the basis of degradation studies. From the several papers concerned with synthesis in this field (28, 69, 70, 73, 77, 177; also *cf.* Sections II,O,1, 2, II,Q, and II,A) only three, which are directly pertinent and which illustrate some of the reactions frequently used, have been selected for inclusion here.

A racemic mixture of acids stereoisomeric with, and presumably including, mycolipenic acid has been elaborated from octadecyl iodide (CV) (27). Alkylation of ethyl methylmalonate with this iodide, followed by the usual hydrolysis and decarboxylation, gave 2-methyleicosanoic acid (CVI). The series, reduction with lithium aluminum hydride, iodination with phosphorus and iodine, and malonate extension with methylmalonic ester, when applied twice afforded 2,4,6-trimethyltetracosanoic acid (CVII). Hell–Volhard–Zelinsky bromination on the α-position, followed by esterification, dehydrohalogenation with pyridine, and saponification, introduced the α,β-unsaturation and gave rise to the stereoisomers of 2,4,6-trimethyl-2-tetracosenoic acid (mycolipenic acid) (CVIII).



A mixture of the stereoisomers of 2,4,6-trimethyloctacosanoic acid (CXIV), possibly including mycoceranic acid, has been synthesized from eicosanoic acid

(203). The twenty-carbon acid chloride CIX was converted to the twenty-two carbon β-keto ester CX by combination with acetoacetic ester followed by de-

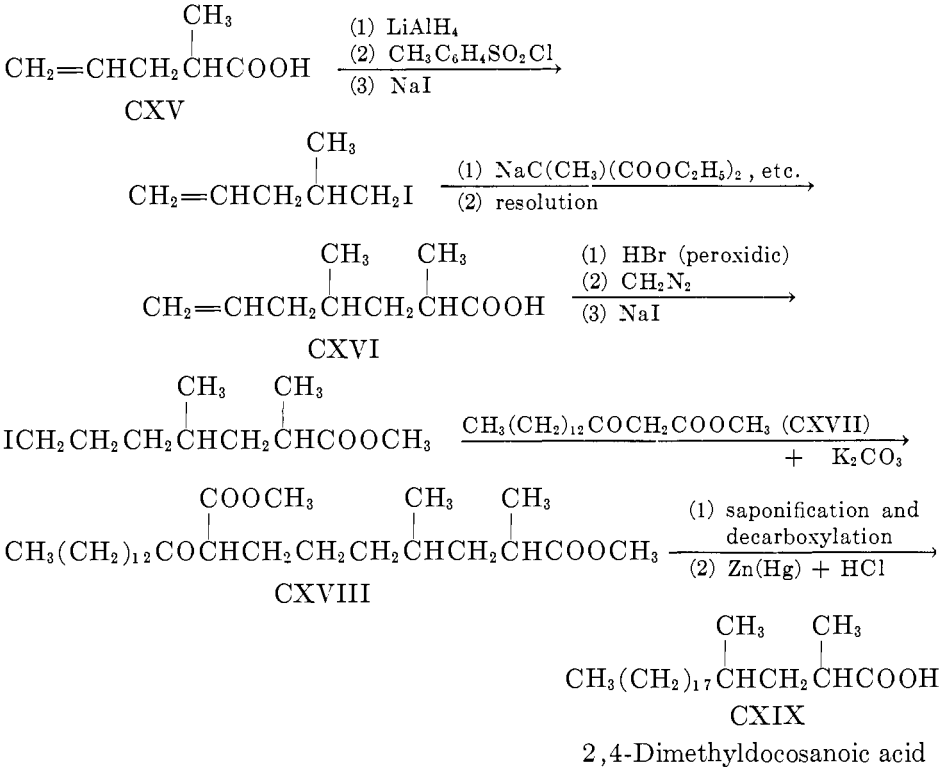


2, 4, 6-Trimethyloctacosanoic acid

acetylation. Alkylation of the β-keto ester with optically active 4-iodo-3-methylbutyric ester (derived from optically active methyl hydrogen 3-methylglutarate) led to optically active 3-methyl-6-oxopentacosanoic acid (CXI). Clemmensen reduction removed the ketone oxygen and gave 3-methylpentacosanoic acid. Decarboxylation of the silver salt with bromine gave the alkyl bromide CXII, which in the malonate process with methylmalonate was converted to 2,4-dimethylhexacosanoic acid (CXIII). Reduction with lithium aluminum hydride, iodination with phosphorus and iodine, and finally alkylation of methylmalonate led to the desired acid (CXIV). The center of asymmetry at the 6-position was in a single stereochemical configuration; both forms of the centers at 2 and at 4 were present. The product mixture could be described therefore as 2,4,6-(D)-trimethyloctacosanoic acid.

Optically active 2,4-dimethyldocosanoic acid (CIII), a key degradation product from mycolipenic acid, was synthesized as follows (130): Optically

active 2-methyl-4-pentenoic acid (CXV) was converted to 2-methyl-4-pentenyl iodide by reduction with lithium aluminum hydride, tosylation of the alcohol,



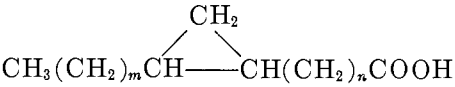
2,4-Dimethyldocosanoic acid

and replacement of the tosyloxy group with iodide. Alkylation of methylmalonate gave 2,4-dimethyl-6-heptenoic acid (CXVI), which on resolution gave the optically pure material. Peroxidic addition of hydrogen bromide formed the ω-bromide. The methyl ester, after conversion to the iodide, was used to alkylate the β-keto ester CXVII. Hydrolysis of the alkylation product (CXVIII), followed by decarboxylation and Clemmensen reduction, gave acid CXIX. Recrystallization with quinine led to dextrorotatory 2,4-dimethyldocosanoic acid, identical with the oxidation product (CIII) from mycolipenic acid. Since the formal synthesis of mycolipenic acid could be completed by its reconstitution from optically active 2,4-dimethyldocosanoic acid, which may now be obtained from degradation as a relay intermediate, and since reliable methods are available for converting RCOOH to RCH=C(CH$_3$)COOH, the prognosis for the successful total synthesis of mycolipenic acid is good.

G. CYCLOALKYL FATTY ACIDS

Syntheses of compounds related to lactobacillic acid (23) and to the antileprosy acids have been reported. Interest in the synthesis of vitamin A, as well as of carotenes in general, has continued unabated.

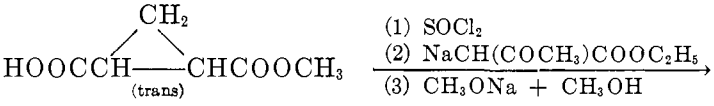
Lactobacillic acid, a C_{19} acid from *Lactobacillus arabinosus*, contains a cyclopropane ring and is thought to have the structure shown in formula CXX (161). One possibility, with $m = n = 7$, has been synthesized starting with *trans*-cyclopropane-1,2-dicarboxylic acid (161) and building outwards from both



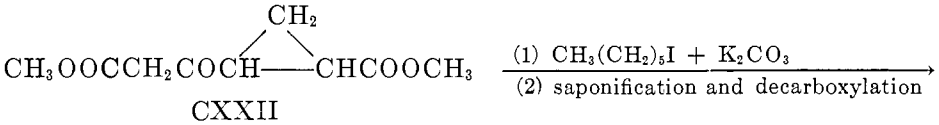
CXX

Lactobacillic acid: $m + n = 14$

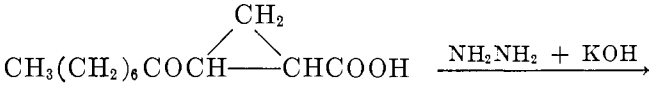
carboxyl groups. The acid chloride of methyl hydrogen *trans*-cyclopropane-1,2-dicarboxylate (CXXI) was used to acylate acetoacetic ester. Deacetylation by methanolysis furnished the β-keto ester CXXII, which on alkylation with hexyl iodide, saponification, and decarboxylation gave the keto acid CXXIII. Wolff–Kishner reduction led to *trans*-2,3-methyleneundecanoic acid (CXXIV). Very



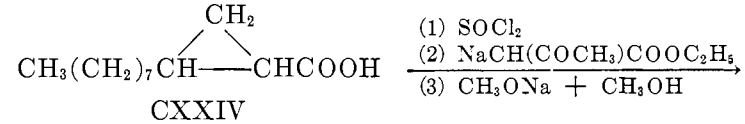
CXXI



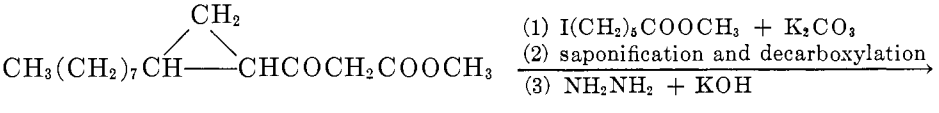
CXXII

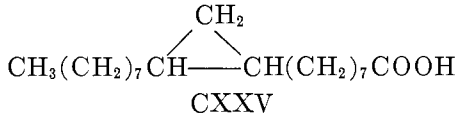


CXXIII



CXXIV





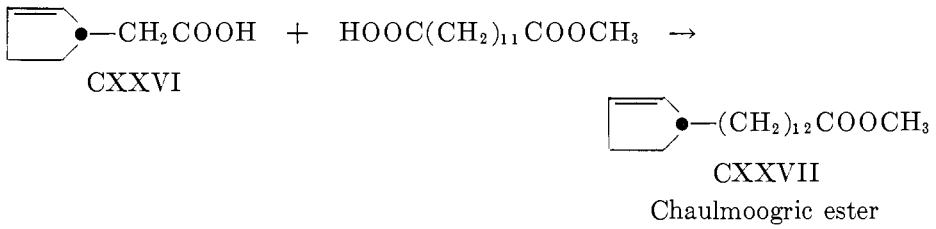
CXXV

trans-9,10-Methyleneoctadecanoic acid

much the same kind of process of first extending the carboxylic acid by two carbon atoms by forming a β-keto ester and then extending the chain further by alkylating the β-keto ester, etc., gave the desired *trans*-9,10-methyleneoctadecanoic acid (CXXV). This compound was not the same as lactobacillic acid, but did

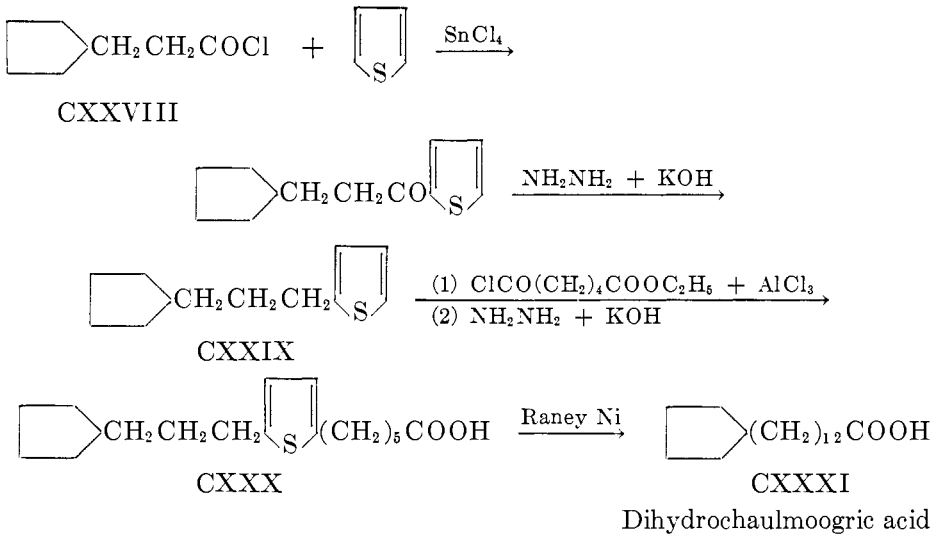
show points of similarity. Further, neither *trans*-11,12-methyleneoctadecanoic acid, prepared by an analogous synthesis, nor *cis*-9,10-methyleneoctadecanoic acid, prepared by hydrogenating sterculic acid, a cyclopropene acid, was identical with lactobacillic acid.

Chaulmoogric acid (207) and other cycloalkyl and cycloalkenyl fatty acids (183, 212, 296) have been prepared by mixed Kolbe couplings. For example,



dextrorotatory 2-cyclopenteneacetic acid (CXXVI) anodically oxidized with methyl hydrogen tridecanedioate gave dextrorotatory chaulmoogric ester (CXXVII), identical with the natural product (207). This synthesis showed that the configuration in natural chaulmoogric acid and that in cyclopentenylacetic acid (CXXVI) are the same. Accordingly, determination of the configuration in the latter established the configuration of chaulmoogric acid, as indicated in formula CXXVII.

Thiophene intermediates were involved in new syntheses of dihydrochaulmoogric acid and related compounds (65). Formulas CXXVIII to CXXXI show how 2-(cyclopentylpropyl)thiophene (CXXIX) was prepared from cyclopentylpropionyl chloride and thiophene by Friedel–Crafts acylation followed by

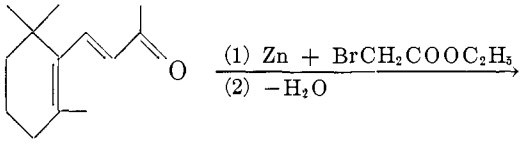


Wolff–Kishner reduction. Disubstituted thiophene CXXX was prepared by acetylating cyclopentylpropylthiophene with the acid chloride of ethyl hydrogen adipate and again removing the acyl oxygen with hydrazine and potassium

hydroxide. Desulfurization with Raney nickel (Section II,H) furnished dihydrochaulmoogric acid (CXXXI).

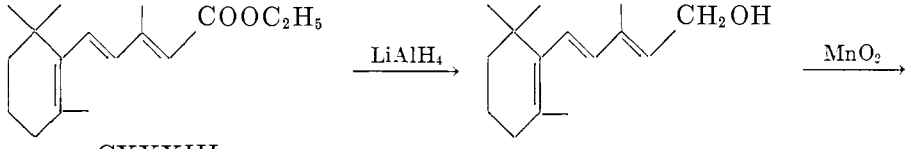
For the present purpose, the various syntheses of vitamin A may be looked upon as extensions of a methyl-substituted chain by methods eventually providing a geometrically correct conjugated system terminating in an oxygen function. In this light, much if not all of the extensive synthetic work on vitamin A (and, in general, on carotenoids) is of immediate or potential interest in the synthesis of cyclic, branched, unsaturated, or saturated fatty acids. However, because reviews of vitamin A and of carotenoids are available (35, 54, 172, 181, 251), illustrations of only two syntheses will be given.

In one preparation of vitamin A, two carbon atoms were added to β-ionone (CXXXII) by Reformatsky addition of bromoacetic ester followed by loss of

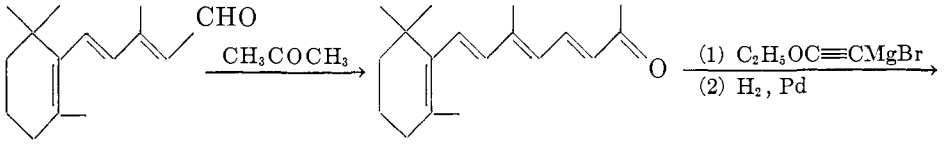


CXXXII

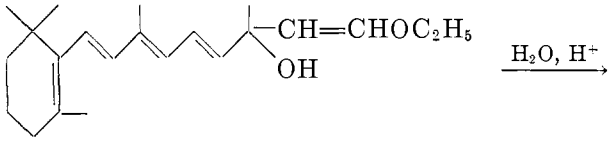
β-Ionone

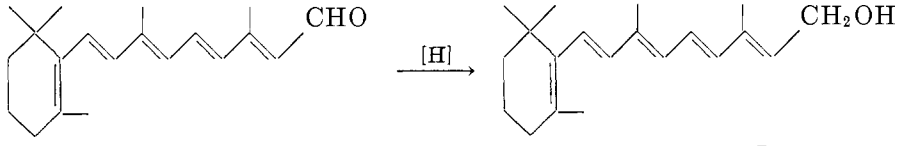


CXXXIII



CXXXIV CXXXV





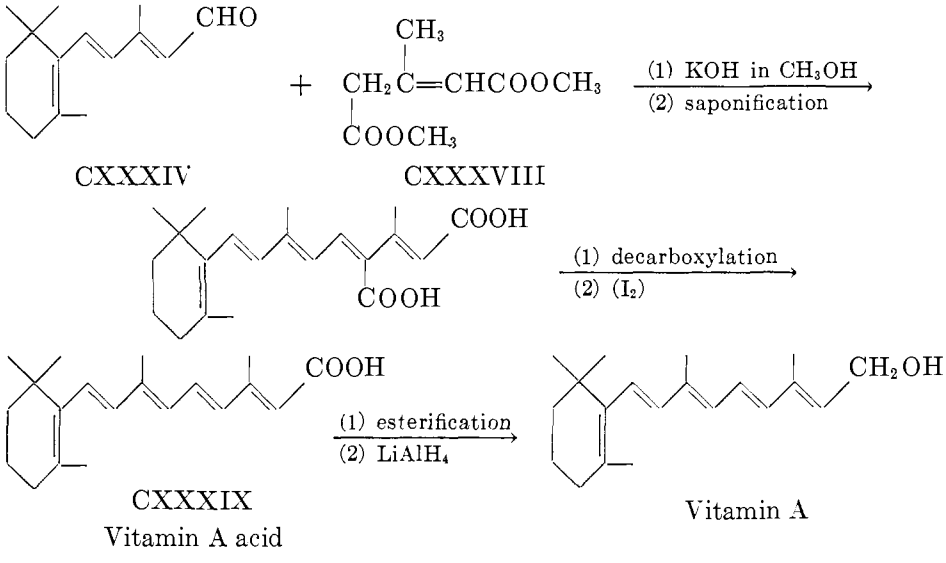
CXXXVI
Vitamin A aldehyde

CXXXVII
Vitamin A

water. The resulting fifteen-carbon ester (CXXXIII) was converted to the corresponding fifteen-carbon aldehyde (CXXXIV) by reduction with lithium aluminum hydride followed by reoxidation with manganese dioxide. Aldehyde

CXXXIV, condensed with acetone, afforded an eighteen-carbon methyl ketone (CXXXV). Addition of ethoxyacetylenemagnesium bromide, half-hydrogenation of the product to the vinyl ether, and hydrolysis in aqueous acid gave vitamin A aldehyde (CXXXVI), which on reduction gave vitamin A (CXXXVII).

In another synthesis (242) the fifteen-carbon aldehyde CXXXIV was extended by one isoprene unit by alkali-catalyzed condensation with dimethyl 3-methylglutaconate (CXXXVIII) followed by decarboxylation. The single cis bond in the product was isomerized under iodine catalysis to the all-trans vitamin A acid (CXXXIX), which was then reduced with lithium aluminum hydride to vitamin A.



H. HYDROXY ACIDS

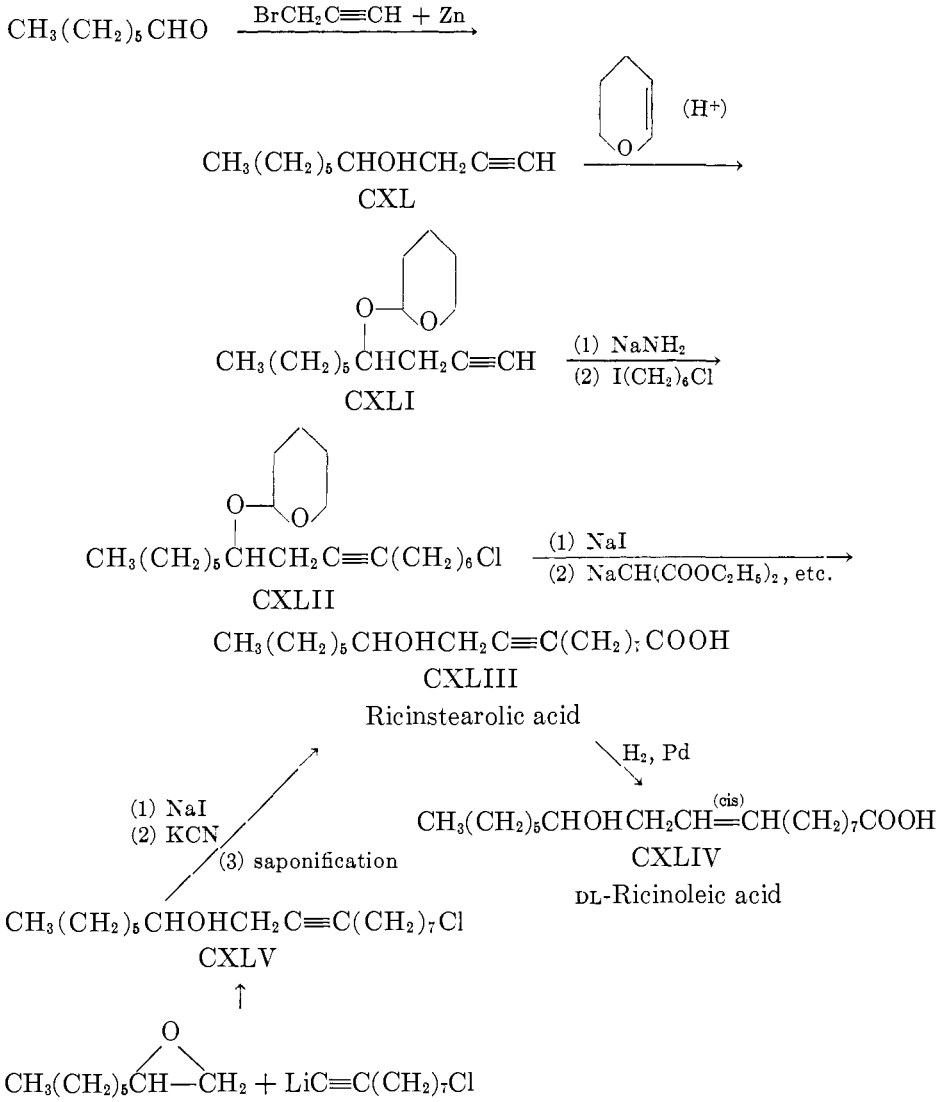
Activity in synthetic work on hydroxy acids has been considerable. Syntheses of, or relating to, ricinoleic acid, phloionolic acid, 9,10-dihydroxystearic acid, and mycolic acids have been reported. General methods for the preparation of β-hydroxy acids have been developed and exploited. All seventeen of the hydroxystearic acids have been made available. Synthetic pathways leading to unsaturated acids by way of intermediate hydroxy acids have been explored. Stereospecific conversion of vicinal glycols to ethylenic compounds (Section II,O,5) was found to be both general and useful.

The broad topic of oxygen-substituted fatty acids, including hydroxy acids, has been ably summarized by Swern (275).

1. Ricinoleic acid

Ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid) (CXLIV) has been synthesized. According to one report (113), heptaldehyde and propargyl bromide were combined in a Reformatsky-like process to form 1-decyn-4-ol (CXL). The hydroxyl hydrogen was replaced with the tetrahydropyran group, and the re-

sulting terminal acetylenic derivative (CXLI) combined with 1-chloro-6-iodohexane in the usual manner. The iodide corresponding to the sixteen-carbon chloride CXLII was converted to ricinstearolic acid (CXLIII) by the application of the malonate synthesis supplemented by mild acid treatment to expose the alcohol group. Half-hydrogenation of ricinstearolic acid gave racemic ricinoleic acid (CXLIV). Ricinstearolic acid (CXLIII) could also be obtained (133) by adding the lithium derivative of 9-chloro-1-nonyne to 1,2-epoxyoctane. The intermediate CXLV was converted to ricinstearolic acid by the nitrile synthesis.



Another synthesis was characterized by operations on the carboxyl side of the molecule instead of on the methyl side (184). Coupling of 8-chloro-1-octyne

(CXLVI) with bromoacetal gave the acetylenic acetal CXLVII. The cis ethylenic aldehyde CXLVIII was obtained by half-hydrogenation followed by acid-catalyzed hydrolysis of the acetal grouping. Addition of hexylmagnesium bromide to the aldehyde developed the β-hydroxy olefin system as in CXLIX, and extension of the chain by application of the malonate process led to ricinoleic acid (CL).

$$\underset{\text{CXLVI}}{HC{\equiv}C(CH_2)_6Cl} \xrightarrow[(2)\ BrCH_2CH(OCH_3)_2]{(1)\ LiNH_2}$$

$$(CH_3O)_2CHCH_2C{\equiv}C(CH_2)_6Cl \xrightarrow[(2)\ H_2O,\ H^+]{(1)\ H_2,\ Pd}$$

$$\underset{\text{CXLVII}}{}$$

$$O{=}CHCH_2\overset{(cis)}{CH{=}CH}(CH_2)_6Cl \xrightarrow{CH_3(CH_2)_5MgBr}$$

$$\underset{\text{CXLVIII}}{}$$

$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_6Cl \xrightarrow[(2)\ NaCH(COOC_2H_5)_2,\ \text{etc.}]{(1)\ NaI}$$

$$\underset{\text{CXLIX}}{}$$

$$\underset{\text{CL}}{CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH}$$

DL-Ricinoleic acid

2. 9,10-Dihydroxystearic acid

Phloionic acid (9,10-dihydroxyoctadecanedioic acid), from cork, was proved by synthesis (140) and by resolution (141) to have the threo configuration. The half-ester (CLI) of phloionic acid was converted to 9,10,18-trihydroxystearic acid (CLII), which by selective tosylation on the primary hydroxyl, replacement

$$C_2H_5OOC(CH_2)_7\overset{(threo)}{\underset{OH}{CH}}-\underset{OH}{CH}(CH_2)_7COOH \xrightarrow{Na\ +\ C_2H_5OH}$$

$$\underset{\text{CLI}}{}$$

$$HO(CH_2)_8\overset{OH}{CH}-\overset{OH}{CH}(CH_2)_7COOH$$

$$\underset{\text{CLII}}{}$$

$$\xrightarrow[(3)\ Zn\ +\ acid]{\substack{(1)\ CH_3C_6H_4SO_2Cl\ \text{in pyridine}\\(2)\ NaI}} \underset{\text{CLIII}}{CH_3(CH_2)_7\overset{OH}{CH}-\overset{OH}{CH}(CH_2)_7COOH}$$

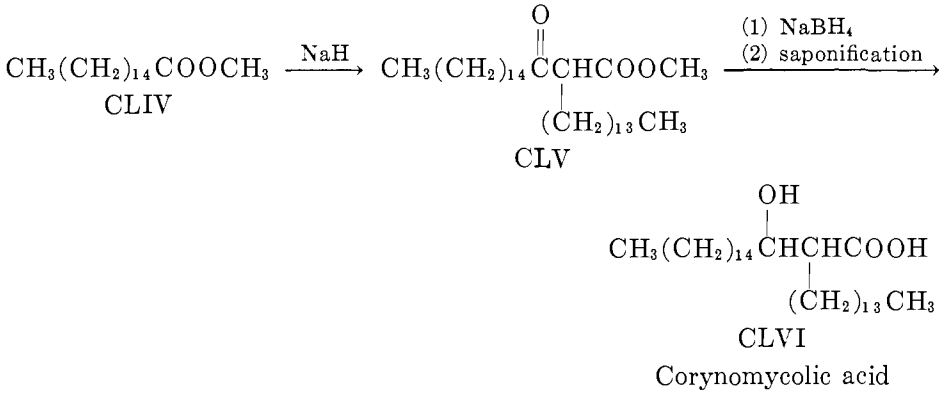
threo-9,10-Dihydroxystearic acid

of the tosyloxy group by iodide, and dehalogenation with zinc gave 9,10-dihydroxystearic acid (CLIII), m.p. 94–95°C. Since the configuration at the 9- and 10-positions was not disturbed, these conversions established the threo nature of "low-melting" 9,10-dihydroxystearic acid. Arguments have been presented

(141) that the structure of phloionolic acid, also isolated from cork, may not be that of 9,10,18-trihydroxystearic acid (CLII).

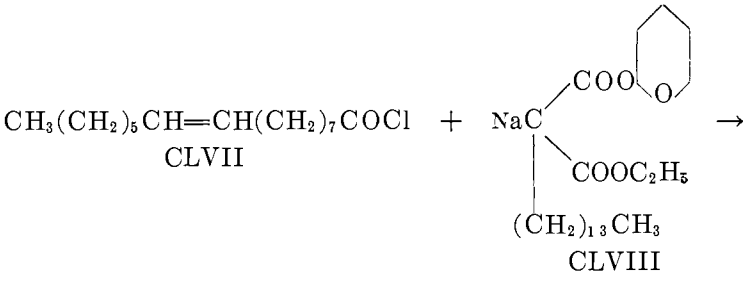
3. Corynomycolic and related acids (23)

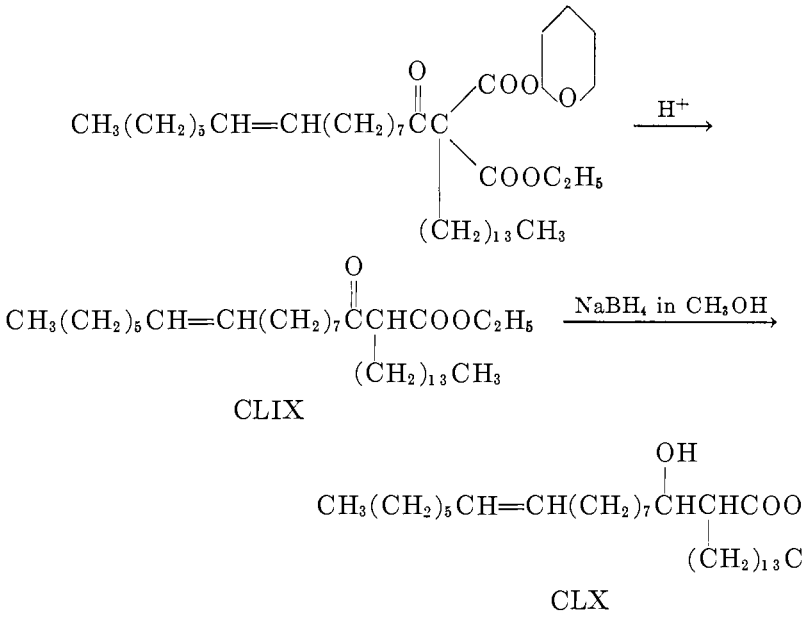
Corynomycolic acid, $C_{32}H_{64}O_3$, has been isolated from the lipide from *Corynebacterium diphtheriae*. This fatty acid has structural features in common with various "mycolic acids" from *Mycobacteria*: namely, a long chain at the α-position and hydroxyl at the β-position. The synthesis of corynomycolic acid described below (191, 227) is illustrative of considerable work on the mycolic acids and related compounds. β-Keto ester CLV was obtained by Claisen condensation



(with sodium hydride) of methyl palmitate (CLIV). Reduction of the keto group with sodium borohydride or with hydrogen over a catalyst led to the β-hydroxy ester, which on saponification gave hydroxy acid CLVI. Separation of the two racemates was effected either at the hydroxy ester or hydroxy acid stage by recrystallization and chromatography. One of the racemates proved to be *dl*-corynomycolic acid (CLVI). Homologation of this material was possible by the Arndt–Eistert method (123) (see Section II,A).

β-Keto esters derived formally from two different esters were formed by applying a scheme developed by Bowman and Fordham (see Section II,J,2). For example, keto ester CLIX was prepared by acylating malonic acid derivative CLVIII with acid chloride CLVII, and exposing the product to the action of mild aqueous acid. Sodium borohydride reduction gave hydroxy ester CLX, which showed an infrared absorption spectrum identical with that of methyl corynomycolenate (230; also *cf.* 123).

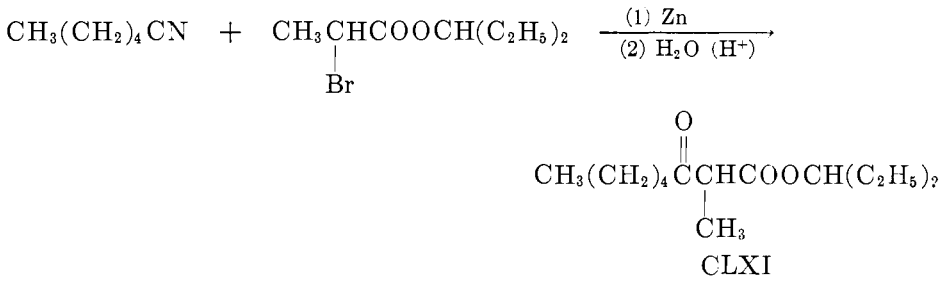




CLIX

CLX

A reaction of potential usefulness for the preparation of such compounds as CLIX carries out a zinc condensation of an α-bromo ester not with an aldehyde or ketone as in the familiar Reformatsky process, but with a nitrile (81). In this way, for example, capronitrile with α-bromopropionic ester gave the α-methyl β-keto ester CLXI. Bulky groups in the bromo ester, either in the alkyl attached to the carboxyl group or in the α-position, promoted the process instead of hindering it.

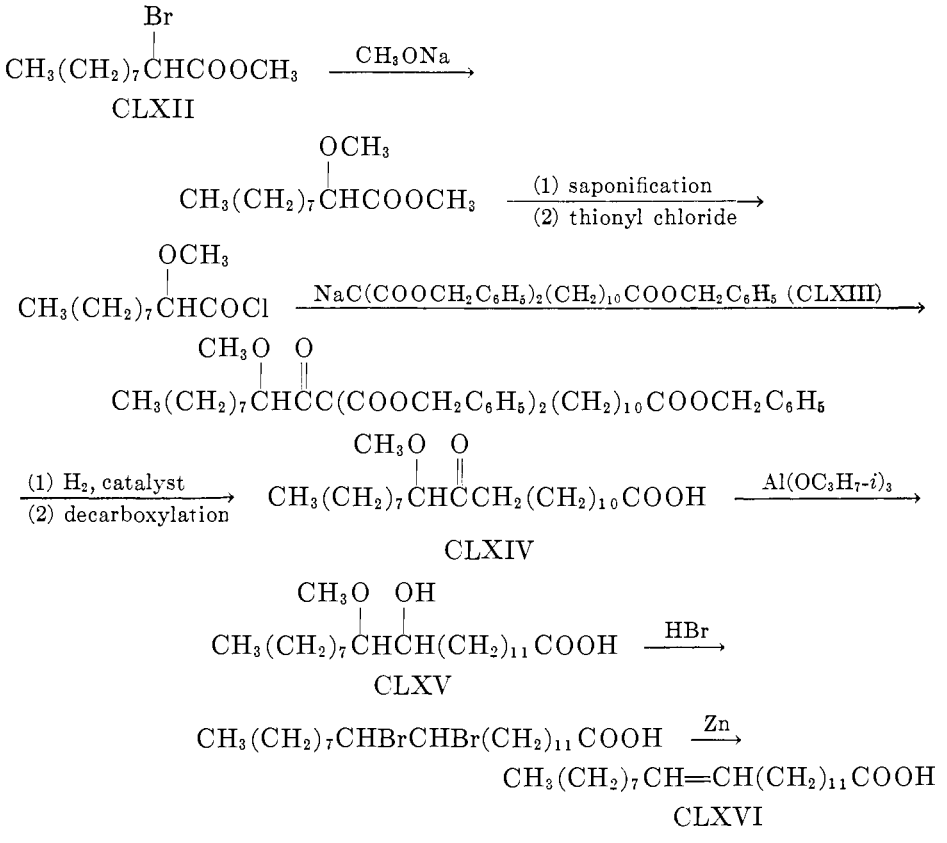


CLXI

4. Hydroxy acids prepared according to Ames and Bowman: utilization of such acids for the introduction of ethylenic unsaturation

Two methods have been developed for the synthesis of vicinal dihydroxy acids and monomethoxylated vicinal dihydroxy acids. Such compounds can be converted by standard processes to olefinic acids (Section II,O,5). The synthesis of brassidic and erucic acids (*trans*- and *cis*-13-docosenoic acids (CLXVI)) via a vicinal methoxy hydroxy intermediate will illustrate one of the methods (52). Methyl 2-bromodecanoate (CLXII), obtained by the bromination of decanoic acid, was converted to 2-methoxydecanoyl chloride, and then by way of the

substituted malonic ester (CLXIII) to 14-methoxy-13-oxodocosanoic acid (CLXIV) according to the method described in Section II,J,2. Reduction of this ketone with aluminum isopropoxide gave a mixture of two stereoisomeric 13-hydroxy-14-methoxydocosanoic acids (CLXV). In this case (but not in all) the two forms could be separated by fractional crystallization. Hydrogen bromide converted the individual methoxy alcohols to the corresponding 13,14-dibromodocosanoic acids, which by debromination with zinc gave brassidic and erucic

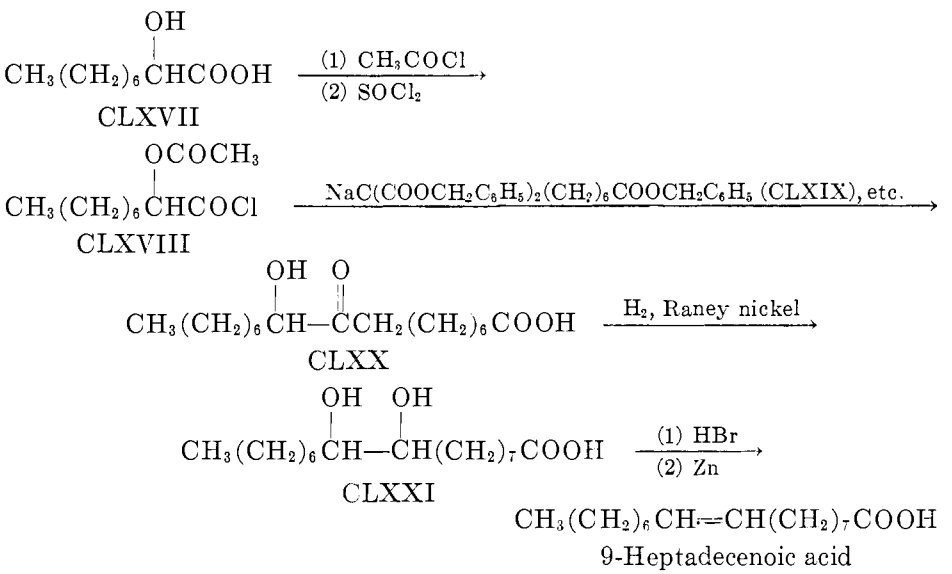


Brassidic and erucic acids

acids (CLXVI). In much the same way 2-methoxydecanoic acid was combined with the tribenzyl ester of heptane-1,1,7-tricarboxylic acid to give eventually oleic and elaidic acids (8; also *cf.* 9).

The second method (8) makes use not of the methoxy acid but of the acetoxy acid, and, although closely related to the method just described, is somewhat more attractive because of more convenient stereochemical control. The synthesis of pure *cis*-9-heptadecenoic and *trans*-9-heptadecenoic acids proceeded by reaction of 2-hydroxynonanoic acid (CLXVII) (from the 2-bromo acid) first with acetyl chloride to give the 2-acetoxy acid and then with thionyl chloride to give the acid chloride (CLXVIII). Combination of the acid chloride with sub-

stituted malonic ester (CLXIX), followed by hydrogenolysis, loss of two molecules of carbon dioxide, and deacetylation gave 10-hydroxy-9-oxoheptadecanoic

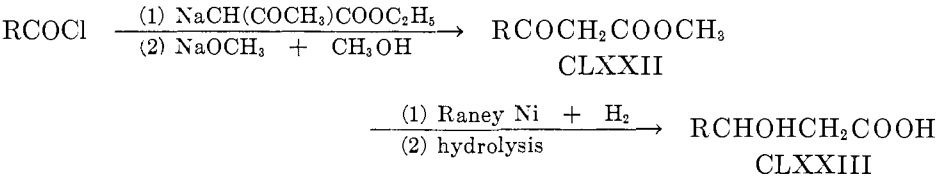


acid (CLXX). A mixture of two dihydroxy acids (CLXXI) was obtained on reduction either with hydrogen and Raney nickel or with aluminum isopropoxide. However, separation of the two solid forms by fractional crystallization was straightforward. Treatment of the pure threo and the pure erythro dihydroxy acids (CLXXI) with hydrobromic acid to form the homogeneous dibromides, and then with zinc to bring about debromination, produced pure *trans*-9-heptadecenoic and *cis*-9-heptadecenoic acids, respectively.

5. Miscellaneous hydroxy acids

β-Hydroxy acids have been prepared by Reformatsky coupling of α-bromo esters and carbonyl compounds (*cf.* 59, 80, 83, 104, 150, 169, 176, 177, 209, 242). For example, a series of β-hydroxy α-methyl acids, β-hydroxy β-methyl acids, and β-hydroxy α,β-dimethyl acids was made available (59) by zinc condensation of aldehydes and α-bromopropionic ester, of methyl ketones and bromoacetic ester, and of methyl ketones and α-bromopropionic ester, respectively.

Skogh (258) has prepared β-hydroxy acids by hydrogenating the corresponding β-keto ester (i.e., CLXXII to CLXXIII). The keto esters were obtained by acylating acetoacetic ester with a straight-chain acid chloride and then deacetylating (see Section II,J,1). In the accompanying formulas R ranges from



pentyl to heneicosyl, so that all linear β-hydroxy acids from C_8 to C_{24} were prepared. Further examples of the preparation of β-hydroxy esters from β-keto esters will be found in Section III,H,3.

Mixed Kolbe electrolysis of fatty acids with optically active methyl hydrogen 3-acetoxyglutarate (CLXXIV) (253) or with 3-acetoxy-3-carbethoxypropionic acid (162b) has been found possible. Since optically active β-hydroxy and α-hydroxy acids, respectively, are obtained, the difficult resolution of racemic hydroxy acids for the preparation of the optically active forms is obviated. Also of considerable interest is the possibility of directly correlating configuration

$$CH_3(CH_2)_5COOH + HOOCCH_2\underset{\displaystyle OCOCH_3}{\underset{|}{C}}HCH_2COOCH_3 \xrightarrow[(2)\ \text{hydrolysis}]{(1)\ \text{anodic oxidation}} CH_3(CH_2)_6\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOH$$

CLXXIV (optically active); product: (optically active)

and rotation. Other hydroxy acids have been formed by the Kolbe method (Section II,M).

The formation of vicinal dihydroxy acids by the hydroxylation of ethylenic acids by means of per acids is probably the most common and the most satisfactory method now available (*cf.* 188, 274). The triple bond is relatively resistant to the action of per acids, so that selective hydroxylation of the ethylenic unsaturation in an enynoic acid such as ximenynic acid (CLXXV) becomes possible (147, 149).

$$CH_3(CH_2)_5CH{=}CHC{\equiv}C(CH_2)_7COOH \xrightarrow{HCOOOH} CH_3(CH_2)_5CHOHCHOHC{\equiv}C(CH_2)_7COOH$$

CLXXV, Ximenynic acid; 11,12-Dihydroxy-9-octadecynoic acid

An impressive work has made all the monohydroxystearic acids available (36). Most of the acids were prepared by Raney nickel hydrogenation of the corresponding keto acids, which in turn were obtained either from acetoacetic ester by acylation-deacetylation procedures (Section II,J,1) or by the dialkylcadmium method (Section II,I). 2-Hydroxystearic acid was formed by the alkaline hydrolysis of 2-bromostearic acid (*cf.* 190, 203b). 18-Hydroxystearic acid (CLXXVII) was formed by Raney nickel desulfurization and reduction of derivative CLXXVI of octadecanedioic acid.

$$HOOC(CH_2)_{16}COOCH_3 \xrightarrow[(2)\ C_2H_5SH]{(1)\ SOCl_2} C_2H_5SCO(CH_2)_{16}COOCH_3 \xrightarrow{\text{Raney Ni}} HO(CH_2)_{17}COOH$$

CLXXVI; CLXXVII

The *trans* and *cis*-9,10-epoxystearic acids are available from oleic or elaidic acid, respectively, by reaction with per acids. In a reaction of unusual selectivity, hydrogenolysis over palladium in acetic acid furnishes *only* 10-hydroxystearic acid (202).

15,16-Dihydroxypalmitic acid (ustilic acid A), a fermentation product from *Ustilago zeae*, has been utilized effectively in the syntheses of several 15-keto fatty acids, as well as of 15-methylpalmitic acid. Advantage is taken of the easily oxidized vicinal dihydroxy grouping to convert the distal end of the starting material to the carboxyl group of the product (115a).

I. ELEOSTEARIC ACID AND OTHER ACIDS WITH CONJUGATED UNSATURATION

α-Eleostearic acid (*cis*-9,*trans*-11,*trans*-13-octadecatrienoic acid), from tung oil, has been synthesized as follows (112): The diunsaturated alcohol CLXXVIII was obtained from the Reformatsky condensation of *trans*-2-decenal and propargyl bromide. After a third unsaturation (as in CLXXIX) was introduced by transforming the hydroxyl group to chloride, and then dehydrochlorinating with 20 per cent alcoholic potassium hydroxide, application of the Ahmad and

$$CH_3(CH_2)_3\overset{(trans)}{CH}{=}CHCHO \xrightarrow[Zn]{BrCH_2C{\equiv}CH}$$

$$CH_3(CH_2)_3CH{=}CHCHOHCH_2C{\equiv}CH \quad \text{CLXXVIII} \xrightarrow[(2)\ KOH]{(1)\ PCl_3}$$

$$CH_3(CH_2)_3CH{=}CHCH{=}CHC{\equiv}CH \quad \text{CLXXIX} \xrightarrow[(2)\ I(CH_2)_7Cl]{(1)\ NaNH_2}$$

$$CH_3(CH_2)_3CH{=}CHCH{=}CHC{\equiv}C(CH_2)_7Cl \xrightarrow[(2)\ KOH]{(1)\ NaI,\ NaCN}$$

$$CH_3(CH_2)_3\overset{(trans)}{CH}{=}CHCH\overset{(trans)}{=}CHC{\equiv}C(CH_2)_7COOH \quad \text{CLXXX} \xrightarrow{H_2,\ Pd}$$

$$CH_3(CH_2)_3\overset{(trans)}{CH}{=}CHCH\overset{(trans)}{=}CHCH\overset{(cis)}{=}CH(CH_2)_7COOH$$

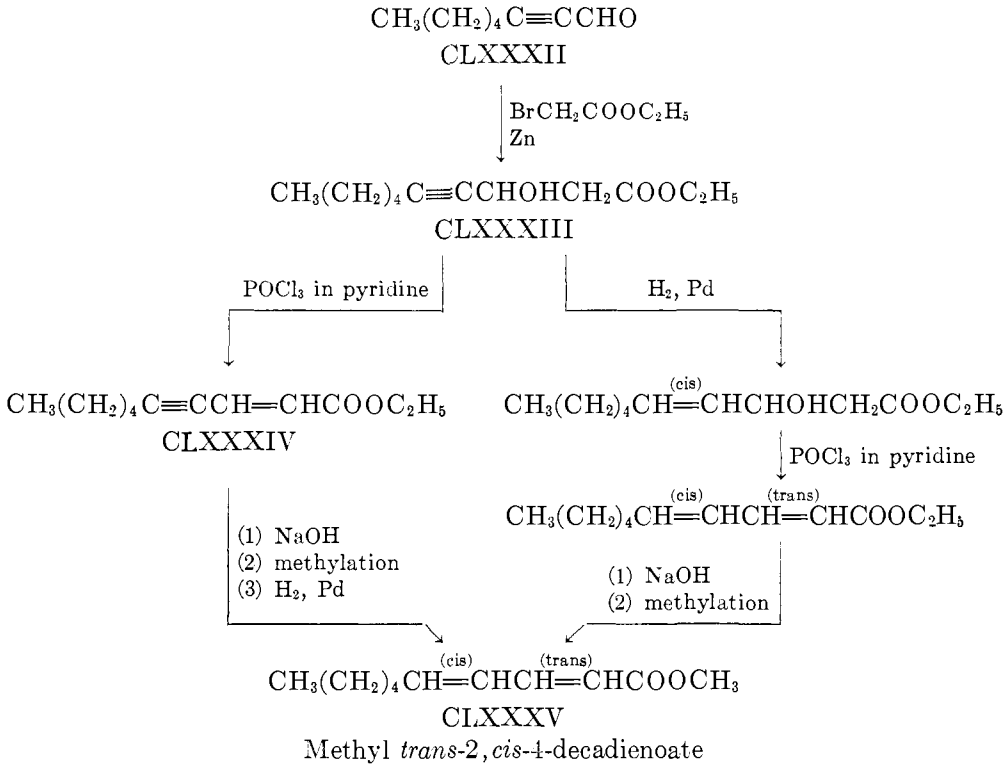
CLXXXI

α-Eleostearic acid

Strong reactions led to acid CLXXX. The unsaturation at position 11, generated by dehydrohalogenation, was obtained in two geometric forms. However, purification at the acid stage by clathrate formation led to homogeneous *trans*-11,*trans*-13-octadecadien-9-ynoic acid (CLXXX). Half-hydrogenation over the Lindlar catalyst gave a mixture from which, after crystallization, α-eleostearic acid (CLXXXI) could be isolated.

The conjugation in α-eleostearic acid is the result of an elimination process. Other more or less closely related processes have been reported. For example, in the synthesis of *trans*-2,*cis*-4-decadienoic methyl ester (CLXXXV), Reformatsky addition of bromoacetic ester to 2-octynal (CLXXXII) gave β-hydroxy

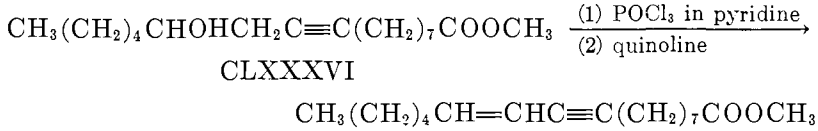
ester CLXXXIII. Dehydration introduced a trans α,β double bond, as in CLXXXIV, and half-hydrogenation produced the conjugated 2-*trans*,4-*cis* system, as in CLXXXV. Alternately, hydrogenation of CLXXXIII before dehydration gave the expected cis ethylenic compound, which with phosphorus

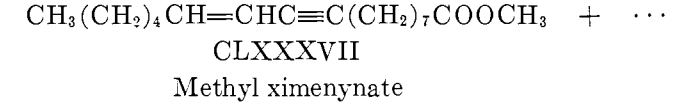


Methyl *trans*-2,*cis*-4-decadienoate

oxychloride in pyridine was dehydrated to the 2-*trans*,4-*cis* compound containing appreciable amounts of the 2-*trans*,4-*trans* isomer (104).

Methyl ricinstearolate (CLXXXVI) reacts with phosphorus oxychloride or with thionyl chloride to yield the corresponding chloro compound. This with





Methyl ximenynate

boiling quinoline or with alcoholic potassium hydroxide gave a mixture containing approximately 75 per cent of the conjugated ene-yne compound CLXXXVII, which proved to be the same as methyl ximenynate (113, 147). Castor oil or methyl ricinoleate treated first with thionyl chloride and then with alcoholic

potassium hydroxide gives *trans*-9,*trans*-11-octadecadienoic derivatives, geometric isomerization occurring as well as dehydrochlorination (147). Direct dehydration of the ricinoleic compounds produces more than twice as much nonconjugated product as conjugated product (228). Allylic bromination of ethylenic and acetylenic acids with *N*-bromosuccinimide followed by dehydrobromination gives mixtures from which acids containing conjugated unsaturation can be isolated (204, 216; also *cf.* Section II,O,1).

Two of the four possible isomers of 3,5-tridecadienoic acid were prepared according to the accompanying formulations (92). Here, nonynylmagnesium bromide with acrolein gave carbinol CLXXXVIII. This carbinol when treated first with phosphorus tribromide and then with cuprous cyanide formed the thirteen-carbon nitrile, which was converted to the methyl ester of *trans*-3-tridecen-5-ynoic acid (CLXXXIX). Half-hydrogenation over the Lindlar catalyst

$$CH_3(CH_2)_6C{\equiv}CMgBr \xrightarrow{CH_2{=}CHCHO}$$

$$CH_3(CH_2)_6C{\equiv}CCHOHCH{=}CH_2 \xrightarrow{PBr_3}$$

CLXXXVIII

$$CH_3(CH_2)_6C{\equiv}C\overset{(trans)}{C}H{=}CHCH_2Br \xrightarrow[(2)\ CH_3OH + HCl(H_2O)]{(1)\ CuCN}$$

$$CH_3(CH_2)_6C{\equiv}CCH{=}CHCH_2COOCH_3 \xrightarrow{H_2,\ Pd}$$

CLXXXIX

$$CH_3(CH_2)_6\overset{(cis)}{C}H{=}CHC\overset{(trans)}{H}{=}CHCH_2COOCH_3$$

CXC

Methyl *trans*-3,*cis*-5-tridecadienoate

furnished the desired conjugated ester, methyl *trans*-3,*cis*-5-tridecadienoate (CXC). The *trans*-3,*trans*-5 form was obtained by isomerization with iodine and light. Other conjugated systems have been synthesized in a related manner (e.g., 45, 159; also *cf.* Sections II,A and II,B).

The conversion of conjugated ene-ynes, such as CLXXX, CLXXXIV, and CLXXXIX, to conjugated dienes by half-hydrogenation appears to be a useful general method, although both stereospecificity and selectivity may be poor. Other examples of such half-hydrogenations, as well as half-hydrogenations of conjugated diynes, are available. Thus ximenynic acid (CLXXXVII) with one mole of hydrogen yielded *cis*-9,*trans*-11-octadienoic acid (149); methyl 2,4-decadiynoate with two moles of hydrogen yielded methyl *cis*-2,*cis*-4-decadienoate (104; but see 7); and 9,11-octadecadiynoic acid with two moles of hydrogen yielded *cis*-9,*cis*-11-octadecadienoic acid (7). The last acid could be isomerized with iodine to the cis,trans and then to the trans,trans form. In contrast to these successful hydrogenation experiments, all of which made use of the Lindlar catalyst, 10,12-docosadiynedioic dimethyl ester over Raney nickel at 100°C. failed to yield significant amounts of conjugated ene-yne or diene (240).

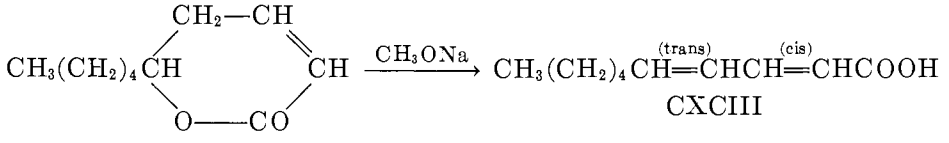
A different method develops conjugated unsaturation by combining an α,β-unsaturated aldehyde with malonic acid in the presence of pyridine (Doebner condensation). For example, *trans*-2-octenal leads to *trans*-2,*trans*-4-decadienoic acid (CXCI) (104; also *cf.* 114, 174).

$$CH_3(CH_2)_4\overset{(trans)}{CH}{=}CHCHO \xrightarrow{CH_2(COOH)_2} CH_3(CH_2)_4\overset{(trans)}{CH}{=}\overset{(trans)}{CH}CH{=}CHCOOH$$

CXCI

trans-2,*trans*-4-Decadienoic acid

Other preparations of fatty acids incorporating conjugated unsaturation include extending the carbon chain of sorbic acid (*trans*-2,*trans*-4-hexadienoic acid) by standard steps to a longer acid, such as all-*trans*-2,6,8-decatrienoic acid (175; *cf.* Section III,C) and opening an unsaturated lactone ring with methoxide, e.g., CXCII to CXCIII (104, 125). The many reaction schemes lead-



CXCII

CXCIII

ing to vitamin A or to carotenes (*cf.* Section III,G) present a wealth of suggestions for the means of introducing conjugated unsaturation. The Wittig–Geissler reaction (Section II,N) is readily adaptable to the production of conjugated unsaturation. The synthesis of cortisalin, isolated from *Corticium salicinum* Bres., shows another useful way of building a conjugated system (203a).

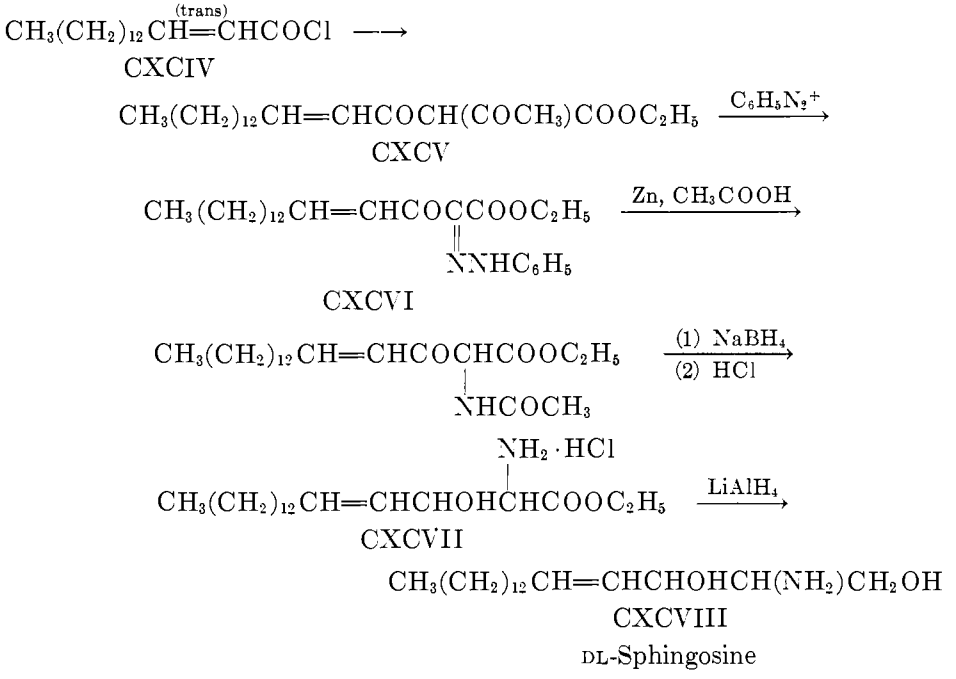
Strong alkali is known to convert skipped unsaturation, as in linoleic or linolenic acids, to conjugated unsaturation. Conditions making use of potassium *tert*-butoxide at temperatures no higher than 99°C. have been found to be particularly suitable in this isomerization (117). Although stillingic acid (*trans*-2,*cis*-4-decadienoic acid) is stable to boiling dilute potassium hydroxide, isomerization over potassium hydroxide does occur in ethylene glycol at 170–180°C. (115). The major product still retains the conjugated diene system but, interestingly enough, the unsaturation is displaced away from the carboxylic acid group.

Conjugated diacetylenic unsaturation has been introduced by Glaser coupling (Section II,L) as well as by other methods summarized elsewhere (232).

J. SPHINGOSINE

Sphingosine (*trans-erythro*-1,3-dihydroxy-2-amino-4-octadecene), although an amine, is classed as a lipide material. Dihydrosphingosine, the corresponding saturated compound, has been synthesized (*cf.* 4, 66, 67, 68, 176, 244, 245, 254), as has sphingosine itself (254). The synthesis of the latter proceeded from *trans*-2-hexadecenoic acid, which in the form of the acid chloride (CXCIV) was combined with acetoacetic ester to give CXCV. Phenyldiazonium coupling effected deacetylation and furnished the phenylhydrazone CXCVI. Reduction of the hydrazone group by zinc followed by reduction of the keto group by means of

sodium borohydride gave a mixture of diastereoisomers which could be separated. Deacetylation of the erythro form with hydrochloric acid gave the hydrochloride of the aminoalcohol ester CXCVII, and finally reduction with lithium aluminum hydride gave racemic sphingosine (CXCVIII).



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V. APPENDIX (ADDED IN PROOF)

The opportunity is taken to include further pertinent papers. Brief descriptive titles are given with the references in lieu of a more detailed review. Attention is directed to Cronbie's recent review on natural fatty acids. Also deserving of special mention are the comprehensive treatments of carboxylic acids and of aldehydes in the new edition of Houben-Weyl.

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