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THE HIGHER SATURATED BRANCHED CHAIN FATTY ACIDS

by

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PREFACE

In this part we have attempted to outline the present knowledge concerning the chemistry of the higher saturated branched chain fatty acids. Advances in analytical techniques in recent years have revealed that acids of this type are of frequent occurrence in nature.

Methods of synthesis and structure analysis are discussed as well as several aspects of the physical chemistry of this class of compounds. The literature has been covered up to the middle of 1960.

THE AUTHORS

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THE HIGHER SATURATED BRANCHED CHAIN FATTY ACIDS

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I. INTRODUCTION

A. Number of isomers

THE fatty acid components of fats and other lipids of natural origin possess, as a rule, unbranched hydrocarbon chains. However, these acids, so abundant in nature, form only a very small group within the "higher fatty acids" when all branched chain isomers are taken into account. Table 1, based on the work of Blair and Henze (1932) shows the number of theoretically possible

Table 1. Number of isomers of saturated carboxylic acids
with 12 to 21 carbon atoms

Number of carbon atoms	Stereoisomers	Non-stereoisomers	Total isomers
12	4,326	110	4,436
13	12,648	184	12,832
14	37,186	310	37,496
15	109,980	520	110,500
16	327,216	876	328,092
17	979,020	1,471	980,491
18	2,944,414	2,475	2,946,889
19	8,897,732	4,159	8,901,891
20	27,004,290	6,996	27,011,286
21	82,287,516	11,759	82,299,275

isomers for saturated carboxylic acids in the C_{12}–C_{21} range. The addition of one carbon atom increases the number of isomers by a factor of approximately 3. To take one example, stearic acid (n-octadecanoic acid) has 2,946,888 structurally different branched chain isomers for which formulae can be written. A number of these isomers are probably not capable of physical existence because of overcrowding of atoms, but it is very difficult to estimate how many isomers corresponding to a certain empirical formula are ruled out for this reason.

The higher branched chain acids received practically no attention from organic chemists until some 30 years ago when Roger Adams and his collaborators (Stanley, Jay and Adams 1929; Armendt and Adams 1930; Greer and Adams 1930) in search of synthetic substitutes for chaulmoogra oil in the treatment of leprosy (Stanley *et al.* 1932), prepared several series of higher branched chain acids of the disubstituted acetic acid type.

At about the same time evidence for the occurrence of higher branched chain fatty acids in nature was forthcoming, in that R. J. Anderson and his collaborators showed (Anderson and Chargaff 1929–30; Anderson 1932; Spielman 1934) that acids of this type are present in the lipids of acid-fast bacteria. Much of the subsequent interest in the chemistry of higher branched chain fatty acids arose out of the discovery (Sabin 1932) that some of these acids, when injected into animals, cause cellular responses similar to those found in tuberculosis.

The present review will deal with saturated branched chain acids possessing 12 carbon atoms or more.

B. Nomenclature

The Geneva system of numbering with the carbon atom of the carboxyl group as number 1 will be used (cf. e.g. *J. Chem. Soc.* Editorial Report on Nomenclature 1951). The systematic names are in certain cases supplemented with trivial names, or with commonly used names when the latter more readily visualize the structure than the systematic ones. Thus the prefix anteiso introduced by Weitkamp (1945) will be used to indicate a s-butyl end group.

In all cases where the absolute configuration of an optically active tertiary carbon atom is known the figure giving the position of the active centre along the chain is followed by a small Roman capital D or L depending on whether the alkyl substituent falls to the right or left in the Fischer projection (Fischer 1891; Hudson 1948), when the numbering of the carbon atoms in the projection proceeds from above downwards (Ställberg-Stenhagen 1949 b; Klyne 1951; Serck-Hanssen, Ställberg-Stenhagen and Stenhagen 1953). The similar use of italic capitals *D* and *L* in the nomenclature of optically active branched chain acids has been proposed (Linstead, Lunt and Weedon 1950; Mills and Klyne 1954), but in our opinion there is no strong reason to depart from the symbolism developed in the carbohydrate (cf. Hudson 1948) and amino acid fields (cf. Vickery 1947). The R, S system (Cahn, Ingold and Prelog 1956) for specification of configuration is not introduced, as we feel that its use in the field under review would make the subject unnecessarily complicated to the non-specialist. In the case of optically active quaternary carbon atoms it is of course sufficient to indicate the orientation of one of the alkyl side chains as the other will necessarily fall on the opposite side, but in certain cases it may be better, in the interests of clarity, to indicate the orientation of each substituent separately.

II. Synthesis of Branched Chain Fatty Acids

As it is impossible here to deal with or to point out all possible methods of synthesizing branched long chain fatty acids, the following discussion will be limited to methods that are of a general nature and have proven useful in practical work.

Generally speaking, it is best to synthesize long chain acids with short branches by first preparing a smaller unit that contains the tertiary or quaternary centre (or centres) as the case may be. The desired branched long chain acid is then obtained by lengthening the chain of the smaller unit. The reverse procedure, i.e. the introduction of small side chains into a long chain structure is generally less satisfactory because of the difficulty of separating the desired product from unreacted starting material. This argument may carry less weight after the development of the gas chromatographic separation technique.

Both chain-lengthening and chain-shortening methods have been the subject of recent comprehensive reviews by Gensler (1957) and by Gunstone (1957), and there is no need to deal with these except to point out the limitations of the methods when applied to the synthesis of branched chain fatty acids. Branched chain fatty acids are to some extent dealt with in reviews by Breusch (1950) and by Kaufmann (1958).

A. Optically inactive acids

1. Acids containing one tertiary carbon atom

(a) *2-Alkyl-substituted acids.* A very large number of disubstituted acetic acids RR'CHCOOH have been prepared by malonic ester synthesis. When R and R' are of different size the shorter alkyl group should be introduced first. If, for instance, a long chain malonic ester is alkylated with a methyl halide the 2-methyl-substituted acid obtained as final product will usually be contaminated with a normal chain acid that may be difficult to remove.

On the other hand, reaction of sodio-malonic ester with one equivalent of methyl bromide results in a mixture of unreacted malonic ester and methylmalonic ester which cannot be separated by simple distillation. Directions for the preparation of methylmalonic ester free from unsubstituted malonic ester are given in Organic Syntheses (1943).

The yields in the malonic ester synthesis are excellent when R and R' are normal chain primary halides (bromides or iodides) (class 1, according to Whitmore's classification (Whitmore 1937)). α-Methyl-substituted halides (class 2) give satisfactory yields (Cason and Allen 1953) but α, α-dialkyl-substituted halides (class 3) fail to react.

(b) *3-Alkyl-substituted acids.* Monoalkylation of malonic ester with secondary bromides (or iodides) leads to 3-alkyl-substituted acids. For example, 3-methylhendecanoic acid (Prout, Cason and Ingersoll 1948) and 3-methyl-octadecanoic acid (Kuhn, Köhler and Köhler 1936, Weitzel and Wojahn 1951 b) have been prepared in this way. The preparation of bromides from secondary alcohols with 5 or more carbon atoms may involve some risk that

the product contains isomeric bromides arising from dehydrobromination followed by addition of hydrogen bromide to the double bond during the bromination reaction (Sherrill, Otto and Pickett 1929; Sherrill, Baldwin and Haas 1929). The phosphorus tribromide procedure (Hsueh and Marvel 1928) appears to give little or no isomerization. Weitzel and Wojahn (1951 b) are of the opinion that the risk of impurity in the final product due to this cause is very small, but Cason and co-workers (Cason *et al.* 1949) have expressed the view that the use of secondary halides for the synthesis of pure compounds is undesirable.

A convenient route to 3-alkyl-substituted long chain acids starts with a β-alkylglutaric acid. The dibasic acid is converted via the anhydride into the mono-ester, and the desired hydrocarbon chain added on to the side carrying the free carboxyl group through the use of one of the standard chain-lengthening methods (Gensler 1957; Gunstone 1957). β-Alkylglutaric acids are readily available, e.g. by the method of Day and Thorpe (Day and Thorpe 1920; Org. Synth. 1955). β-Methylglutaric anhydride is conveniently prepared by a slight modification (Ställberg-Stenhagen 1947) of the method of Auwers *et al.* (Auwers, Köbner and v. Meyenburg 1891). A large number of 3-methyl-substituted acids have been prepared by this route.

Racemic 3-methyl-substituted acids have also been prepared by other routes, for example, from methyl ketones via the Reformatsky reaction (Cason *et al.* 1949), and through the addition of Grignard reagents to s-butyl crotonate (Munch–Petersen 1958).

(c) *4-Alkyl-substituted acids.* Acids with a side chain in position 4 may be obtained by lengthening the chain of 3-alkyl-substituted acids via nitrile synthesis. In small scale runs the Arndt–Eistert synthesis (cf. Organic Reactions 1942) is very convenient:

$$RR'CHCH_2COOH \rightarrow RR'CHCH_2COCl \xrightarrow{CH_2N_2} RR'CHCH_2COCHN_2$$
$$\xrightarrow[\text{rearrangement}]{\text{Wolff}} RR'CHCH_2CH_2COOH$$
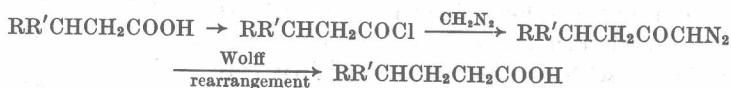
Great care must be taken to let the reactions at the acyl chloride and diazoketone stages go to completion, if not, the product may contain unchanged initial material which may be very difficult to remove as it contains only one carbon atom less than the desired product.

Cason and co-workers (Cason, Brewer and Pippen 1948) have developed a method for the synthesis of 4-methyl-substituted acids via γ-alkyl-γ-valero-lactones obtainable through the reaction of Grignard reagents (2) with esters of levulinic acid (1). The lactone ring (3) is opened by means of thionyl chloride.

$$CH_3CO-(CH_2)_2-COOC_2H_5 + R-MgBr \rightarrow$$

(1)   (2)

compound (3) with reagents SOCl₂, C₂H₅OH, heat

$$R'-\underset{(or\ isomers)}{\overset{\overset{\displaystyle CH_3}{|}}{C}}=CH-(CH_2)_2-COOC_2H_5 \xrightarrow{H_2,\ Pt} R-\underset{(5)}{\overset{\overset{\displaystyle CH_3}{|}}{CH}}-(CH_2)_2-COOC_2H_5$$

(4)

$$\xrightarrow{hydrolysis} R-\underset{(6)}{\overset{\overset{\displaystyle CH_3}{|}}{CH}}-(CH_2)_2-COOH$$
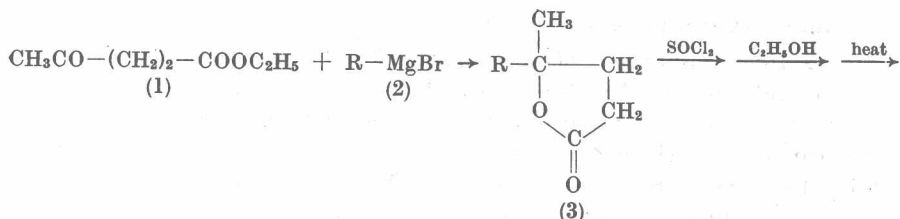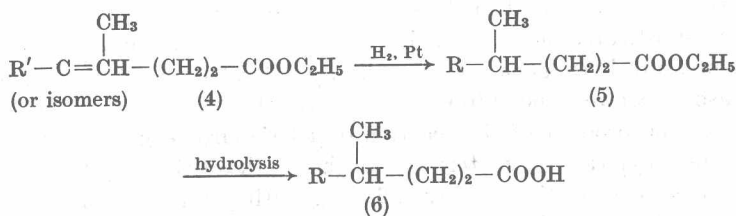
In the case of 4-methyltetradecanoic acid (R = n-decyl) the yield of lactone (3) was 84 per cent and the overall yield of ethyl ester (5) was 55 per cent calculated on the starting material. The original paper contains a detailed discussion of the reaction mechanisms.

(d) *Acids with an alkyl side chain in position 5 or higher.* Acids with the methyl side chain in positions 5 or higher can be prepared from 2-methyl-substituted acids by the long chain β-oxo-ester method (Ställberg-Stenhagen and Stenhagen 1944). The synthesis of 9-methyloctadecanoic acid from 2-methylundecanoic acid by this route (Ställberg-Stenhagen 1948b) is shown below. The method has so far been applied only to the synthesis of methyl-branched acids but it is probably capable of extension to acids with ethyl or longer side chains.

$$CH_3(CH_2)_8-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}-COOH \xrightarrow[C_6H_6]{(COCl)_2} CH_3(CH_2)_8-\underset{\underset{\displaystyle CH_3}{|}}{CH}-COCl \xrightarrow[C_6H_6]{NaCH_3COCHCOOC_2H_5}$$

(7)　　　　　　　　　　　　　　　　(8)

$$\xrightarrow[CH_3OH]{Na} CH_3(CH_2)_8\underset{\underset{\displaystyle CH_3}{|}}{CHCOCH_2COOCH_3} + CH_3OOC(CH_2)_5I \xrightarrow[PrCOMe]{K_2CO_3} \xrightarrow[CH_3OH]{Na}$$

(9)　Yield 64 %, calcd. on (7)

$$CH_3(CH_2)_8\underset{\underset{\displaystyle CH_3}{|}}{CHCOCH_2(CH_2)_5COOH} \xrightarrow[HCl,\ C_2H_5OH]{ZnHg_x} \xrightarrow[C_2H_5OH]{KOH,\ H_2O}$$

(10)　Yield 52 %, calcd. on (9)

$$CH_3(CH_2)_8-\underset{\underset{\displaystyle CH_3}{|}}{CH}-(CH_2)_7COOH$$

(11)　Yield 72 % calcd. on (9), Overall yield 24 %, calcd. on (7)
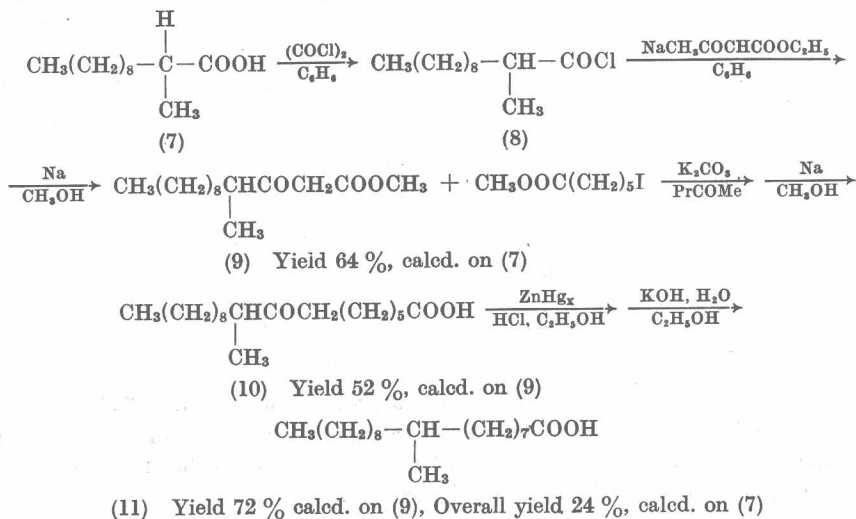
Racemic methyl-substituted acids with the methyl side chain in a variety of positions have been prepared by lengthening the chain of racemic 3-methyl-substituted acids using standard chain-lengthening procedures. For example, long chain iso-acids and racemic anteiso-acids have been built up starting from isopropyl bromide (Arosenius *et al.* 1948) and s-butyl bromide (Ställberg-Stenhagen 1945a), the first step being a malonic ester synthesis giving 3-methylbutanoic (isovaleric) acid and racemic 3-methylpentanoic acid respectively.

4-Methyl-substituted alcohols useful as intermediates in the synthesis of methyl-substituted acids may be obtained in yields of 80–88 per cent by high pressure hydrogenation of γ-alkyl-γ-valerolactones over copper chromite (Cason, Brewer and Pippen 1948). The analogous chlorides may be obtained as the product of the reaction of a Grignard reagent with 5-chloro-2-pentanone, acylation of the tertiary alcohol with acetic anhydride, removal of the elements of acetic acid by refluxing with p-toluenesulphonic acid in benzene solution, and catalytic hydrogenation of the unsaturated product formed. Cason and Winans (1950) have synthesized 9-methyloctadecanoic acid (15) in the following manner:

$$CH_3COCH_2CH_2CH_2Cl + CH_3(CH_2)_8MgBr \rightarrow CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-(CH_2)_3Cl \xrightarrow{Ac_2O}$$
$$(11)$$

$$CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle OAc}{|}}{C}}-(CH_2)_3Cl \xrightarrow{p\text{-}TSO_3} CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{C}=CH(CH_2)_2Cl \xrightarrow{H_2,\ Pt}$$

$$CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle}{}}{CH}}(CH_2)_3Cl \xrightarrow[(C_2H_5)_2O]{Mg,\ CdCl_2} CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-(CH_2)_3Cd_{\frac{1}{2}}$$
$$(12)$$

$$+\ ClCO(CH_2)_3COOCH_3 \rightarrow CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-(CH_2)_3CO(CH_2)_3COOCH_3 \xrightarrow[\text{red.}]{\text{Wolff-Kishner}}$$

$$(13) \quad \text{Yield 39,5 \%, calcd. on (12)}$$

$$CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-(CH_2)_7COOCH_3 \rightarrow CH_3(CH_2)_8-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-(CH_2)_7COOH$$

$$(14) \quad \text{Yield 69 \% calcd. on (13)} \qquad\qquad (15)$$
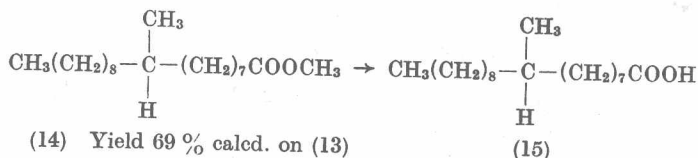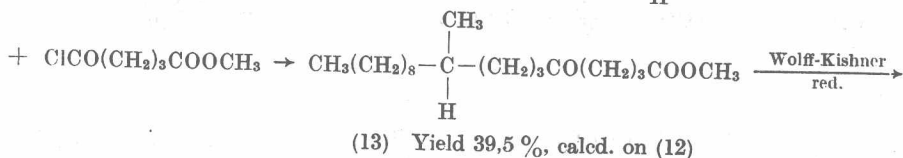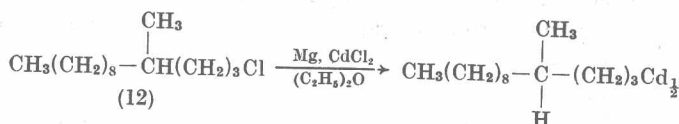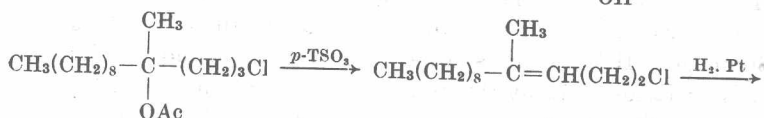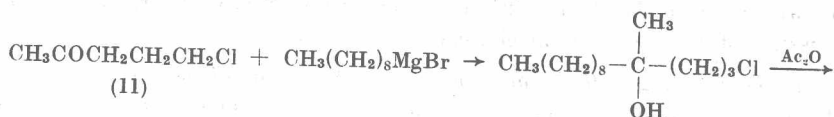
Side chains may be introduced by allowing the sodium derivative or Grignard complex of an alkylacetylene containing a suitable functional group to react with a ketone. As an example we may take a synthesis of 9-methyl-octadecanoic acid described by Leese and Raphael (1950).

$$[R = o-MeO-C_6H_4]$$

$$R-O-(CH_2)_5-C\equiv CH \xrightarrow[\text{ether}]{C_2H_5MgBr} R-O-(CH_2)_5-C\equiv CMgBr + CH_3(CH_2)_8COCH_3$$
$$(16)$$

$$\rightarrow CH_3(CH_2)_8-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-C\equiv C-(CH_2)_5-OR \xrightarrow[\text{heat}]{KHSO_4}$$

$$(17) \quad 69 \%, \text{ calcd. on (16)}$$

$$CH_3(CH_2)_7-CH=C-C\equiv C-(CH_2)_5-O-R \xrightarrow{Pt, H_2}$$

with CH_3 branch on the second carbon

(18) 71 %, calcd. on (17)

$$CH_3(CH_2)_7-CH_2-CH-(CH_2)_7-O-R \xrightarrow{HBr} \xrightarrow{KCN} \xrightarrow{hydrolysis}$$

with CH_3 branch

$$CH_3(CH_2)_8-CH(CH_2)_7-COOH$$

with CH_3 branch
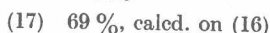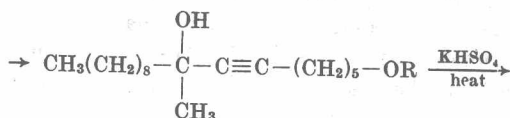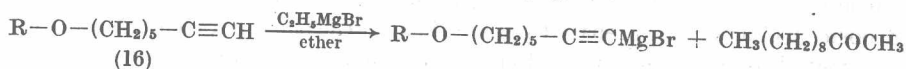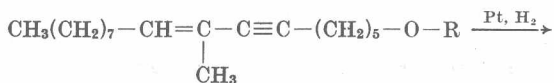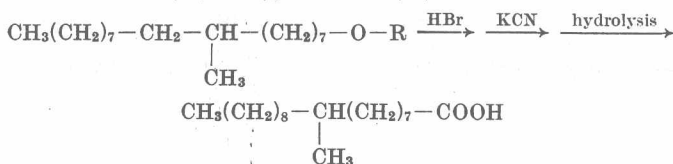
(15) 58 %, calcd. on (17)

The yield in each step is good, but owing to the large number of steps the synthesis appears rather laborious.

The iso- and anteiso-acids occurring naturally in wool wax (Weitkamp 1945, Truter 1951a) have been synthesized via several different routes starting from smaller molecules with isopropyl and s-butyl end groups respectively (cf. Milburn and Truter 1954 and references given for individual acids in Table 17).

Several branched chain acids with methyl side chains at positions higher than 4 have been prepared by methods involving cyclic intermediates. Nunn (1951) has synthesized a number of anteiso-acids by the oxo-acid synthesis described by Fieser and Szmuszkovicz (1948). Reaction of the Grignard reagent from 1-bromo-3-methylpentane with the appropriate cycloalkanone gave cycloalkanols (19).

$$CH_3-CH_2-CH-(CH_2)_2-C---(CH_2)_n$$

with CH_3 and OH branches

(19)
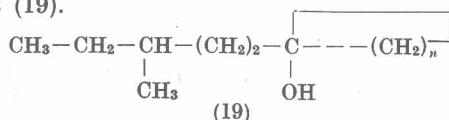
which were oxidized to oxo-acids (20)

$$CH_3-CH_2-CH-(CH_2)_2-CO(CH_2)_{n-1}-COOH$$

with CH_3 branch

(20)
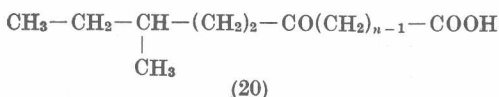
The yield of crude oxo-acid is reported as less than 50 per cent. The method is limited by the availability of the appropriate cycloalkanones.

Buu-Hoi and collaborators (Sy, Buu-Hoi and Dat-Xuong 1954) have described a synthesis of 10-methyloctadecanoic acid (21) by lengthening the chain of 2-methyldecanoic acid using thiophene as coupling unit (Badger, Rodda and Sasse 1954).

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$$\xrightarrow[\text{PhNO}_2]{\text{AlCl}_3} \quad CH_3-(CH_2)_7-\underset{\underset{CH_3}{|}}{CH}-CH_2-\underset{\underset{S}{\diagdown\diagup}}{C}\underset{}{\overset{HC-CH}{\underset{}{\|\quad\|}}}C-CO-CH_2-CH_2COOH$$

$$\xrightarrow{\text{red. Wolff-Kishner}} \quad CH_3-(CH_2)_7-\underset{\underset{CH_3}{|}}{CH}-CH_2-\underset{\underset{S}{\diagdown\diagup}}{C}\underset{}{\overset{HC-CH}{\underset{}{\|\quad\|}}}C-(CH_2)_3-COOH$$

$$\xrightarrow{\text{Raney-Ni, H}_2} \quad CH_3(CH_2)_7-\underset{\underset{CH_3}{|}}{CH}-(CH_2)_8-COOH$$

$$(21)$$
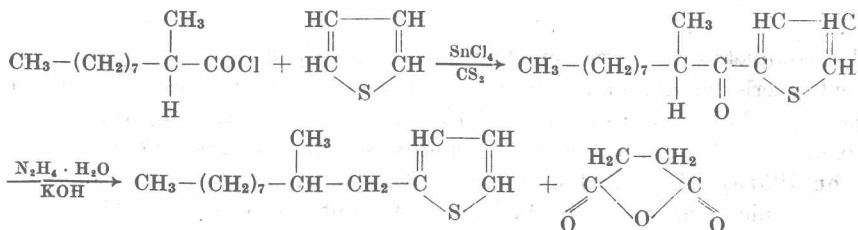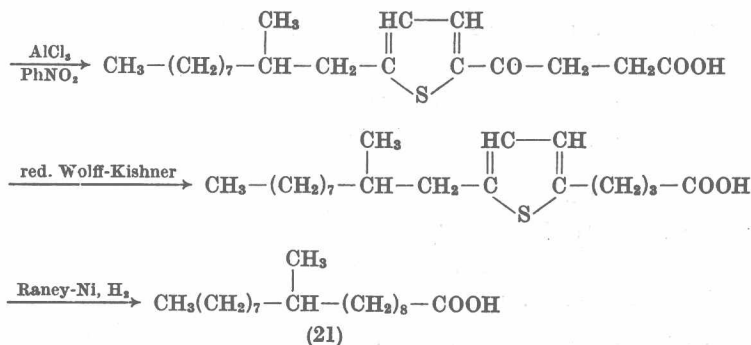
Another synthesis of 10-methyloctadecanoic acid involving ring intermediates has been described by Hünig and Salzwedel (1959). 1-Morpholinocyclohexenes were used as chain extenders as follows. 4-Methyl-1-morpholinocyclohexene (22) was acylated with n-hexanoyl chloride and the product (23) subjected to alkaline cleavage (Hünig, Lücke and Benzing 1958). Reduction of the resulting oxo-acid (24) gave 4-methyldodecanoic acid (25) in an overall yield of 53 per cent. An analogous series of reactions using 1-morpholinocyclohexene gave a chain extension of 6 carbon atoms leading to 10-methyloctadecanoic acid in 42 per cent yield, calculated on (25).

$$+ CH_3(CH_2)_4COCl \rightarrow CH_3-(CH_2)_4-\underset{\underset{O}{\|}}{C}\diagdown$$

$$(22) \qquad\qquad (23)$$

$$\xrightarrow{\text{OH}^-} \quad CH_3(CH_2)_4-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{CH_3}{|}}{CH}-CH_2-CH_2-COOH$$

$$(24)$$

$$\xrightarrow{\text{red.}} \quad CH_3(CH_2)_7-\underset{\underset{CH_3}{|}}{CH}-CH_2-CH_2-COOH$$

$$(25)$$
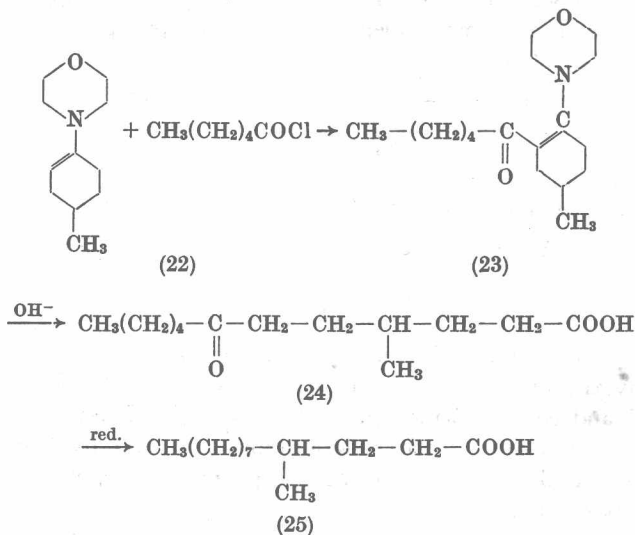
The complete series of monomethyl-substituted C_{19} acids and several acids of the C_{25} series have been synthesized by Cason and co-workers. Weitzel and Wojahn (1951 b) have also prepared the complete C_{19} series, as well as the complete C_{13}, C_{15} and C_{17} series of methyl-substituted acids (Weitzel and Wojahn 1951 a). These authors introduced a methyl group in position 2 or 3 via malonic ester synthesis. Malonic ester synthesis was used extensively

for lengthening the chains in two-carbon steps, but furfurol was also used as a chain extender (Nolte 1947).

Comparatively few long chain acids with a side chain longer than methyl in positions other than position 2 have so far been reported. Prout and Cason (1949) have prepared a number of acids with symmetrical end groups RRCH— $(CH_2)_n$—COOH. The end group was introduced by the reaction of the Grignard reagent RMgBr (R varied from ethyl to n-octyl) with an oxo-ester RCO—$(CH_2)_n$—COOC$_2$H$_5$, dehydration of the tertiary alcohol group formed, and hydrogenation of the unsaturated product.

2. Acids containing one quaternary carbon atom

(a) *2,2-Dialkyl-substituted* (*trialkylacetic*) *acids.* A general method of synthesizing 2,2-dialkyl-substituted acids involves chain extension of the unsymmetric half-ester (with free primary carboxyl group) of an α, α-dialkyl-substituted succinic acid:

$$\overset{\displaystyle R_1}{\underset{\displaystyle R_2}{\overset{|}{\underset{|}{ROOCC}}}}-CH_2-COOH$$

(26)
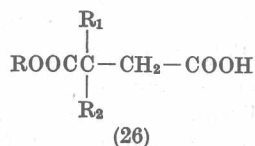
The rate of hydrolysis of the ester at the tertiary carboxyl group is much slower than that of the primary carboxyl group which allows the preparation of the desired unsymmetrical mono-ester by partial hydrolysis of the di-ester (Bone, Sudborough and Sprankling 1904, Meyer 1938).

It might be pointed out in this connection that in the case of α-monoalkyl-substituted succinic acids the difference in the rate of hydrolysis is not large enough to allow the easy preparation of the required unsymmetrical mono-ester free from the isomeric mono-ester (Meyer 1938, Hancock and Linstead 1953).

The lengthening of the chain of unsymmetrical mono-esters of the type (26) in the direction of the primary carboxyl group can be performed by standard methods, the Kolbe electro-synthesis being particularly convenient. The method has been applied to the synthesis of 2,2-dimethyl (Bergström *et al.* 1954, Tryding and Westöö 1956) and 2-methyl-2-ethyl-substituted acids. (Ställberg-Stenhagen 1951a). It can probably be extended to acids with longer alkyl substituents. The α, α-dialkyl-succinic acids required as starting material are readily accessible (Higson and Thorpe 1906; Vogel 1928).

Trialkylacetic acids may be obtained by hydrolysis of trialkylacetonitriles prepared by the method of Ziegler and Ohlinger (1932), involving the alkylation of nitriles by alkyl halides in the presence of sodium amide. The trialkylacetonitriles are hydrolysed to the corresponding trialkylacetamides by means of 80 per cent sulphuric acid. The amides are resistant to hydrolysis with standard hydrolytic agents, but Sperber, Papa and Schwenk (1948) found that they can be hydrolysed to the trialkylacetic acids in 80–90 per cent

yield by treatment with an excess of an alkyl nitrile and gaseous hydrogen chloride. The overall yields in this synthesis calculated on the unsubstituted nitriles used as initial material are about 50 per cent of the theoretical.

Other methods for the synthesis of trialkylacetic acids described in the literature are either of limited applicability or give rise to by-products that are difficult to remove. The method of Haller and Bauer (1914) involves the dialkylation of an alkylphenyl ketone by means of sodium amide and alkyl iodide, followed by decomposition of the trialkylacetophenone by sodium amide to the trialkylacetamide and hydrolysis of the amide with nitrous acid. 2,2-Dimethyl-substituted acids prepared by this method are difficult to obtain in a pure state (Cason, Sumrell and Mitchell 1950) and the method often fails when the substituents in the 2-position are longer than methyl, the acidic product obtained being benzoic acid instead of the desired trialkylacetic acid (Carter and Slater 1946).

The method of Hudson and Hauser (1940, 1941), which involves the α-alkylation of esters with sodium triphenylmethyl and alkyl halides in ether solution, has been used by Polgar and Robinson (1943) for the preparation of several trialkylacetic acids with one short (methyl or ethyl) and two long alkyl groups. The shortest alkyl is introduced in the last step and the method suffers from the disadvantage (analogous to that mentioned in connection with the preparation of dialkylacetic acids by malonic ester synthesis) that it is difficult to remove dialkylacetic acid derived from unreacted dialkylacetic ester from the desired trialkylacetic acid.

(b) *3,3-Dialkyl-substituted acids.* 3,3-Dialkyl-substituted acids are perhaps best synthesized by lengthening the chain of mono-esters of β, β-dialkylglutaric acids. The dibasic acids are readily available (Guareschi 1900–1901; Vogel 1934). 3,3-Dialkyl-substituted acids may furthermore be prepared from 2,2-dialkyl-substituted acids via the Arndt–Eistert reaction (Lane and Wallis 1941a). Hook and Robinson (1944) have devised a synthesis of 3,3-dialkylbutyric acids (28) based on the reaction between alkylidenecyanoacetates (27) and Grignard reagents, followed by hydrolysis, decarboxylation, and hydrolysis of the nitrile.
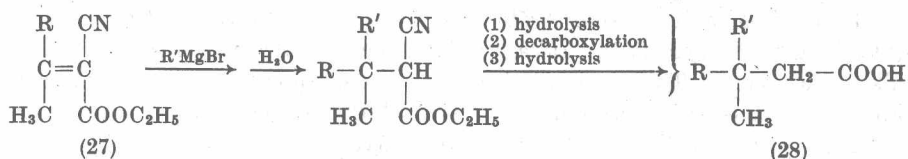
(c) *Acids with a quaternary carbon atom at position 4 or higher.* Acids with a quaternary carbon atom further removed from the carboxyl group may be obtained by lengthening the chain of 2,2- and 3,3-dialkyl-substituted acids. For example, 20,20-dimethylheneicosanoic (ω-neopentylstearic) acid (31, n = 16) has been synthesized (Arosenius, Ställberg-Stenhagen and Stenhagen

1949) by lengthening the chain of trimethylacetic acid (29).

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-\text{COOH}}} \rightarrow \underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-\text{COCH}_2\text{COOCH}_3}} + \text{I(CH}_2)_n-\text{COOCH}_3 \xrightarrow[\text{(2) hydrolysis}]{\text{(1) alkylation}}$$

(29)

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-\text{CO(CH}_2)_{n+1}-\text{COOH}}} \xrightarrow{\text{red.}} \underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-\text{CH}_2(\text{CH}_2)_{n+1}-\text{COOH}}}$$

(30)   (31)
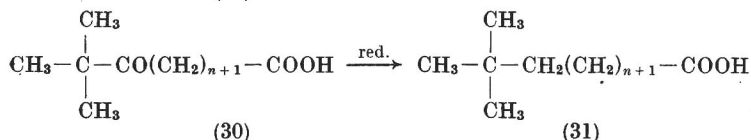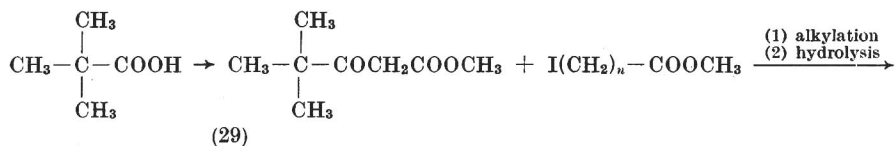
The reduction of oxo-acid (30) was performed by Huang-Minlon's (1946) modification of the Wolff–Kishner procedure.

ω-Neopentylsubstituted acids have been prepared by Sobotka and Stynler (1950) starting from neohexyl chloride. A simple route to acids of this type is anodic coupling of t-butylacetic acid and a mono-ester of a straight chain dibasic acid (Hedlund–Stoltz and Stenhagen 1957). t-Butylacetic acid (32) is readily prepared by Wideqvist's method (Wideqvist 1946).

3. Acids with branches at two or more positions

Tryding and Westöö (1957a) have prepared 2,2,17,17-tetramethyl-(1-^{14}C)-octadecanoic acid (33) as follows:

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-\text{CH}_2\text{COOH}}} + \text{HOOC(CH}_2)_{12}\text{COOCH}_3 \xrightarrow[\text{electrolysis}]{\text{Na, CH}_3\text{OH}}$$

(32)

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-(\text{CH}_2)_{13}\text{COOCH}_3}} \xrightarrow{\text{hydrolysis}} \underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{(\text{CH}_3)_3\text{C}(\text{CH}_2)_{13}\text{COOH}}}$$

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-(\text{CH}_2)_{13}\text{COOH}}} + \text{HOOCCH}_2-\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}-^{14}\text{COOCH}_3}} \rightarrow \xrightarrow[\text{electrolysis}]{\text{Na, CH}_3\text{OH}}$$

$$\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-(\text{CH}_2)_{14}-}}\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}-^{14}\text{COOCH}_3}} \xrightarrow{\text{hydrolysis}} \underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{CH}_3-\text{C}-(\text{CH}_2)_{14}-}}\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{C}-^{14}\text{COOH}}}$$

(33)
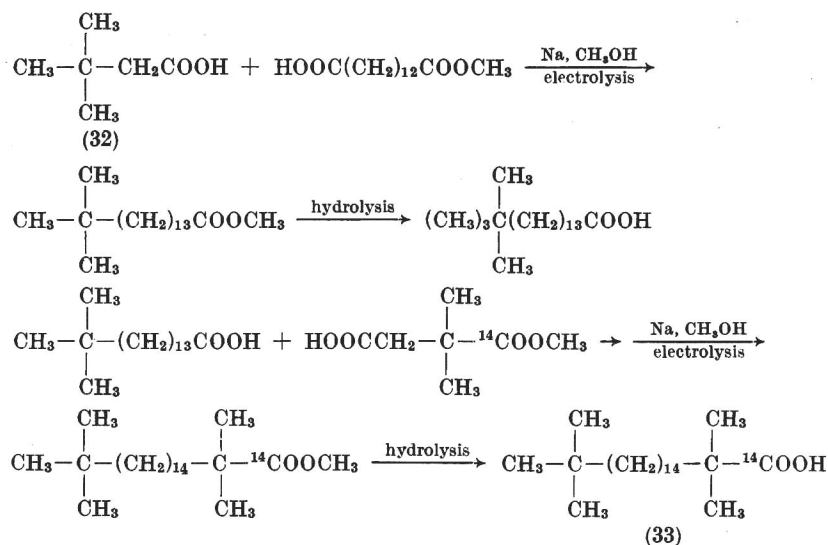
The synthesis of a branched chain acid with n asymmetric centres (tertiary or quaternary carbon atoms) from optically inactive smaller branched chain molecules, or by methods in which the asymmetric centres are created in the final step of the synthesis, leads to a mixture of 2^n diastereoisomers. If the acid contains one asymmetric carbon atom ($n = 1$) the optically inactive

(racemic; DL) form consists of the D- and L-enantiomers in equal amounts.

$$
\begin{array}{cc}
\text{COOH} & \text{COOH} \\
| & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 \\
| & | \\
\text{R} & \text{R} \\
2\text{L} & 2\text{D}
\end{array}
$$

$$\underbrace{\qquad\qquad\qquad\qquad}_{2\,\text{DL}}$$

$$n = 1$$
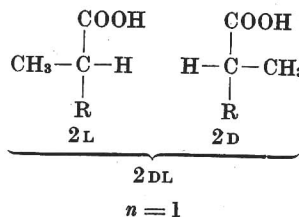
If we have two asymmetric centres there are $2^2 = 4$ diastereoisomers which combine pair-wise to two racemic forms, usually referred to as the *erythro*- and the *threo*-form respectively.

$$
\begin{array}{cccc}
\text{COOH} & \text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 \\
| & | & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 \\
| & | & | & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 & \text{H}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{H} \\
| & | & | & | \\
\text{R} & \text{R} & \text{R} & \text{R} \\
2\text{L},\,4\text{L} & 2\text{D},\,4\text{D} & 2\text{L},\,4\text{D} & 2\text{D},\,4\text{L}
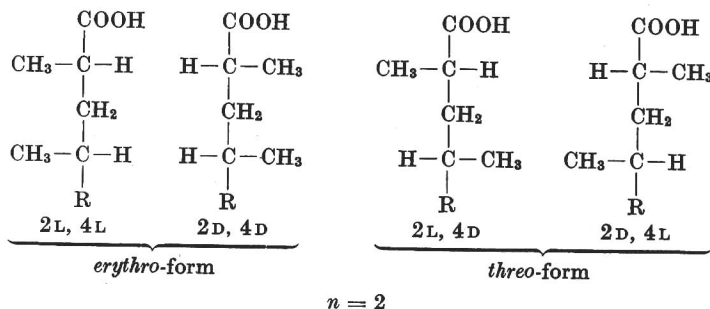\end{array}
$$

$$\underbrace{\qquad\qquad}_{\textit{erythro}\text{-form}}\qquad\qquad\underbrace{\qquad\qquad}_{\textit{threo}\text{-form}}$$

$$n = 2$$

The separation of the components of the mixture of the two racemic forms may be difficult. The mixture has usually a broad melting range and its purity is difficult to assess. Crystallization from solvents often leads to a partial separation of the two forms, and in some cases one of the racemic forms has been obtained pure in this way. For example, one of the racemic forms of 2,3-dimethyloctadecanoic acid was isolated in this way (Cason *et al.* 1949).

With three active centres the matter becomes much worse, in that we have $2^3 = 8$ diastereoisomers and consequently 4 pairs of enantiomorphs with opposite configurations giving four racemic forms (I–IV).

$$
\begin{array}{cccc}
\text{COOH} & \text{COOH} & \text{COOH} & \text{COOH} \\
| & | & | & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 \\
| & | & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 \\
| & | & | & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 \\
| & | & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 \\
| & | & | & | \\
\text{CH}_3-\text{C}-\text{H} & \text{H}-\text{C}-\text{CH}_3 & \text{H}-\text{C}-\text{CH}_3 & \text{CH}_3-\text{C}-\text{H} \\
| & | & | & | \\
\text{R} & \text{R} & \text{R} & \text{R} \\
2\text{L},\,4\text{L},\,6\text{L} & 2\text{D},\,4\text{D},\,6\text{D} & 2\text{L},\,4\text{L},\,6\text{D} & 2\text{D},\,4\text{D},\,6\text{L}
\end{array}
$$

$$\underbrace{\qquad\qquad}_{\text{I}}\qquad\qquad\underbrace{\qquad\qquad}_{\text{II}}$$

$$n = 3$$