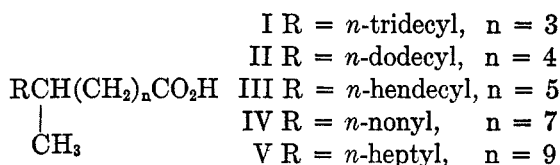


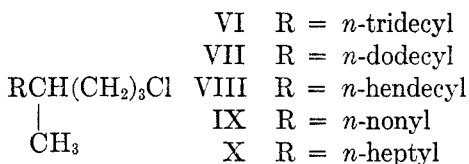
BRANCHED-CHAIN FATTY ACIDS. XIII. PREPARATION OF BRANCHED AND NORMAL ACIDS FOR USE IN THE STUDY OF MELTING POINTS OF BINARY MIXTURES. COMPLETION OF THE METHYLOCTADECANOIC ACID SERIES

JAMES CASON AND W. ROBERT WINANS¹*Received August 2, 1949*

The program of synthesizing all the monomethyloctadecanoic acids has been completed by preparation of 5-methyl- (I), 6-methyl- (II), 7-methyl- (III), 9-methyl- (IV), and 11-methyl-octadecanoic acid (V).



These isomers were prepared from the appropriate 1-chloro-4-methylalkanes, which were obtained by the recently-developed procedure (1) starting with the reaction between a Grignard reagent and 5-chloro-2-pentanone. The product of the Grignard reaction was allowed to react with acetic anhydride to yield a 1-chloro-4-acetoxyalkane. Removal of the elements of acetic acid, followed by catalytic hydrogenation yielded the desired branched-chain halide. This method has proved to be the most convenient yet developed for preparation of branched-chain alkyl halides from straight-chain starting materials. The branched-chain chlorides prepared for the present syntheses are represented by formulas VI-X, and the *n*-alkyl bromides required for their preparation are those containing the alkyl groups represented by R in these formulas.

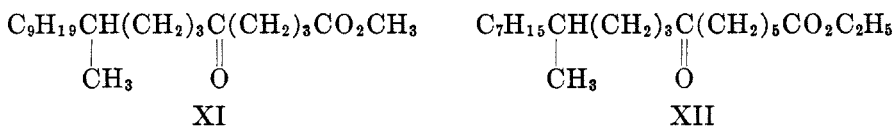


For preparation of acids I-III, there were used well-established methods for extending a chain by a few carbons. Use of the nitrile synthesis on 1-chloro-4-methylheptadecane (VI) gave 5-methyloctadecanoic acid. A high-molecular-weight aliphatic Grignard reagent gives a poor yield of acid by reaction with solid carbon dioxide. Reasonably good yields may be obtained conveniently by reaction with carbon dioxide under pressure, but much higher yields (often 90%) may be obtained by the nitrile synthesis; and the latter method has been used in the present work for most of the preparations of acids from alkyl halides.

¹ Present address: Department of Chemistry, Occidental College, Los Angeles, California.

6-Methyloctadecanoic acid (II) was prepared from chloride VII by use of the malonic ester synthesis, and 7-methyloctadecanoic acid (III) was prepared from chloride VIII by two chain-extensions. 6-Methyl-1-heptadecanol was prepared by reaction of ethylene oxide with the Grignard reagent, and the corresponding bromide was converted to the desired acid, III, by use of the nitrile synthesis.

The longer chain-extensions required for isomers IV and V were accomplished by way of the keto esters XI and XII, prepared by the cadmium reaction so frequently used (2) in this work.



Reduction of these esters yielded the desired acids, IV and V. The 9-methyl isomer (IV) has previously been prepared by Ställberg-Stenhagen (3) using a different method of synthesis, and the properties of our acid and amide are in agreement with those reported.

In Figure 1 have been plotted the melting points of the *dl*-methyloctadecanoic acids and two of their derivatives, the amides and the 2,4,6-tribromoanilides. It is of interest that the curve through the melting points of the acids is a fairly regular line, with the exception of two points, with the minimum melting points occurring when the methyl group is near the middle of the chain. There is an uncertainty about which polymorph to consider for the three acids with methyl near the middle of the chain, but this does not affect the deduction concerning the general pattern of the melting points. In the case of the 9-methyl isomer, which falls above the regular curve, it will be noted that three adjacent isomers exist in polymorphic forms. It might be suspected that there is also a low-melting polymorph of the 9-methyl isomer, but all efforts have failed to detect such a polymorph. It might be mentioned that we were unable to prove definitely the existence of the low-melting polymorph of the 10-methyl isomer, and this form was reported by Ställberg-Stenhagen (3), but this investigator did not report a polymorph for the 9-isomer.

It will be noted that the melting points of the amides do not follow a regular pattern, but tend to fall in groups of three with nearly identical melting points. Furthermore, nearly half the isomeric amides have melting points near 80°, and it is apparent that the melting point of this derivative is less useful for characterization purposes than is the melting point of the acid. Not all polymorphic forms of the amides are indicated on the chart. Additional data are found in Table III, and in Table IV of Ref. 2.

In connection with this unusual pattern for the melting points of the amides, it should be mentioned that Weitkamp (4) has noted a periodic variation in the melting points of a homologous series of even-carbon isoaliphatic amides. Also, Velick (5) has reported a periodic sequence in the long crystal spacings of this same homologous series, and has discussed the possibility that these amides

possess a spiral chain configuration. A group of Swedish workers (6) has conducted an X-ray investigation of a homologous series of odd-carbon iso amides,

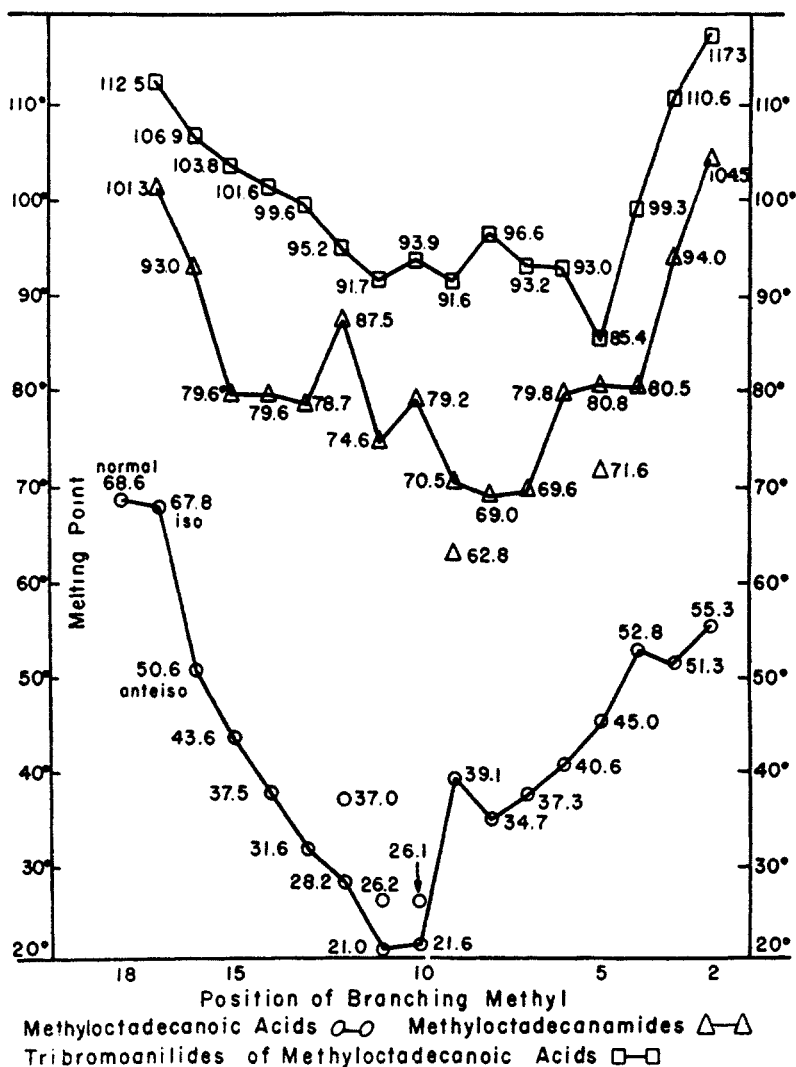


FIG. 1. MELTING POINTS OF THE METHYLOCTADECANOIC ACIDS, AMIDES, AND 2,4,6-TRIBROMOANILIDES. Data not presented in this paper were obtained from previous publications in this series, except for the low-melting polymorph of 10-methyloctadecanoic acid, obtained from Ref. 3. The points are connected by lines merely to add to clarity. In the case of polymorphs, it is not inferred that the lines connect similar crystal forms. No information concerning this matter has been sought.

as well as certain even-carbon iso amides. The latter workers found a variety of crystal structures in these amides, but stated that the evidence does not seem to support the hypothesis of a spiral chain configuration.

The melting points of the tribromoanilides decrease in a regular manner as the position of methyl approaches the center of the chain, but there is a group of six isomers with similar melting points. This derivative is more useful than the amide, and in relation to the acid has the advantage of high melting point and low solubility. Several of the tribromoanilides exhibited interesting polymorphism which is described in Table III. This behavior observed in a capillary melting point tube is presented for use in characterization of the compounds. A more careful study of the time-temperature curves obtained on freezing of larger samples is regarded as beyond the scope of this work, and not necessarily applicable to the objectives of the present investigation.

In connection with the validity of applying the observations in this series to monomethyl acids of different molecular weight, it is noteworthy that certain facts already known suggest that such an application has some validity. 12-Methyloctadecanoic acid is dimorphic (2), as is 12-methyltetracosanoic acid (7). Also, the 2,4,6-tribromoanilide of 6-methyloctadecanoic acid is definitely polymorphic, and the broad melting point of the tribromoanilide of 6-methyltetracosanoic acid (8) also suggests polymorphism. Further, the melting-point behavior of binary mixtures, as investigated by Weitkamp (4) and in the next paper of the present series, appears to depend on the position of branching and not on the molecular weight. In addition, molecular rotation of optical isomers (4) is a function of position of methyl in relation to the ends of the chain, and is nearly independent of molecular weight.

For use in the study of the melting points of binary mixtures, one additional branched-chain acid and several odd-carbon normal acids have been prepared. 16-Methylheptadecanoic (isostearic) acid was prepared *via* the 9-keto-16-methylheptadecanoic acid, hendecanoic acid was obtained by hydrogenation of undecylenic acid, and the other odd-carbon acids were prepared from the even-carbon alkyl bromides by the nitrile or the Grignard syntheses.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses are by the Microanalytical Division of the Department of Chemistry of the University of California. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with tantalum wire spiral and partial reflux head. All solid compounds were dried in a vacuum to constant weight, for analysis, and purification of the branched-chain acids was continued until the observed equivalent weights were in agreement with theory.

n-Alkyl halides, except tridecyl bromide, were distilled commercial grades or were prepared from the alcohol by the usual method (9), using hydrogen bromide gas from a cylinder.

Tridecyl bromide. To a stirred suspension of 66 g. (0.2 mole) of dried silver myristate (prepared from technical myristic acid) in 250 ml. of dried carbon tetrachloride, there was added during about ten minutes a dried solution of 32 g. (0.2 mole) of bromine in 20 ml. of carbon tetrachloride, the mixture being cooled in an ice-bath during the addition. After completion of the addition, the cooling bath was removed and stirring continued for about thirty minutes without heating, and finally with heating under reflux until evolution of carbon dioxide had ceased (about ten minutes). To the cooled reaction mixture was added 50 ml. of a 1 molar sodium carbonate solution and enough (about 1 ml.) 12 *N* sodium hydroxide to remove bromine. This mixture was stirred briefly, then 50 ml. of a 1 molar barium chloride solution was added and stirring continued for about ten minutes. The precipitate of

silver bromide and barium myristate was removed by suction filtration, and the residue remaining after removal of solvent from the filtrate was distilled in a Claisen flask to yield 37 g. (70%) of crude tridecyl bromide, b.p. 135–150° (5 mm.). This product contains a trace of hendecyl bromide and several per cent of pentadecyl bromide. Distillation through the column yields pure tridecyl bromide, b.p. 135–136° (4 mm.).

Ester acid chlorides were prepared from the dibasic acids by usual procedures (10).

1-Chloro-4-methylalkenes were prepared by the procedure described for 1-chloro-4-methylnonene, and the reaction proceeded as previously described (1) except that with the higher molecular weight compounds used in the present work a very heavy precipitate separated when the product of the Grignard reaction was treated with acetic anhydride. The mass was rendered stirrable by the addition of benzene (200 ml. for a 0.4-mole run), and the reaction completed as before.

The alkenes were hydrogenated immediately to *1-chloro-4-methylalkanes*, at room temperature and low pressure, using for each 0.1 mole of alkene 0.1 g. of commercial platinum oxide

TABLE I
1-CHLORO-4-METHYLALKANES

CHLORIDE SYNTHESIZED	CHLOROALKENE		CHLOROALKANE		OVER-ALL YIELD
	YIELD, %	B.P., °C. (MM.)	YIELD, %	B.P., °C. (MM.)	
VI	50	172–173 (4)	80	166–168 (2.4)	40
VII	71	160–161 (4)	87	160–161 (3.5)	61.5
VIII	64	152–154 (4)	89.5	153–154 (3.5)	57
IX	47	133–135 (5)	83	134–136 (5)	39
X	69	108–110 (8)	84	116–117 (10)	58

TABLE II
ANALYSES OF 1-CHLORO-4-METHYLALKANES

COMPOUND	n_D^{20}	CALC'D		FOUND	
		C	H	C	H
VI	1.4540	74.82	12.91	74.84	12.53
VII	1.4528	74.27	12.83	75.03	12.71
VIII	1.4517	73.66	12.75	73.88	12.65

catalyst and a solvent consisting of 25 ml. of diethyl ether and 75 ml. of glacial acetic acid. The compounds were not sufficiently soluble in glacial acetic acid or ethanol. Hydrogenation was complete in twenty to forty minutes.

Data on these preparations are found in Table I. In order to make certain that these reactions had followed the same course as in the example previously described, three of the chloroalkanes were analyzed, and the data are found in Table II. In all distillations of the saturated chlorides, there was a small fore-run which was insoluble in concentrated sulfuric acid and probably consisted of the hydrocarbon resulting from hydrogenolysis at chlorine.

Methyl 5-methyloctadecanoate was prepared from 1-chloro-4-methylheptadecane (VI), by way of the nitrile, following a procedure essentially identical with that previously described (11) for ethyl nonadecanoate, except that four mole per cent of potassium iodide was added to the initial reaction mixture. The product boiled at 178–185° (3 mm.) and had n_D^{20} 1.4467.

Anal. Calc'd for $C_{20}H_{40}O_2$ C, 76.86; H, 12.90.

Found: C, 76.52; H, 13.02.

Methyl 6-methyloctadecanoate. Diethyl malonate was alkylated with 1-chloro-4-methyl-

hexadecane (VII), using potassium iodide as a catalyst, following the procedure previously described (12) for alkylation with chlorides, except that the alkylation was continued for twenty hours under reflux. The diethyl alkylmalonate obtained from the reaction was not distilled but was saponified directly with alcoholic potassium hydroxide. The resultant malonic acid was decarboxylated by heating for two hours at 180–190° at 60–90 mm., and the monocarboxylic acid was esterified by heating for two hours with twenty equivalents of methanol containing 10% sulfuric acid. The ester was obtained in 62% yield (based on chloride VII), b.p. 167–172° (2 mm.), n_D^{18} 1.4475.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.

Found: C, 77.20; H, 12.69.

6-Methyl-1-heptadecanol was prepared by the reaction of the Grignard reagent from 1-chloro-4-methylpentadecane (VIII) with 1.5 mole-equivalents of ethylene oxide which had been passed through a soda lime tube. The procedure was essentially identical with that which has been described (13) for the preparation of isononyl alcohol. In a run starting with 57 g. (0.22 mole) of chloride VIII, there was obtained 38.9 g. (66%) of 6-methyl-1-heptadecanol; b.p. 159–161° (1.8 mm.), n_D^{20} 1.4537.

Anal. Calc'd for $C_{18}H_{36}O$: C, 79.92; H, 14.16.

Found: C, 80.78; H, 13.85.

There was considerable fore-run in distilling the above alcohol, and a principal fraction (8.8 g.), b.p. 108–110° (1.8 mm.), was insoluble in concentrated sulfuric acid and yielded an analysis in agreement with *4-methylpentadecane*.

Anal. Calc'd for $C_{16}H_{34}$: C, 84.86; H, 15.13.

Found: C, 84.92; H, 15.18.

Methyl 7-methyloctadecanoate was prepared in 81% yield from the bromide (b.p. 172–173° at 1.7 mm.) of the above alcohol. The ester distilled at 170–172° (2.5 mm.), n_D^{20} 1.4465.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.

Found: C, 77.28; H, 12.96.

Methyl 5-keto-9-methyloctadecanoate (XI), prepared by the usual procedure (10) for keto esters from 1-chloro-4-methyltridecane (IX) and the ester acid chloride of glutaric acid, was obtained in 39.5% yield (based on chloride IX), b.p. 186–189° (2 mm.), n_D^{20} 1.4530.

Anal. Calc'd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73.

Found: C, 73.12; H, 11.77.

Methyl 9-methyloctadecanoate. Keto ester XI was reduced by the Huang-Minlon (14) modification of the Wolff-Kishner reduction, as previously described (15) for aliphatic keto esters. The yield of crude acid was 92%, but when this was esterified with fifteen equivalents of methanol containing 10% sulfuric acid, the over-all yield of ester was 69%, b.p. 172–173° (2.2 mm.), n_D^{20} 1.4467. This method of esterification, applied to pure acids, has repeatedly given yields of 95% or better.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.

Found: C, 76.43; H, 12.97.

Ethyl 7-keto-11-methyloctadecanoate (XII) was obtained from 1-chloro-4-methylhendecane (X) and the ester acid chloride of pimelic acid in 49% yield (based on chloride X), b.p. 190–192° (2 mm.), n_D^{20} 1.4499.

This ester appeared to contain appreciable quantities of impurities, presumably distilling azeotropically, for the analysis for carbon was about 2% below theory, and saponification of 1 g. of ester with alcoholic potassium hydroxide yielded only 0.69 g. of crude acid. However, the *7-keto-11-methyloctadecanoic acid* was readily purified, reaching the constant m.p. of 38.8–39.5° after two crystallizations from acetone. It separated as burrs of short needles.

Anal. Calc'd for $C_{18}H_{36}O_3$: C, 73.03; H, 11.62.

Found: C, 72.97; H, 11.71.

Methyl 11-methyloctadecanoate was obtained from keto ester XII by the reduction and esterification procedure described for the 9-methyl isomer. The yield of product boiling at 170–172° (2 mm.), n_D^{20} 1.4463, was 65%.

TABLE III
 METHYLOCTADECANOIC ACIDS AND DERIVATIVES

—OCTADECANOIC ACID	M.P., °C.	M.P., °C. OF AMIDE	M.P., °C. OF TRIBROMOANILIDE
5-Methyl (I)	44.5–45.0	79.6–80.8 ^c 71.6	80.5–85.4 ^a
6-Methyl (II)	40.0–40.6	79.1–79.8	86.0–93.0 ^f
7-Methyl (III)	36.8–37.3	71.6–72.0 ^c 69.6	92.5–93.2
9-Methyl ^e (IV)	38.5–39.1	69.8–70.5 ^c 62.8	90.0–91.6 ^e
11-Methyl (V)	21.0 ^b 26.2	71.6–75.3 ^d 74.6	91.0–91.7

^a Literature (3): acid, m.p. 38.7–39.2°; amide, m.p. 70.0–70.5°, re-m.p. 61.5° (cf. note c, below). ^b These values were determined on a sample of several grams, with the thermometer in the liquid. The higher value is obtained when a sample crystallized from acetone is melted, while the lower-melting form usually separates from the melt. ^c Higher-melting form obtained on crystallization from methanol, lower-melting form separates from melt. ^d The broad m.p. is obtained on samples crystallized from a solvent, and varies somewhat with rate of heating and on different samples. The lower-melting form separates from the melt. ^e Clusters of small blades first separate from ethanol, but these rapidly change to a dense granular crystallizate. Material crystallized from ethanol always showed the broad m.p. A sample solidified from the melt re-melts at once when immediately placed in a bath at 81.5° or higher, but not in a bath at 81.4°. When placed in a bath at 81.4°, re-m.p. 83.2° (taken at once). ^f Crystallized from ethanol as small hard crystals, but fine needles separated from the melt. On slowly cooling a molten sample, re-crystallization set in at 85°, and re-melting occurred at 86°, but a sample crystallized from ethanol did not melt completely when placed in a bath at 89°. A sample which was melted, resolidified, and ground, melted in a capillary at 84.7–86.0°. ^g This m.p. was obtained on a sample which had stood overnight; freshly crystallized samples show broad melting points. A solidified sample re-melted at 90.4°.

 TABLE IV
 ANALYSES OF ACIDS AND DERIVATIVES

ACID	ACID			AMIDE		TRIBROMOANILIDE
	C	H	EQ. WT.	C	H	N
I	76.29	12.84	300.2	77.04	13.29	2.29
II	76.06	12.56	299.7	77.04	13.39	2.23
III	76.71	12.81	298.7	77.17	13.14	2.30
IV	76.66	12.73	298.6	76.54	13.14	2.29
V	75.95	12.64	299.1	76.92	13.16	2.29
Calc'd	76.45	12.83	298.5	76.71	13.21	2.29

Anal. Calc'd for C₂₀H₄₀O₂: C, 76.86; H, 12.90.

Found: C, 76.21, H, 12.72.

Methyloctadecanoic acids were obtained from the esters by saponification with alcoholic potassium hydroxide and crystallization from acetone until a constant melting point was reached. Data on these acids are found in Tables III and IV.

Amides and 2,4,6-tribromoanilides of the methyloctadecanoic acids were prepared as previously described (2), and the data are found in Tables III and IV.

Ethyl 9-keto-16-methylheptadecanoate was prepared by the usual procedure (10) from isononyl bromide (13) and the ester acid chloride of azelaic acid. The yield (based on isononyl bromide) was 55% of material boiling at 196–199° (4 mm.), n_D^{20} 1.4492.

The ester was characterized by saponification to 9-keto-16-methylheptadecanoic acid, m.p. 70.8–73.4°, re-m.p. 72.5–73.0°.

Anal. Calc'd for $C_{18}H_{34}O_3$: C, 72.45; H, 11.48.

Found: C, 72.18; H, 11.66.

16-Methylheptadecanoic (isostearic) acid. The above keto ester was reduced by the modified Clemmensen method (16) to give a 75% yield of ethyl 16-methylheptadecanoate, b.p. 183–186° (4 mm.). Saponification of the ester and crystallization from acetone yielded isostearic acid, m.p. 68.8–69.7°, eq. wt., 282.8 (Calc'd 284.5). Literature, m.p. 67.6–68.2° (17), 69.5° (4).

Normal acids. Commercially available acids were purified by esterification and distillation of the esters, followed by saponification and crystallization of the acids (nonanoic and decanoic acids were not crystallized).

TABLE V
NORMAL ACIDS AND AMIDES

ACID	ACID	AMIDE
	m.p., °C.	m.p., °C.
Nonanoic		98.7–99.1
Decanoic		97.6–98.2
Hendecanoic	28.2–28.6	98.0–98.7
Dodecanoic	42.8–43.6	99.6–100.2
Tridecanoic	41.0–41.9	99.6–100.2
Tetradecanoic	53–54.2	102.5–103.7
Pentadecanoic	49.2–51.5 ^a	102.4–103.1
Hexadecanoic	61.2–62.0	104.9–105.3
Heptadecanoic	59.2–60.5	105.0–106.0

^a Not crystallized to constant m.p.

Hendecanoic acid was prepared by hydrogenation of a sample of distilled undecylenic acid (b.p. 139.5–140° at 3.5 mm.). Hydrogenation of 0.28 mole at room temperature and low pressure in 250 ml. of glacial acetic acid with 0.8 g. of commercial platinum oxide catalyst was complete in 33 minutes. Crystallization of the product by addition of water gave a quantitative yield of acid, m.p. 28.2–28.6°.

Tridecanoic acid was prepared by reaction of dodecylmagnesium bromide with carbon dioxide under the initial pressure from a cylinder of carbon dioxide. Shaking of the bomb was continued overnight, and the reaction was worked up as usual for a Grignard reaction. The crude (technical dodecyl bromide was used) acid was esterified and distilled to give a 55% yield of methyl tridecanoate, b.p., 130–132° (4 mm.). Saponification and one crystallization from acetone gave tridecanoic acid of m.p. 41.0–41.9°.

Pentadecanoic acid was prepared by the nitrile synthesis. The over-all yield of methyl pentadecanoate from tetradecyl bromide was 77%, b.p. 156–157° (5.5 mm.). The acid was obtained as described above.

Heptadecanoic acid was prepared by reaction of hexadecylmagnesium bromide with solid carbon dioxide. In the best run, using a very large excess of carbon dioxide added in several portions, the yield was 32%.

The data on the normal acids and their amides are found in Table V.

SUMMARY

There is reported the preparation of five methyloctadecanoic acids. This work completes the synthesis of the series of monomethyloctadecanoic acids. The melting point patterns of the acids, amides, and tribromoanilides are discussed.

A new synthesis of isostearic acid is also reported, and the preparation of pure samples of the amides of the normal acids from C₉ to C₁₇ is described.

BERKELEY, CALIFORNIA

REFERENCES

- (1) CASON, BREWER, AND PIPPEN, *J. Org. Chem.*, **13**, 239 (1948).
- (2) CASON, PIPPEN, TAYLOR, AND WINANS, *J. Org. Chem.*, preceding article.
- (3) STÄLLBERG-STENHAGEN, *Arkiv Kemi, Mineral. Geol.*, **A26**, No. 12 (1948).
- (4) WEITKAMP, *J. Am. Chem. Soc.*, **67**, 447 (1945).
- (5) VELICK, *J. Am. Chem. Soc.*, **69**, 2317 (1947).
- (6) AROSENIUS, STÄLLBERG, STENHAGEN, AND TÄGTSTRÖM-EKETORP, *Arkiv Kemi, Mineral. Geol.*, **A26**, No. 19 (1948).
- (7) STÄLLBERG-STENHAGEN, *Arkiv Kemi, Mineral. Geol.*, **A22**, No. 19 (1946).
- (8) CASON AND PROUT, *J. Am. Chem. Soc.*, **66**, 46 (1944).
- (9) REID, RUHOFF, AND BURNETT, *Org. Syntheses*, Coll. Vol. II, 246 (1946).
- (10) CASON, *Chem. Revs.*, **40**, 15 (1946); CASON AND PROUT, *Org. Syntheses*, **28**, 75 (1948).
- (11) CASON, WOLFHAGEN, TARPEY, AND ADAMS, *J. Org. Chem.*, **14**, 147 (1949).
- (12) CASON, WALLCAVE, AND WHITESIDE, *J. Org. Chem.*, **14**, 41 (1949).
- (13) CASON, *J. Am. Chem. Soc.*, **64**, 1109 (1942).
- (14) HUANG-MINLON, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
- (15) CASON, *J. Org. Chem.*, **13**, 227 (1948).
- (16) SCHNEIDER AND SPIELMAN, *J. Biol. Chem.*, **142**, 345 (1942).
- (17) FORDYCE AND JOHNSON, *J. Am. Chem. Soc.*, **55**, 3368 (1933).