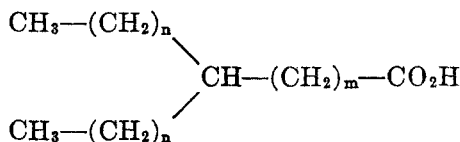


## BRANCHED-CHAIN FATTY ACIDS. IX. SYNTHESIS OF ACIDS WITH SYMMETRICAL END-GROUPS

JAMES CASON AND WILLIAM L. STANLEY<sup>1</sup>*Received September 10, 1948*

In the preceding paper (1) of this series, there was reported the synthesis of a C<sub>18</sub> acid (I) and a C<sub>19</sub> acid (II) with symmetrical end-groups in which the branching groups were ethyl. These acids proved to have melting points more than twenty-five degrees below those of the normal isomers.



I    n = 1, m = 12

II   n = 1, m = 13

III  n = 1, m = 18

IV   n = 2, m = 16

V    n = 5, m = 10

VI   n = m = 7

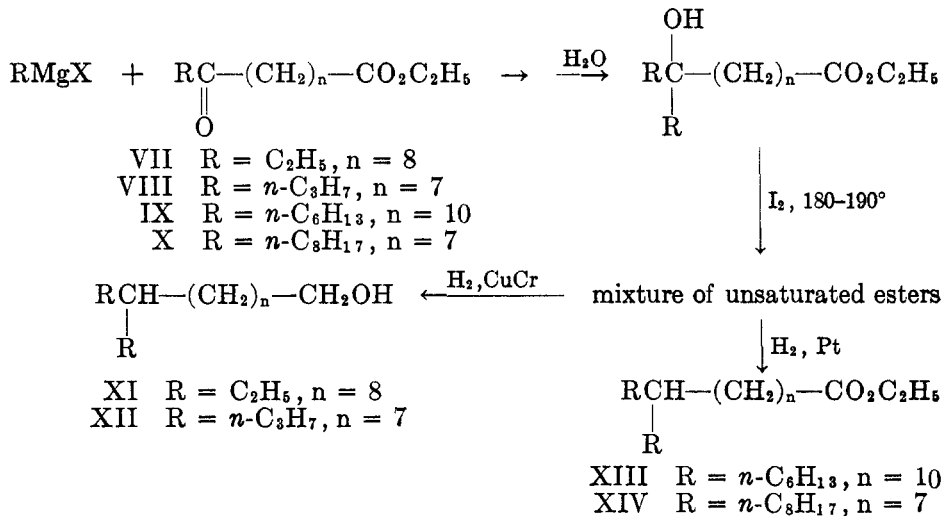
In the present paper there is reported the synthesis of four higher molecular weight acids with symmetrical end-groups: 20-ethyldocosanoic acid (III), 18-*n*-propylheneicosanoic acid (IV), 12-*n*-hexyloctadecanoic acid (V), and 9-*n*-octylheptadecanoic acid (VI). The melting points of these acids, respectively, are 64.8–65.5°, 51.9–52.2°, 28.3–28.7°, and 9–14°. It is seen that as the branching group becomes larger the melting point drops progressively further below that of the normal isomer, and is lowest for the C<sub>25</sub> acid, VI, in which the tertiary carbon carries three chains of equal length. Thus, any apparent symmetry about the tertiary carbon does not tend to raise the melting point, but the melting point becomes progressively lower as the branching end-group becomes larger. As the tertiary carbon is shifted further toward the carboxyl, thus shortening the chain carrying carboxyl, the melting point must begin to increase again at some point, for didodecylacetic acid (2) melts about 17° below the normal isomer. It is of interest that in the series of branched-chain alkanes synthesized by Whitmore, Sutherland, and Corby (3), the melting point again becomes progressively further below that of the normal isomer as the tertiary carbon carrying two of the same group approaches the center of the chain.

Of the types of acids which it was previously suggested (4) might have melting points within the "excluded region" of about ten degrees below the melting point of the normal isomer, there have now been eliminated all but the acids having on a quaternary carbon either four groups of equal size or three equal groups and

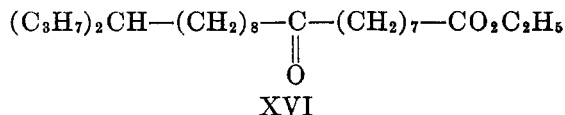
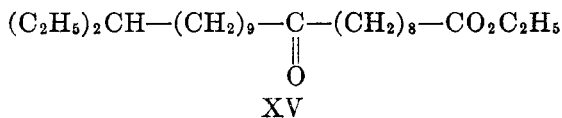
<sup>1</sup> Holder of a United States Rubber Company Graduate Fellowship in Chemistry at the University of California, 1947–48. Present address: Western Regional Research Laboratory, Albany, California.

the carboxyl.<sup>2</sup> Further attempts to prepare acids of this type are in progress; however, such acyclic acids of high molecular weight have not yet been found in nature. It seems likely that acids from natural sources with melting points in the "excluded region" are mixtures. There has already been presented (5) convincing evidence that two acids from tubercle bacillus, which melt in this region, are mixtures of normal isomers rather than homogeneous substances.

The two symmetrical acids reported in the previous paper (1) were prepared by chain extension of the commercially available 2-ethyl-1-butanol, but alcohols with larger symmetrical end-groups are not available. Those required for synthesis of acids, III and IV, were prepared by high-pressure hydrogenation of unsaturated esters obtained by the illustrated sequence of reactions.



The carbon chains of alcohols, XI and XII, were extended as before (1) by reaction of the corresponding cadmium reagents with the appropriate ester acid chlorides. The resultant keto esters, XV and XVI, were converted to the desired branched-chain acids (III, IV)

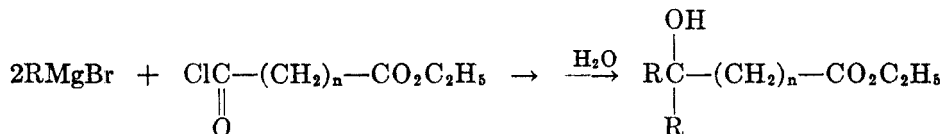


by Clemmensen or Wolff-Kishner reduction of the keto group.

<sup>2</sup> There has just appeared [Sperber, Papa, and Schwenk, *J. Am. Chem. Soc.*, 70, 3091 (1948)] a report of synthesis of trialkylacetic acids with three of the same alkyl group. Although tri-*n*-propylacetic acid melted at 65.5–67.5°, tri-*n*-butylacetic acid melted at 35.5–37.5°, and tri-*n*-amylacetic acid presumably was an oil since no m.p. was reported. Thus, it appears that high molecular weight acids of this type do not have relatively high melting points. (Footnote added Oct. 12, 1948).

For synthesis of acids, V and VI, no further chain extension was necessary. The unsaturated esters obtained from keto esters, IX and X, were hydrogenated at low pressure with platinum catalyst, and saponification of the resultant saturated esters (XIII, XIV) gave the desired acids (V, VI).

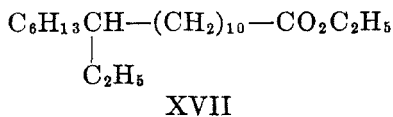
Ethyl 12-ketooctadecanoate (IX) was prepared by esterification of the keto acid obtained by oxidation of crude 12-hydroxyoctadecanoic acid from saponification of hydrogenated castor oil. The keto acid was separated with difficulty from stearic acid present in the hydrogenated castor oil, but the ethyl ester (IX) was easily purified by fractional distillation. The other three starting keto esters (VII, VIII, X) were prepared in good yield by reaction between the appropriate dialkylcadmium reagent and ester acid chloride. Since the next step in the synthesis is reaction of the keto ester with the same Grignard reagent used for making the cadmium reagent, it was thought possible that an easier approach to the hydroxy ester would be reaction of the Grignard reagent directly with the ester acid chloride, according to the following scheme.



Unfortunately, considerably lower over-all yields were obtained by this procedure, for the reactivity of the acid chloride group toward the Grignard reagent is only slightly greater than the reactivity of the ester group. In the preparation of 10-ethyl-1-dodecanol (XI), the over-all yield based on  $\omega$ -carbethoxynonyl chloride (the more valuable starting material) was 49% in the process proceeding by way of preparation and isolation of the keto ester, but only 18% when the ester acid chloride was treated directly with the Grignard reagent.

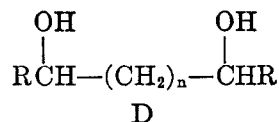
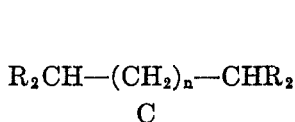
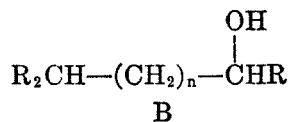
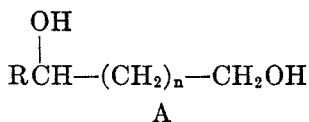
The selective reaction of a Grignard reagent with a keto ester to give a hydroxy ester has previously been used (6) as an approach to branched-chain acids. The over-all yields of saturated branched-chain acids or esters have been in the range, 20–44%. A major difficulty has been the unstirred mass obtained in the Grignard reaction. Since the yields in preparation of  $\gamma$ -valerolactones (7) by a nearly identical process were doubled by addition of benzene to break up this unstirred mass, this device was tried in the present work. Results were favorable, in that the over-all yields of saturated esters (XIII, XIV) or saturated alcohols (XI, XII) were in the range, 39–55%.

It would seem that an additional improvement in this process might be realized by introducing steric hindrance around the ester grouping. This possibility was investigated by the preparation of cyclohexyl 12-ethyloctadecanoate starting with ethylmagnesium iodide and cyclohexyl 12-ketooctadecanoate. The over-all yield of this unsaturated ester was 73%. By hydrogenation and transesterification, an over-all yield (based on keto ester) of ethyl 12-ethyloctadecanoate (XVII) amounting to 54% was obtained.



Thus, the use of the cyclohexyl ester appears an advantage, although the increase in boiling point is a handicap with higher molecular weight compounds, and trans-esterification is necessary if hydrogenation is carried out in ethanol.

A major problem encountered in synthesis of pure compounds by the scheme used in the present work is separation of the large number of compounds obtained from the reaction between a Grignard reagent and a keto ester. When the saturated alcohol (XI or XII) is the desired end-product, there must be considered the separation of (a) the diol, A, from hydrogenation of the starting keto ester; (b) the alcohol, B, from hydrogenation of the unsaturated ketone resulting from dehydration of the keto alcohol arising from reaction of the Grignard reagent with both keto and ester group; (c) the hydrocarbon, C, arising from reaction of three moles of Grignard reagent with the keto ester, dehydration and hydrogenation. The diol, D, arising from reaction of only one mole of Grignard reagent with the ester group and no reaction with the keto groups would be expected in very small amount.



From a consideration of the contribution to boiling point of the various groups present in these by-products, it was estimated that when R is ethyl compounds A and B would boil about 20° above the desired alcohol, XI, while compound C would have about the same boiling point and compound D would boil about 40° above XI. Since the hydrocarbon, C, is inert, its presence in small amount in the desired alcohol is no disadvantage, for it is easily separated from the higher molecular weight compounds obtained later in the synthesis. The other compounds should be easily separated in an efficient half-meter fractionating column. This proved the case, and a sample of crystalline diol, A, was isolated from the fraction boiling about 20° above the desired alcohol, XI. When R is propyl, all products except A should boil 20° or more above XII; however, the diol, A should boil no more than 10–15° above XII. This proved to be the case, and the construction of a four-foot Podbielniak type column was necessary for efficient separation of this diol.

When the saturated ester (XIII or XIV) is the desired product, separation of the products obtained by low-pressure hydrogenation must be considered. When R is octyl, the separation is simple, for all by-products differ in boiling point by 40° or more from the desired ester. When R is hexyl, the only separation problem concerns the unreacted keto ester, IX. This is reduced, in part, by platinum at low pressure to give the corresponding hydroxy ester, which was separated from the saturated ester, XIII, with difficulty, even in the four-

foot column. This difficulty was avoided, however, by fractional distillation of the unsaturated ester, before hydrogenation, for the keto ester, IX, boils at least ten degrees below the corresponding hydroxy ester. Some loss of unsaturated ester may have occurred during the long heating necessary for fractional distillation, for the yield of XIII (39%) was appreciably lower than obtained for XIV (55%).

## EXPERIMENTAL

Microanalyses are by C. W. Koch and V. H. Tashinian. All melting points are corrected; all boiling points are uncorrected. All distillations, unless otherwise specified, were carried out in a half-meter Podbielniak type column with heated jacket and partial reflux head.

TABLE I  
KETO ESTERS

ESTER	YIELD, %	B.P., °C	MM. HG	$n_D^{20}$	ANAL.			
					CALC'D		FOUND	
					C	H	C	H
VII	88-89	169-173	10	1.4429	69.38	10.82	68.68	10.86
VIII	94.5	165-167	7	1.4420	69.38	10.82	68.96	10.52
X	45 <sup>a</sup>	211-212	5	<sup>b</sup>	73.07	11.61	73.12	11.28
XV	74	235-240	1	solid			<sup>c</sup>	
XVI	72	236-240	1	1.4550	76.04	12.27	76.03	12.81

<sup>a</sup> The  $\omega$ -carbethoxycaprylyl chloride used in this preparation was prepared from an old sample of half ester which had disproportionated (9) to considerable di-acid chloride and di-ester. The di-ester is inert, but the di-acid chloride yielded 9,17-hexacosanedione, b.p. 247-248° (2 mm.); 19.7 g. isolated from an 0.33 mole run. After two crystallizations from acetone, this diketone melted at 92.8-93.4°.

*Anal.* Calc'd for  $C_{26}H_{48}O_2$ : C, 78.88; H, 12.71. Found: C, 79.09; H, 12.88.

<sup>b</sup> After two crystallizations from acetone, m.p. 38.2-38.7°.

<sup>c</sup> Not analyzed, characterized as acid, cf. Table II.

*Alkyl halides.* The simple normal halides used as starting materials were purified commercial products or obtained from commercial alcohols by usual methods. All were distilled through the half-meter column or a 1-meter column packed with glass helices, and collected over a range of about one degree. Branched-chain bromides were prepared from anhydrous hydrogen bromide taken from a cylinder, following the usual procedure (8). 10-Ethyl-1-bromododecane was obtained in 83% yield, b.p. 159.5-161.5° (11 mm.),  $n_D^{20}$  1.4653.

*Anal.* Calc'd for  $C_{14}H_{29}Br$ : C, 60.66; H, 10.55.

Found: C, 59.47; H, 10.80.

9-n-Propyl-1-bromododecane was obtained in 63% yield, b.p. 168-171.5° (13 mm.),  $n_D^{20}$  1.4648.

*Anal.* Calc'd for  $C_{15}H_{31}Br$ : C, 61.84; H, 10.73.

Found: C, 61.68; H, 10.93.

*Keto esters* were prepared by the usual method (9) from dialkylcadmium reagent and ester acid chloride and isolated as described previously for keto esters. Data for the products are found in Tables I and II, yields being based on ester acid chloride. For esters, VII, VIII, and X, there were used two equivalents of alkyl halide (ethyl iodide, *n*-propyl bromide, and *n*-octyl bromide) for one of ester acid chloride. For esters, XV and XVI, the equivalency of branched-chain halide was 1.25.

*Ethyl 12-ketooctadecanoate (IX)*. A suspension of 200 g. (0.67 mole) of crude 12-hydroxy-octadecanoic acid (from saponification of commercial hydrogenated castor oil) in 1100 ml. of glacial acetic acid was stirred vigorously as there was added during two hours a solution of 50 g. (0.50 mole) of chromic anhydride in 270 ml. of glacial acetic acid. The temperature of the mixture did not rise above 37°. After stirring, without heating, had been continued for an additional two hours, the mixture was poured, with stirring, into ten liters of water. The solid product was crystallized from acetone, after treatment with Norit. The yield of pale lavender keto acid, m.p. 80.5–83°, was 155 g. (78%, assuming homogeneous starting material). The impure acid so obtained was esterified by heating for two hours with 450 ml. of absolute ethanol containing 24.5 g. of hydrogen chloride gas. After dilution of the reaction mixture with water and extraction with ether, the ester was distilled. After a fore-run of 15 g., consisting largely of ethyl stearate, the crystalline keto ester was collected at 199–200° (3.0 mm.), m.p. 35–37.5°, wt. 132.2 g. (61% yield from crude hydroxy acid).

Saponification of a sample of the ester and crystallization of the keto acid from acetone yielded lustrous blades, m.p. 82.0–82.3°. Perrotte (11) reported m.p. 81.0–81.5°.

*10-Ethyl-1-dodecanol (XI)*. (A) A Grignard reagent was prepared in an atmosphere of nitrogen from 63 g. of ethyl iodide and 8.9 g. of magnesium in 200 ml. of ether. After about half the ether had been distilled, 500 ml. of dry thiophene-free benzene was added

TABLE II  
DERIVATIVES OF KETO ESTERS

ESTER	DERIVATIVE	SOLVENT FOR CRYST.	M.P., °C.
VII	Semicarbazone	Acetone	74.6–75.8 <sup>a</sup>
VIII	Keto acid <sup>b</sup>	Hexane	55.9–56.4
XV	Keto acid <sup>c</sup>	Acetone	67.0–67.8

<sup>a</sup> Polymorphic, remelts at 79.5–81.0°. Paraskova (10) reports m.p. 81.0–82.0°.

<sup>b</sup> Mol. wt. found, 217.0 (calc'd 214.3).

<sup>c</sup> Calc'd for C<sub>24</sub>H<sub>46</sub>O<sub>2</sub>: C, 75.30; H, 12.10. Found: C, 75.53; H, 12.40.

and the solution forced under nitrogen pressure into a separatory funnel. This solution was added dropwise, during one hour, to a stirred solution of 87.4 g. of ethyl 10-ketododecanoate (VII) in 450 ml. of benzene, the mixture being cooled in an ice-salt bath just insufficiently to freeze the benzene. After addition was complete, stirring was continued for an additional twenty minutes, then the organometallic complex was decomposed with ice and acid. The organic layer and an additional benzene extract of the aqueous phase were washed with water, 5% sodium carbonate solution, water, and saturated sodium chloride solution. After solvent had been distilled, last traces in a vacuum, the residue was heated for one hour with a few crystals of iodine, at 180–190°. Distillation of the unsaturated esters from a Claisen flask yielded 75.3 g. of b.p. 164–170° (10 mm.). This distillate was hydrogenated with 15 g. of copper chromite catalyst (12) at 250° and an initial cold pressure of 3180 lbs. per sq. in. The final pressure at 250° was 2870 lbs., and hydrogenation was complete in 3 hrs., 10 mins. from the time shaker and heater were started. Distillation of the product at 10 mm. pressure gave the following fractions: (a) 10-ethyl-1-dodecanol, wt. 43.1 g., b.p. 155–160°; (b) intermediate fraction, wt. 2.1 g.; (c) 1,10-dodecanediol, wt. 12.9 g., b.p. 174.5–175.5°. The yield of alcohol, XI, is 55%, based on keto ester. For the sample analyzed,  $n_D^{20}$  1.4487.

*Anal.* Calc'd for C<sub>14</sub>H<sub>30</sub>O: C, 78.43; H, 14.11.

Found: C, 77.82; H, 13.91.

(B) A solution of ethylmagnesium iodide, prepared as in Method (A) from 38 g. of ethyl iodide, was added during 80 minutes to a stirred solution of 29.8 g. of  $\omega$ -carbethoxynonyl chloride in 85 ml. of benzene, with cooling in ice and salt. The reaction mixture was worked

up, and the unsaturated ester obtained and hydrogenated as above. Distillation of the product at 10 mm. pressure gave the following fractions: (a) 10-ethyl-1-dodecanol, wt. 4.6 g., b.p. 153–158°; (b) intermediate; (c) 1,10-dodecanediol, wt. 3.5 g., b.p. 172.5–173°. Thus, the over-all yield of XI is only 18%.

The *phenylurethan* of XI, after two crystallizations from hexane, melted at 54–56.1°. It is apparently polymorphic since a sample melted completely at once when placed in a bath at 55.5°.

*Anal.* Calc'd for  $C_{21}H_{38}NO_2$ : C, 75.63; H, 10.58.

Found: C, 75.29; H, 10.26.

*1,10-Dodecanediol*, *Frac. (c)*, Method (A), after repeated crystallization from hexane-acetone, melted at 38.6–39.8°.

*Anal.* Calc'd for  $C_{12}H_{26}O_2$ : C, 71.23; H, 12.95.

Found: C, 71.16; H, 12.69.

*Ethyl 10-ethyldodecanoate* was prepared by hydrogenation of 14.9 g. of unsaturated esters [obtained as in Method (A) above] at room temperature and low pressure, with 0.3 g. of platinum oxide catalyst in 100 ml. of 95% ethanol. Hydrogenation was complete in 40 minutes, and distillation gave 11.4 g. (64% over-all yield from keto ester) of saturated ester, b.p. 162–163° (10 mm.).

*9-n-Propyl-1-dodecanol* (XII) was prepared according to Method (A) described for alcohol, XI. From 0.5 mole of ethyl 9-ketododecanoate and *ca.* 0.58 mole of *n*-propylmagnesium bromide, distillation through a 4-foot Podbielniak type column at 4 mm. pressure of the products obtained after high-pressure hydrogenation gave the following fractions: (a) 9-*n*-propyl-1-dodecanol, wt. 54.3 g. (45.5%, over-all) b.p. 150–153°,  $n_D^{20}$  1.4507; (b) intermediate, wt. 3.6 g.; (c) 1,9-dodecanediol, wt. 18.9 g., b.p. 167–172°.

The alcohol, XII, was characterized as the *α-naphthylurethan*, which crystallized in nodular clusters from acetone and appears to be polymorphic. After four crystallizations, the m.p. was 51–57°, but complete melting occurred at once when the sample was placed in a bath at 55°.

*Anal.* Calc'd for  $C_{26}H_{38}NO_2$ : N, 3.54. Found: N, 3.47.

The 3,5-dinitrobenzoate of this alcohol is an oil and the *p*-phenylbenzoate is a low-melting solid.

*1,9-dodecanediol*, *Frac. (c)* above, after repeated crystallization from hexane-acetone melted at 38.2–38.8°.

*Anal.* Calc'd for  $C_{12}H_{26}O_2$ : C, 71.23; H, 12.95.

Found: C, 71.30; H, 13.13.

*Ethyl 12-n-hexyloctadecanoate* (XIII). Starting with 0.12 mole of ethyl 12-ketooctadecanoate (IX) and the Grignard reagent from 0.21 mole of *n*-hexyl bromide, a mixture of unsaturated esters was prepared as described under Method (A) for 10-ethyl-1-dodecanol. The lower ratio of keto ester was used in order to simplify the separation of this starting material. Distillation through the column of the mixture remaining after dehydration yielded 4.3 g. of fore-run and 33.1 g. (69% yield) of pale yellow unsaturated esters, b.p. 211–215° (2 mm.). There was 11 g. of distillation residue. The ester fraction was immediately hydrogenated at room temperature and low pressure with 0.2 g. of platinum oxide catalyst in 125 ml. of 95% ethanol. The ester was sparingly soluble in ethanol and hydrogenation required 12 hours. After solution of the product in ether, removal of catalyst, and distillation of solvent, the ester was distilled; yield 18.5 g. (39%), b.p. 213–215° (2 mm.),  $n_D^{20}$  1.4508.

*Anal.* Calc'd for  $C_{26}H_{52}O_2$ : C, 78.72; H, 13.21.

Found: C, 78.58; H, 13.38.

*Ethyl 9-n-octylheptadecanoate* (XIV) was prepared in the same manner as described for XIII except that the unsaturated esters were distilled from a Claisen flask. In a run starting with 0.067 mole of ethyl 9-ketoheptadecanoate and the Grignard reagent from 0.11 mole of *n*-octyl bromide, the yield of crude unsaturated esters was 21.5 g. After hydrogenation as for XIII, distillation yielded the following fractions: (a) fore-run, wt. 4.3 g.

and containing 1.0 g. of ethyl 9-ketoheptadecanoate; (b) ethyl 9-*n*-octylheptadecanoate, wt. 15.3 g. (55% over-all yield), b.p. 224–227° (2 mm.),  $n_D^{25}$  1.4512.

*Anal.* Calc'd for  $C_{27}H_{54}O_2$ : C, 78.95; H, 13.26.

Found: C, 78.98; H, 13.15.

*Ethyl 12-ethyloctadecanoate (XVII).* Since the ethyl ester, IX, had been prepared in quantity, cyclohexyl 12-ketooctadecanoate was prepared by allowing a mixture of 61.5 g. (0.612 mole) of cyclohexanol, 50 g. (0.153 mole) of ethyl 12-ketooctadecanoate (IX), and 6.2 g. of hydrogen chloride gas to stand at room temperature for eight days. Solvent was then removed in a vacuum, last traces at 2.5 mm. and 180°, and the residue (54.8 g.) was used for the Grignard reaction.

The Grignard reagent from 14.9 g. (0.095 mole) of ethyl iodide, in 50 ml. of ether and 110 ml. of benzene, was added dropwise to a stirred solution of 30 g. (0.079 mole) of cyclohexyl 12-ketooctadecanoate in 110 ml. of benzene, the temperature being maintained by external cooling at 5–10°. Addition was completed in 15 minutes, and five minutes later the mixture had become an unstirrable jelly, so stirring was continued for an additional 30 minutes at 25–30°. The mixture was worked up and the hydroxy ester dehydrated as described under Method (A) for preparation of 10-ethyl-1-dodecanol (XI). The unsaturated esters, distilled from a Claisen flask, weighed 22.1 g. (73%), b.p. 213–220° (4 mm.).

The unsaturated ester was immediately hydrogenated at low pressure and room temperature with 0.15 g. of platinum oxide catalyst in 150 ml. of 95% ethanol. Hydrogenation was complete in one hour. After catalyst had been removed by filtration, 100 ml. of absolute ethanol and 10.6 ml. of concentrated sulfuric acid were added, and the mixture was heated under reflux for 90 minutes. The ethyl ester, XVII, was isolated by dilution of the reaction mixture with water, extraction with benzene, and distillation; yield 14.5 g. (54% over-all), b.p. 191–194° (3 mm.),  $n_D^{20}$  1.4479. There was 2.5 g. of distillation residue, and the yield on the hydrogenation and trans-esterification step is probably subject to improvement.

*Anal.* Calc'd for  $C_{22}H_{44}O_2$ : C, 77.58; H, 13.02.

Found: C, 77.33; H, 12.96.

*20-Ethyldocosanoic acid (III).* The keto ester, XV, (23.8 g.) was reduced by the Schneider and Spielman modification (6) of the Clemmensen method. The yield of semi-solid *ethyl 20-ethyldocosanoate* was 15.2 g. (66%), b.p. 220–223° (ca. 1 mm.).

*Anal.* Calc'd for  $C_{26}H_{52}O_2$ : C, 78.72; H, 13.21.

Found: C, 79.28; H, 13.86.

By saponification of 19.1 g. of the ester and crystallization from acetone of the resultant acid, there was obtained 17.3 g. (93%) of 20-ethyldocosanoic acid, m.p. 60.5–62°. After four additional crystallizations from hexane, the constant m.p. of 64.8–65.5° was reached.

*Anal.* Calc'd for  $C_{24}H_{48}O_2$ : C, 78.17; H, 13.14; mol. wt., 368.7.

Found: C, 78.53; H, 13.40; mol. wt., 369.0.

For preparation of the amide, 0.7 g. of acid was allowed to stand overnight with 0.45 g. of thionyl chloride then heated under reflux until no further gas evolution was apparent (ca. 45 mins.). Excess thionyl chloride was removed by heating *in vacuo*, and to the residual acid chloride there was added in one portion, with immediate shaking, 10 ml. of ice-cold concentrated ammonium hydroxide. After filtration of the curdy precipitate and one crystallization from acetone, 0.65 g. of *20-ethyldocosanamide* was obtained. After four additional crystallizations from acetone and two from hexane, the pure amide was obtained as fine white blades, m.p. 90.2–90.6°.

*Anal.* Calc'd for  $C_{24}H_{49}NO$ : C, 78.40; H, 13.43.

Found: C, 78.54; H, 13.55.

For preparation of the *tribromoanilide*, the acid chloride, prepared as described above from 0.7 g. of acid, was heated for 2 hours on a steam-bath with 0.5 g. of 2,4,6-tribromoaniline. After one crystallization from ethanol, 0.8 g. of fine needles was obtained. After one additional crystallization from ethanol and three from benzene-hexane, the pure tribromoanilide was obtained, m.p. 104.7–105.3°.



*Anal.* Calc'd for  $C_{30}H_{50}Br_3NO$ : C, 52.95; H, 7.41.

Found: C, 53.17; H, 7.53.

*18-n-Propylheneicosanoic acid (IV)*. The keto ester, XVI, (27.9 g.) was reduced by the modified Wolff-Kishner method, following essentially the procedure of Huang-Minlon (13). After completion of the final heating period and acidification of the cooled and diluted reaction mixture, the precipitated acid was collected; wt. 14.6 g. (58%), m.p. 45–49°. After four crystallizations from acetone, pure 18-*n*-propylheneicosanoic acid was obtained as fine blades, m.p. 51.9–52.2°.

*Anal.* Calc'd for  $C_{24}H_{48}O_2$ : C, 78.17; H, 13.14; mol. wt., 368.7.

Found: C, 78.55; H, 13.23; mol. wt., 371.8.

Derivatives of this acid were prepared as described for the isomer, III. The *amide*, after two crystallizations from acetone, had the constant m.p. 82.1–82.4°

*Anal.* Calc'd for  $C_{24}H_{48}NO$ : C, 78.40; H, 13.43.

Found: C, 78.58; H, 13.12.

The *tribromoanilide*, after four crystallizations from benzene-hexane, was obtained as very fine needles which grew in clusters at first and finally converted the solution into a gel, m.p. 92.6–93.6°.

*Anal.* Calc'd for  $C_{30}H_{50}Br_3NO$ : C, 52.95; H, 7.41.

Found: C, 53.28; H, 7.43.

*12-n-Hexyloctadecanoic acid (V)* was obtained by saponification of 17.4 g. of the ester, XIII. The crude acid (16.2 g.) was a liquid which set to a solid on standing overnight. After two crystallizations from acetone, 7.7 g. of the pure acid was obtained as long needles, m.p. 28.3–28.7°.

*Anal.* Calc'd for  $C_{24}H_{48}O_2$ : mol. wt., 368.7. Found: mol. wt., 368.0.

The *p-bromoanilide* of this acid was prepared by heating a solution of 1.0 g. of *p*-bromoaniline and the acid chloride from 1.0 g. of acid in 10 ml. of benzene under reflux for 3 hours. The benzene solution was washed with water, dilute hydrochloric acid, water, and sodium bicarbonate solution, then the benzene was distilled. The residue was crystallized twice from hexane (Norit), in which solvent it forms a gel, and twice from methanol. The pure anilide separated from methanol in spherical burrs of needles, m.p. 67.2–67.8°.

*Anal.* Calc'd for  $C_{30}H_{52}BrNO$ : C, 68.94; H, 10.03.

Found: C, 68.95; H, 9.96.

*9-n-Octylheptadecanoic acid (VI)* was obtained in 12 g. yield by saponification of 13.7 g. of the ester, XIV. The crude acid was a viscous liquid which crystallized in an ice-salt bath. It was crystallized twice from acetone, cooling to about –30°. After the second crystallization, the crystals were washed with acetone cooled to –70°, and the funnel was placed in a desiccator which was immediately evacuated. Evaporation of acetone prevented melting until nearly all solvent was removed, and the oil was left at about 1 mm. pressure for five days. The recrystallized acid, on chilling and being allowed to warm up, melted at 9–14°,  $n_D^{20}$  1.4585.

*Anal.* Calc'd for  $C_{25}H_{50}O_2$ : mol. wt., 382.9. Found: mol. wt., 381.5, 381.2.

The *p-bromoanilide*, prepared as described for acid, V, after three crystallizations from acetone, was obtained as burrs of fine needles, m.p. 79.7–80.1°.

*Anal.* Calc'd for  $C_{31}H_{54}BrNO$ : C, 69.36; H, 10.13.

Found: C, 69.04; H, 9.80.

The *amide* and *tribromoanilide* of the acid could not be obtained as satisfactory crystalline derivatives.

#### SUMMARY

Four new acids with symmetrical end-groups have been prepared. The branching groups were, respectively, ethyl, *n*-propyl, *n*-hexyl, and *n*-octyl. As the end-group became larger, causing the tertiary carbon to approach the middle of the chain, the melting point dropped further below that of the normal

isomer. This behavior is the same type as that observed when a branching methyl group is moved toward the middle of the chain; hence a symmetrical end-group has no tendency to impart to branched-chain acids a relatively high melting point.

In the course of these syntheses, the selective reaction of a Grignard reagent with the keto group in an aliphatic keto ester has been studied, and improved yields have been realized in this reaction.

BERKELEY, CALIFORNIA

#### REFERENCES

- (1) PROUT AND CASON, *J. Org. Chem.*, preceding article.
- (2) CHARGAFF, *Ber.*, **65**, 745 (1932).
- (3) WHITMORE, SUTHERLAND, AND CORBY, *J. Am. Chem. Soc.*, **64**, 691 (1942).
- (4) CASON, *J. Org. Chem.*, **13**, 227 (1948).
- (5) STÄLLBERG-STENHAGEN AND STENHAGEN, *J. Biol. Chem.*, **165**, 599 (1946).
- (6) SCHNEIDER AND SPIELMAN, *J. Biol. Chem.*, **142**, 345 (1942).  
CASON AND PROUT, *J. Am. Chem. Soc.*, **66**, 46 (1944).
- (7) CASON, ADAMS, BENNETT, AND REGISTER, *J. Am. Chem. Soc.*, **66**, 1764 (1944);  
CASON, BREWER, AND PIPPEN, *J. Org. Chem.*, **13**, 239 (1948).
- (8) REID, RUHOFF, AND BURNETT, *Org. Syn.*, Coll. Vol. II, 246 (1943).
- (9) CASON, *J. Am. Chem. Soc.*, **68**, 2078 (1946).
- (10) PARASKOVA, *Compt. rend.*, **198**, 1701 (1934).
- (11) PERROTTE, *Compt. rend.*, **200**, 746 (1935).
- (12) ADKINS, *Org. Syn.*, Coll. Vol. II, 144 (1943).
- (13) HUANG-MINLON, *J. Am. Chem. Soc.*, **68**, 2487 (1946).