[Contribution from the Chemical Laboratory of the University of California]

BRANCHED-CHAIN FATTY ACIDS. VI. RELATIONSHIP OF MELTING POINT TO STRUCTURE. NEW METHOD OF SYNTHESIS OF ACIDS CONTAINING A QUATERNARY CARBON ATOM

JAMES CASON

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Since the higher fatty acids often form mixed crystals showing a relatively sharp melting point which is not changed by recrystallization, it is often troublesome to determine whether an acid melting lower than the normal isomer is a branched-chain acid or a fortuitous mixture giving the observed molecular weight. Although the accumulation of data concerning the properties of pure synthetic branched-chain acids is not yet great, it seems possible that certain useful predictions may soon be made concerning the melting points possible for a branched-chain acid of a given molecular weight.

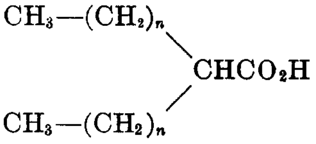
A full consideration of the relationship of melting point to the position of a branching methyl group is best deferred until additional syntheses of methyloctadecanoic and methyltetracosanoic acids in progress in this laboratory are completed and reported. It has already been shown by Weitkamp (1), however, that the iso acid (branching group on the carbon next to the end of the chain) always melts one degree or less below the normal isomer, for acids with fourteen or more carbons, while the *d*-anteiso acid (branching group on the third carbon from the end of the chain) always melts considerably lower than this, 14–24° below the normal isomer. Schneider and Spielman (2) have prepared a series of 2-methyl acids, and all of them melted 11–14° below the normal isomers. A consideration of the melting points of the synthetic 3- (3), 10- (4, 5), 15- (6), and 16-methyloctadecanoic (7) acids, as well as 6- (7), 10- (2, 7), and 14-methyltetracosanoic (6) acids makes it apparent that the 2-methyl acid and anteiso acid have melting points higher than any acid of the same molecular weight with the branching methyl group attached to a carbon between these two positions.

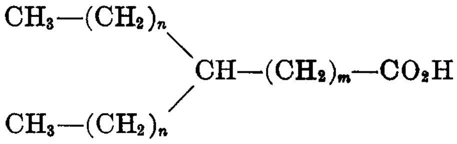
In the instances of 10-methyloctadecanoic acid, 16-methyloctadecanoic acid and 2-methylhexacosanoic acid (2, 8), both *dl*- and optically active isomers have been obtained, and in each case the optically active forms melted below the *dl*-isomer. The *dl*-16-methyloctadecanoic acid (C_{19} anteiso acid) (7) melted about 4° above the *d*-isomer (1). Thus, it seems safe to say that no methyl substituted acid, except the iso acid, can have a melting point less than 10° below that of the normal isomer, and the iso acid melts no more than 1° below the normal isomer. The only additional data which seem desirable in support of this statement are the melting points of *dl*-anteiso acids with twenty-four or more carbons.

These conclusions are based on consideration of acids containing an odd number of total carbon atoms, thus an even number of atoms in the straight-chain portion of the acid. In such instances, the lowering of the melting point caused by introduction of the branching methyl group is nearly the same when referred to the normal acid corresponding to the straight-chain portion of the molecule, or to the normal acid corresponding to the total number of carbons in the branched-chain acid. This follows from the fact that an odd-carbon normal acid having $n+1$ carbon atoms has nearly the same melting point as the even-carbon acid containing n carbon atoms. Actually, in the case of 15-methylheptadecanoic acid (9), the point of reference appears to be the normal acid corresponding to the straight-chain portion of the molecule. This acid melts at 43.5–43.7°, 17.6° below the melting point of *n*-heptadecanoic acid, a differential corresponding well with the 19°-differential between 16-methyloctadecanoic acid and *n*-octadecanoic acid (stearic acid). If the 15-methylheptadecanoic acid is related to stearic acid, there is no such correspondence. Thus, so far as may be deduced from this single known example, it appears that a methyl-substituted branched-chain acid(other than the iso acid) with an even number of carbon atoms must melt even more than 10° below the normal isomer.

Thus, there is a region of at least ten degrees just below the melting point of the normal isomer where a methyl-substituted acid cannot melt, and it seems certain that introduction of additional methyl groups or replacement of methyl by a larger group would not ordinarily give a melting point in this "excluded region". Since several C_{24} acids (10) and one C_{25} acid (11) have been reported as melting in this "excluded region", it becomes of interest to consider whether any special structures might permit a branched-chain acid to melt in this region.

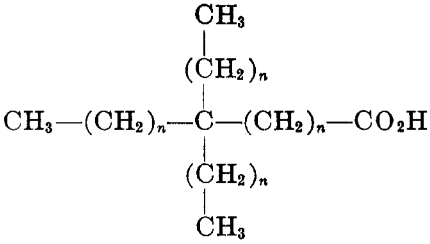
The very high melting point of the iso acids is striking and difficult to explain unless it be attributed to the symmetrical end-grouping. Thus, other types with similar structures, such as represented by formulas I and II, might also have relatively high melting points.

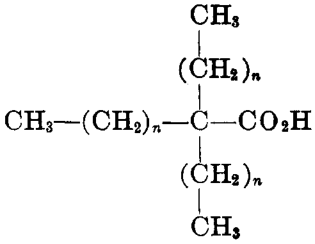

I


II

Data in the literature exclude the possibility of type I having such a melting point. Dioctylacetic acid (12) melts at 35–36°, didodecylacetic acid (13) melts at 70–71°, and dihexadecylacetic acid (14) melts at 68–69°. Although there is no information in the literature concerning acids of type II, work in progress in this laboratory has shown that acids of this type, where n is 1 or 2 and m is much larger, have relatively low melting points. Thus, the high melting points of the iso acids remain without analogy.

Other structures which might result in high melting points are the symmetrical types represented by formulas III and IV. Trimethylacetic acid (15) melts at about 35°, while triethylacetic acid (16) melts at about 39°.


$$\begin{array}{rcl} & CH_3 & \\ & | & \\ & (CH_2)_n & \\ & | & \\ CH_3-(CH_2)_n- & C & -(CH_2)_n-CO_2H \\ & | & \\ & (CH_2)_n & \\ & | & \\ & CH_3 & \end{array}$$
III


$$\begin{array}{rcl} & CH_3 & \\ & | & \\ & (CH_2)_n & \\ & | & \\ CH_3-(CH_2)_n- & C & -CO_2H \\ & | & \\ & (CH_2)_n & \\ & | & \\ & CH_3 & \end{array}$$
IV

These data suggest that higher molecular weight acids of these types might have relatively high melting points. However, no acids of this type have been synthesized, and the synthesis of such types proves very difficult. Robinson and co-workers (17), also Buu-Hoï and Cagniant (18), have made a study of the synthesis of acids containing a quaternary carbon, and it was found that the introduction of two large groups on the quaternary carbon is very difficult. The introduction of three groups, all larger than ethyl, was not attempted. All syntheses developed for introduction of two large groups on the quaternary carbon were tedious and gave very low over-all yields.

It would seem that the most hopeful approach to this problem is introduction on the quaternary carbon of relatively small groups containing terminal functional groups of such a nature that the chains may be extended as desired *after* the step creating the quaternary carbon. These later reactions would then involve groups somewhat removed from the highly hindered center. Of the various starting compounds which might be considered, the γ-cyano aldehydes and γ-cyano ketones obtained by the cyanoethylation reaction of Bruson and Riener (19) seem promising. The present paper reports the development of a synthesis of acids containing a quaternary carbon, starting with 2-ethyl-2-(β-cyanoethyl)hexanal (V) (19). It is hoped that the method may be extended to synthesis of compounds of types III and IV.

The cyano aldehyde, V, readily obtained in quantity and in the yield previously reported (19), was converted in high yield to α-butyl-α-ethylglutaric acid (VI), which was also obtained by Bruson and Riener. On account of the great hindrance around one carboxyl in this acid, it may be converted in excellent yield to either of the two possible half esters. The unhindered carboxyl is esterified by heating for one hour with a large excess of methanol, in the presence of an acid catalyst. Under these conditions no more than a trace of di-ester or di-acid is recovered. Even when the heating period is extended to one hundred forty hours a 10% yield of half ester is obtained; so the essential homogeneity of the half ester, VIII, seems assured. The same half ester is obtained when the acid is first converted to the anhydride, VII, and this allowed to react with methanol. The other half ester, X, is obtained by saponification of the di-ester, IX, with 1.1 equivalent of alkali. Essentially no di-acid is obtained, even when the amount of alkali is increased to 1.25 equivalent.

It was initially assumed that if the half ester, X, were converted to its acid chloride and this allowed to react with dibutylcadmium, the keto ester, XII, would be obtained. This procedure gave a keto ester of the expected composition, and when this keto ester was reduced by the modified Wolff-Kishner procedure (20), there was obtained a liquid acid of the composition and molecular weight expected for *n*-butylethyl-*n*-heptylacetic acid (XIV). When this acid was converted to solid derivatives it became apparent that something was amiss, for the derivatives melted over ranges of ten to fifty degrees, and no sharp-melting products could be obtained by repeated fractional crystallization. As has been briefly reported (21), this behavior has been traced to the fact that the ester acid chloride of either of the half esters, VIII and X, rearranges to a mixture of the two possible ester acid chlorides. Thus, the same tribromoanilide is obtained from either of the half esters. The structure, XI, is assigned to this tribromoanilide, since formation of the other isomer would be subject to high hindrance.

As has been mentioned (21), such a rearrangement of ester acid chlorides has been observed previously, but the mixture of products obtained was ascribed to the starting half esters being non-homogeneous. There are several examples (22), in the literature where ester acid chlorides of unsymmetrical succinic or glutaric acids have been used in synthesis; however, the data are not sufficient to show whether there was rearrangement. There is one instance (23), however, where the data show clearly that such an ester acid chloride was used without rearrangement. In this case, two carbons of the glutaric acid were part of a six-membered ring, and this may have hindered rearrangement; however, it is also true that this ester acid chloride was handled rapidly at temperatures below 40°. When our ester acid chlorides were prepared and used in the cadmium reaction at temperatures of 40° or less, again rearrangement occurred, but less than when the acid chlorides were heated. The composition of the keto ester was determined by separation of the two keto esters or of the acids obtained after Wolff-Kishner reduction. It seems worthy of comment that the excellent procedure of Huang-Minlon (20) gave a 41% yield on reduction of the hindered carbonyl in XIII. The reduction of such hindered carbonyl groups by other methods (*cf.* ref. 17) has been tried, but without success. The data summarized in Table I show that rearrangement occurs, in part at least, after the acid chloride is formed.

TABLE I

EFFECT OF TEMPERATURE ON REARRANGEMENT

REACTION		COMPOSITION OF PRODUCT	
VIII	$\xrightarrow[\text{acid chloride}]{\text{via distilled}}$	XII	61%
		XIII	39%
VIII	$\xrightarrow[\text{below 40°}]{\text{via acid chloride}}$	XII	42%
		XIII	58%
X	$\xrightarrow[\text{acid chloride}]{\text{via distilled}}$	XII	55%
		XIII	45%
X	$\xrightarrow[\text{below 40°}]{\text{via acid chloride}}$	XII	68%
		XIII	32%

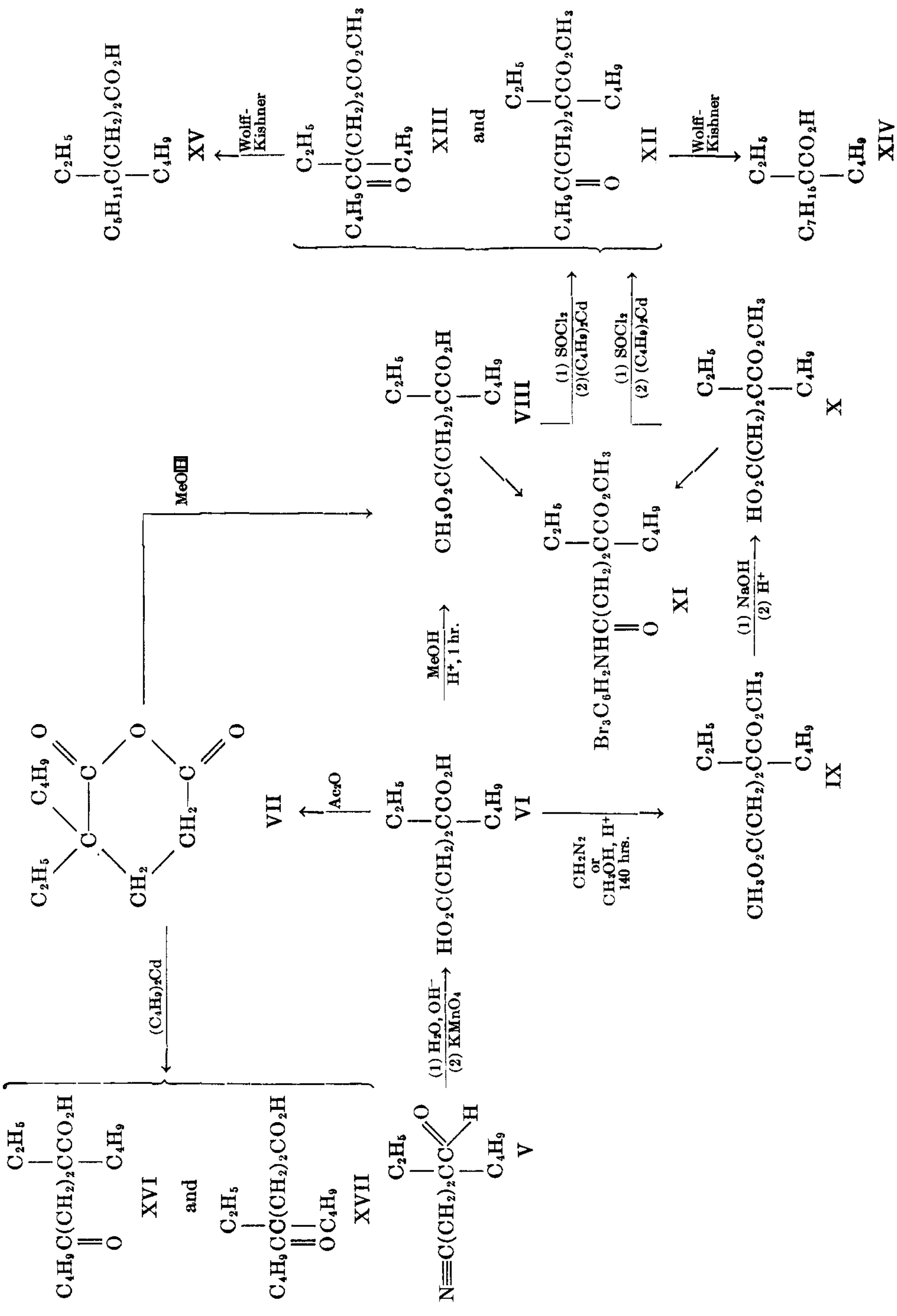
A similar rearrangement has been reported by Prelog and Heimbach-Juhasz (24), who observed that γ-ethoxybutyryl chloride rearranges nearly quantitatively into ethyl γ-chlorobutyrate when heated at 100°. Since such a rearrangement did not occur with ε-ethoxycaproyl chloride, it was postulated and supported by rate measurements that the rearrangement is intramolecular and a cyclic oxonium salt is the intermediate in the rearrangement. A similar explanation has been presented by Johnson and Goldman (25) to explain the ester exchange observed when certain itaconic acid half esters were heated with zinc chloride in acetic acid. Such a hypothesis seems the most reasonable explanation of the rearrangement of ester acid chlorides, and if this is the case only derivatives of succinic and glutaric acids should show this behavior. Although this rearrangement lowers the yield of either quaternary carbon acid eventually obtained, it does not defeat the synthesis, for the two products may be separated essentially quantitatively. When a mixture of the acids, XIV and XV, is heated for two hours with a large excess of methanol in the presence of sulfuric acid, the unhindered isomer (XV) is esterified quantitatively while the hindered isomer (XIV) is essentially unattacked. The keto acids behave similarly. Controlled saponification is only slightly less selective, and the combination of the two processes or repetition of one process gives products of high purity.

Since treatment of the anhydride, VII, with methanol gave only the half ester, VIII, it was hoped that reaction of this anhydride with dibutylcadmium would give only one keto acid, XVI, resulting from addition of butyl at the unhindered carbonyl. Surprisingly enough, the keto acid obtained from this reaction consisted of only 31.5% of this isomer (XVI), the remaining 68.5% being the isomer (XVII) resulting from addition of butyl to the hindered carbonyl. This seems conclusive proof that organocadmium reagents do not react with acid anhydrides and, by inference, acid chlorides by addition to the carbonyl group, for such a mechanism could hardly permit the observed distribution of isomers just mentioned. If, on the other hand, the initial stage of the reaction is approach of cadmium to the central oxygen of the anhydride, followed by breaking of the linkage from oxygen to one or the other of the carbonyl carbons, then the above distribution of isomers is reasonable, for the -CdO- grouping would prefer the unhindered carbonyl. Once this structure is established, the butyl group has no choice but to become attached to the hindered carbonyl. This mode of reaction is consistent with evidence (26) that the mechanism of the reaction of a Grignard reagent with acid halides is different from that of the organo compounds of mercury, zinc, and cadmium.

It seems possible that a different sequence of manipulation of the groups in a cyano aldehyde such as V could result in a synthesis of quaternary-carbon acids not beset by the difficulties encountered in the present work. This is being further investigated.

EXPERIMENTAL

Microanalyses are by C. W. Koch and V. H. Tashinian. All melting points are corrected, all boiling points uncorrected. All distillations, unless otherwise specified, were through a half-meter column of Vigreux type or Podbielniak type. Pressure was measured with a Zimmerli gage and subject to a probable error of 0.2–0.3 mm. of mercury.


Wolff-Kishner
Wolff-Kishner
(1) SOCl₂ (2) (C₄H₉)₂Cd
(1) SOCl₂ (2) (C₄H₉)₂Cd
MeOH
MeOH H⁺, 1 hr.
Ac₂O
(C₄H₉)₂Cd
(1) H₂O, OH⁻ (2) KMnO₄
CH₂N₂ or CH₃OH, H⁺ 140 hrs.
(1) NaOH (2) H⁺
and
and
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV
XV
XVI
XVII

α-Butyl-α-ethylglutaric acid (VI) (19). The cyano aldehyde (V) was prepared as described previously (19), the yields being 79–83.5% in runs varying from 0.1 mole to 3.6 moles, b.p. 119–120° (2 mm.), n_D^{29} 1.4508. Hydrolysis of V to γ-ethyl-γ-formylcaprylic acid was accomplished with aqueous alkali as described by Bruson and Riener except that extension of the heating period to seven hours raised the yield to 87.5% in a 2.75 mole run; b.p. 140–141° (1.25 mm.), n_D^{29} 1.4550. Hydrolysis with various concentrations and equivalencies of alcoholic alkali gave a much lower yield, as did hydrolysis with sulfuric acid in aqueous acetic acid. These latter methods also gave poor material balances, presumably on account of partial reversal of the cyanoethylation reaction.

After trial of several procedures, the permanganate oxidation to VI was modified as follows. In a solution of 160 g. of potassium hydroxide in 2.4 liters of water was dissolved 400 g. (2 moles) of aldehydo acid. To the stirred mixture was added during one hour 316 g. (2 moles) of solid potassium permanganate, the temperature being maintained at 45–50° by external cooling. After stirring for an additional hour at this temperature, the manganese dioxide was removed and extracted on the steam-bath with 500-cc. and 250-cc. portions of water. The total colorless filtrate was acidified with 450 cc. of concentrated hydrochloric acid. The viscous oil which separated began to crystallize slowly after about three hours, and after about five hours the hard, white crystalline mass was ground and dried in a vacuum. Yield of crude product, 397 g. (91.8%), m.p. 72–78°. This crude acid contains appreciable impurities, but purification by crystallization involves much loss, and purification by distillation at later stages in the synthesis is best. Recrystallization was satisfactory only from nitromethane, from which small, hard crystals separated over a period of two to three days. From 7.9 g. of crude acid was obtained 4.3 g. of pure VI, m.p. 78–80°, not raised by further crystallization; eq. wt. 108 (calc'd 108.1); literature (19) m.p. 81–82°.

α-Butyl-α-ethylglutaric anhydride (VII) was prepared by heating under reflux for one and one-quarter hours a mixture of 50 g. of crude VI and 44 cc. of acetic anhydride. Distillation at 5.5 mm. pressure gave 3.1 g. of fore-run, boiling largely at about 120°, and 33.8 g. (74%) of anhydride, b.p. 153–153.5°. There was a residue of 4.5 g. A center cut, b.p. 153.5°, n_D^{30} 1.4647, was used for analysis.

Anal. Calc'd for $C_{11}H_{18}O_3$: C, 66.65; H, 9.15.
Found: C, 67.00, H, 9.23.

α-Butyl-α-ethyl-γ-carbomethoxybutyric acid (VIII). (A) A mixture of 21.6 g. (0.1 mole) of crude VI, 61 cc. (1.5 mole) of methanol, and 3.8 cc. of concentrated sulfuric acid was heated under reflux for one hour, then poured into 250 cc. of water. The products, obtained after distillation of the material obtained by three extractions with ether, consisted of 2.1 g. of fore-run boiling largely below 110° (3 mm.) and 19.3 g. (84%) of half ester, VIII, b.p. 155–159° (3 mm.). There was only a trace of residue. The fore-run obtained here and in other preparations starting with crude VI is not obtained when pure dibasic acid is used (*cf.*, IX, below). A center cut was used for analysis, b.p., 159° (3 mm.), n_D^{28} 1.4530.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.57, H, 9.63.
Found: C, 62.30, H, 9.53.

(B) A mixture of 12.2 g. of anhydride (VII) and 3.0 cc. of methanol was heated under reflux on a steam-bath for two hours, then distilled at 1 mm. pressure to yield, after only 0.1 g. of fore-run, 13.4 g. (94.3%) of half ester, VIII, b.p. 142.0–142.5°, n_D^{28} 1.4526. The homogeneity of this product was tested by heating it under reflux for one hour with 35 cc. (15 equivs.) of methanol and 2.2 cc. of concentrated sulfuric acid. The product, obtained as in procedure (A), was distilled at 1.5 mm. pressure to give (a) 0.6 g., b.p. 104.2–104.5°, n_D^{28} 1.4417; (b) 0.6 g., b.p. 104.5–147.5°; (c) 11.7 g., b.p. 147.5–148.5°, n_D^{28} 1.4525. There was no residue. The high recovery of half ester with no change in index of refraction, and the very small conversion to di-ester (Frac. a) show that treatment of the anhydride with methanol gives essentially pure VIII.

Dimethyl α-butyl-α-ethylglutarate (IX). (A) Using 151 g. of crude VI, procedure (A) for VIII was followed except that refluxing was continued for one hundred forty hours. The fractions obtained on distillation were (a) 8.2 g., b.p. 80–122° (4 mm.); (b) 100.5 g. (58.8%)

of di-ester, b.p. 122–124° (4 mm.); (c) 2.5 g., b.p. 100.5–141.5° (1 mm.); and (d) 16.0 g. of half ester, VIII, b.p. 141.5–143.5° (1 mm.). There was only 4.4 g. of residue, and no other material was recovered.

(B) A solution of 8.0 g. of recrystallized VI in 50 cc. of ether was treated at 0° with an excess of diazomethane in ether and allowed to stand four hours at 0°. After excess diazomethane had been destroyed with acetic acid, the mixture was distilled to give 8.5 g. (94.5%) of IX, b.p. 122–124° (4 mm.). There was only 0.1 g. of fore-run and no residue. On a larger run in which crude VI was used there was 2.3 g. of fore-run, b.p. 84–119° (4 mm.), and 31.0 g. of di-ester, b.p. 119–124° (4 mm.). For analysis, there was used a center cut, b.p. 124° (4 mm.), n_D^{28} 1.4418.

Anal. Calc'd for $C_{13}H_{24}O_4$: C, 63.90, H, 9.90.
Found: C, 63.47, H, 9.80.

γ-Carbomethoxy-γ-ethylcaprylic acid (X). A solution of 100.5 g. (0.412 mole) of IX in 225 cc. of methanol was mixed with 50 cc. of 2 *N* aqueous sodium hydroxide and heated under reflux. At intervals of fifteen minutes were added additional 50-cc. portions of 2 *N* aqueous alkali, until at the end of one hour a total of 225.5 cc. (0.453 mole) of alkali had been added. The solution remained homogeneous throughout. After the mixture had been heated under reflux for an additional two hours it was diluted with 700 cc. of water, acidified with 50 cc. of concentrated hydrochloric acid, and extracted with three portions of ether. Distillation at 1 mm. pressure of the product obtained from the ether extracts gave 2.7 g. of fore-run, b.p. 97–140°, and 89.0 g. (94%) of half ester, X, b.p. 140–142°. The residue was about 0.1 g. For analysis there was used a center cut, b.p. 141.5° (1 mm.), n_D^{28} 1.4502.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.57, H, 9.63.
Found: C, 62.73, H, 9.78.

Tribromoanilide XI. A mixture of 1.2 g. of distilled acid chloride prepared from either VIII or X, 1.4 g. of tribromoaniline, and 20 cc. of dry xylene was heated under reflux for four hours. After removal of xylene *in vacuo* and addition of 10 cc. of acetone the mixture was allowed to stand forty-eight hours at room temperature and eight to ten hours at 5°. The crystalline tribromoanilide which had separated weighed 0.4–0.6 g. and melted at 121–124.5°. After two additional crystallizations from acetone there were obtained beautiful fibrous needles: from VIII, m.p. 127.3–128.3°; from X, m.p. 126.5–127.5°, mixed m.p. 127.0–128.0°.

Anal. Calc'd for $C_{18}H_{24}Br_3NO_3$: C, 39.88, H, 4.45.
Found: C, 39.94, H, 4.50.

Ester acid chlorides from VIII and X. A mixture of the half ester and 3.0 mole equivalents of purified thionyl chloride was allowed to stand fifteen to seventeen hours at about 20°, evolution of gas continuing for at least four hours. Use of benzene as solvent and pyridine as catalyst, as described by Bachmann *et al.* (23), appeared to have no effect on the reaction. When the acid chloride was to be used in a low-temperature cadmium reaction, excess thionyl chloride was removed *in vacuo* at a bath temperature of 40° or less, then dry benzene was added and removed *in vacuo*, the residue being used for the cadmium reaction. When the acid chloride was distilled there was obtained a 97% yield of colorless product, b.p. 119–123° (1.25 mm.).

Keto esters XII and XIII. (A) *From distilled ester acid chloride.* A benzene (80 cc.) solution of dibutylcadmium prepared in the usual way (27) from 19.8 g. of pure *n*-butyl bromide was heated to boiling with stirring and treated during two minutes with a solution of 18.0 g. of the above ester acid chloride in 35 cc. of benzene. After heating under reflux for an additional one and one-half hours, the reaction was worked up as previously described (27) for keto esters. Distillation gave, after 0.4 g. of fore-run, 15.7–16.8 g. (80.7–86.3%, based on ester acid chloride) of keto ester, b.p. 128–129° (1.5 mm.). A center cut, b.p. 129°, n_D^{25} 1.4485 gave the correct analysis for the keto ester (see below).

(B) *From unheated ester acid chloride.* The procedure was as above except that three equivalents of butyl bromide were used and the ester acid chloride solution was added to the cadmium solution at 4–5° and the mixture was initially stirred without heating. The temperature rose to 25–30° after twenty-five to thirty minutes, then heat was applied and stirring continued at 35–40° for three to four hours. The reaction was worked up to yield 90.5–91% (based on half ester) of keto ester, b.p. 127.5–128° (1.25 mm.).

Separation of the keto esters is illustrated by the following procedure applied to 53.2 g. of keto ester prepared by procedure (B) from 50 g. of half ester, X. A solution of the keto ester in 453 cc. of methanol was heated under reflux for four hours with 19.7 cc. of 6 *N* aqueous sodium hydroxide (0.6 equiv. of 0.25 *N* alkali). The homogeneous solution was diluted with 1 liter of water and extracted with one 300-cc. portion and three 100-cc. portions of pentane. The pentane extracts, kept separate, were washed in series twice with a mixture of 75 cc. of water and 25 cc. of methanol. From the pentane extracts was obtained 33.5 g. of unsaponified ester, XII, b.p. 129–130° (1.25 mm.). In order to ensure the homogeneity of XII, the saponification and separation procedure was repeated with 0.3 equiv. of alkali. There was recovered 31.5 g. of *keto ester, XII,* b.p. 126–127° (1 mm.). A center cut, b.p. 127° (1 mm.), n_D^{30} 1.4460 was used for analysis.

Anal. Calc'd for $C_{16}H_{30}O_3$: C, 71.06, H, 11.18.
Found: C, 71.01, H, 11.09.

To obtain the acid, XVII, from the first saponification the total aqueous extracts were concentrated to about 400 cc., acidified with 15 cc. of concentrated hydrochloric acid, and extracted with three portions of hexane. On concentrating the washed and dried hexane extracts to dryness in a vacuum, there was obtained a residue consisting of 18.0 g. of a slightly yellow viscous oil. From the second saponification there was similarly obtained 1.7 g. of oil. The much smaller amount of keto acid obtained on the second saponification suggests that this acid is largely XVI and that a similar amount of XVI should be present in the first lot of 18.0 g.; this is supported by the results of the esterification described below. An attempt was made to obtain a solid *p*-bromoanilide from 1.0 g. of the second lot (1.7 g.) of keto acid, by reaction of the acid chloride with *p*-bromoaniline, but no crystalline material could be isolated.

The total remaining keto acid (18.7 g.) was heated under reflux for two hours with 75 cc. (25 equivs.) of methanol and 3 cc. of concentrated sulfuric acid. The mixture was diluted with 300 cc. of water and extracted with three portions of pentane. The combined pentane extracts were extracted with a mixture of 75 cc. of water, 25 cc. of methanol and 5 cc. of 6 *N* sodium hydroxide. The work-up for neutral and acidic fractions was continued as described above. Distillation of the neutral fraction gave, after 0.3 g. of fore-run, 16.7 g. of *keto ester, XIII,* b.p. 133.5–135.5° (1.5 mm.). A center cut, b.p. 135.5° (1.5 mm.), n_D^{30} 1.4500, was used for analysis.

Anal. Calc'd for $C_{16}H_{30}O_3$: C, 71.06, H, 11.18.
Found: C, 70.68; H, 11.05.

From the acidic fraction there was obtained 2.4 g. of a slightly yellow oil, presumably XVI.

The data in this section were used for calculation of the composition of product in the last line of Table I.

n-Butylethyl-n-heptylacetic acid (XIV). Although the exact Wolff-Kishner procedure described by Huang-Minlon (20) gave rather low yields with our keto acids, more drastic conditions gave excellent results. The following procedure was standardized by reduction of pure keto esters and the yield data applied to analysis of mixtures of keto esters or acids by separation of the reduced acids.

A mixture of 16.5 g. of pure keto ester, XII, 11.9 g. of potassium hydroxide, 11.3 cc. of 85% hydrazine hydrate, and 85 cc. of diethylene glycol was heated under reflux in a salt-bath for two hours (temperature of refluxing mixture, *ca.* 135°). The potassium hydroxide does not dissolve until the mixture reaches boiling, then dissolves rapidly with vigorous evolution of heat. Caution is necessary to prevent material from being driven out the top of the condenser; the flask should be less than half full. After the reflux period, the condenser was removed and the temperature of the salt-bath raised to 225–230° during about fifteen minutes, the inside temperature going to about 215°. The condenser was then replaced and heating continued at this bath temperature for nine and one-half hours, the inside temperature remaining at 215–220°. If the inside temperature dropped below 215°, the condenser was again removed briefly. After the mixture had been cooled to about 100° it was diluted with 300 cc. of water containing 25 cc. of concentrated hydrochloric acid and extracted with three portions of pentane. The extracted material was carefully divided into acidic and neutral fractions as has been described above, and the acidic fraction was distilled at 1 mm. pressure to give a single fraction, XIV, as a colorless oil, b.p. 140.5–141°, weight 13.3 g. (89.9%), n_D^{30} 1.4465. For analysis there was used a center cut, b.p. 141°, n_D^{27} 1.4472.

Anal. Calc'd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48; eq. wt., 242.4.
Found: C, 74.17; H, 12.39; eq. wt. 241.5.

The *p-bromoanilide* was prepared by heating for one hour in 15 cc. of dry benzene a mixture of 2.0 g. of *p*-bromoaniline and 1.1 g. of acid chloride obtained from XIV with thionyl chloride. After the benzene solution had been washed with water, dilute hydrochloric acid, dilute sodium carbonate and water, the benzene was removed *in vacuo* and the residue crystallized from 10 cc. of nitromethane; m.p. of product, 87.5–88.9°. After two additional crystallizations from nitromethane there was obtained 0.6 g. of slender white needles, separating usually in burrs, m.p. 88.5–89.0°. This substance sinters very slightly at 86.5°, and if placed in a bath pre-heated to 87.7°, it melts completely at once except for a barely perceptible haze which disappears at 89.0°. Presumably, it is polymorphic.

Anal. Calc'd for $C_{21}H_{34}BrNO$: C, 63.62; H, 8.65.
Found: C, 63.51; H, 8.72.

The amide of XIV could not be obtained crystalline.

4-Butyl-4-ethylnonanoic acid (XV). The Wolff-Kishner reduction was carried out according to the above procedure, using 12.0 g. of pure keto ester, XIII. The product consisted of 4.5 g. (41.6%) of a slightly yellow oil, b.p. 139–143° (1.25 mm.), n_D^{27} 1.4544. For analysis, there was used a colorless sample of XV, obtained by saponification of its ester; b.p. 141.5° (1 mm.), n_D^{27} 1.4533.

Anal. Calc'd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.48; eq. wt., 242.4.
Found: C, 74.09; H, 12.39; eq. wt. 245.7.

The *p-bromoanilide* prepared as described for its isomer, was obtained in 72% yield after one crystallization from hexane-acetone, m.p. 121–121.8°. After two additional crystallizations there were obtained fibrous white needles of the consistency of cotton, m.p. 121.6–122.2°.

Anal. Calc'd for $C_{21}H_{34}BrNO$: C, 63.62; H, 8.65.
Found: C, 63.95; H, 8.55.

The tribromoanilide of XV could not be obtained crystalline.

Separation of mixtures of acids XIV and XV. The data in the first three lines of Table I were obtained by separating the mixtures of XIV and XV which resulted from reduction of the mixed keto esters obtained from the cadmium reaction. Illustrative of this procedure is separation of 9.3 g. of mixed acids obtained by reduction of 15.5 g. of mixed keto esters. This mixture of keto esters was prepared according to Procedure (B) by the reaction of dibutylcadmium with the acid chloride from 14.6 g. of half ester, VIII.

The mixed acids (9.3 g.) were heated under reflux for two hours with 54 cc. (35 equivs.) of methanol and 2.35 cc. of concentrated sulfuric acid. The mixture was poured into 250 cc. of water and extracted with three portions of ether. After the extracts had been washed with water and dried, the solvent was flash-distilled and the residue distilled at 2 mm. pressure to give (a) 3.6 g. of the ester of XV, b.p. 121–121.5°, n_D^{28} 1.4437; (b) 0.1 g. of intermediate fraction; and (c) 5.3 g. of the acid, XIV, b.p. 148–152°, n_D^{28} 1.4475. Fraction (a), *methyl 4-butyl-4-ethylnonanoate*, was used for analysis.

Anal.. Calc'd for $C_{16}H_{32}O_2$: C, 74.95; H, 12.58.
Found: C, 74.69; H, 12.38.

From the yield data obtained by reduction of the pure keto esters, it may be calculated that 1 g. of the ester of XV is obtained from 2.53 g. of the keto ester, XIII, while 1 g. of the acid, XIV, is obtained from 1.24 g. of the keto ester, XII. Thus, the amounts of Fractions (a) and (c) above indicate that the keto ester from which they were obtained consisted of 6.6 g. of XII and 9.1 g. of XIII, in reasonable agreement with the 15.5 g. of mixed keto ester actually reduced. Thus, the percentage of XII is calculated as 42%, and that of XIII as 58%.

In a similar manner were obtained the data on the composition of the keto ester obtained from the samples of distilled ester acid chlorides. These analyses are probably accurate to ±2-3%.

Reaction of dibutylcadmium with α-butyl-α-ethylglutaric anhydride. A benzene (220 cc.) solution of dibutylcadmium prepared in the usual way from 55.4 g. of pure *n*-butyl bromide was treated with a solution of 20.0 g. of anhydride, VII, in 75 cc. of benzene, no heat being evolved during the addition. After the mixture had been heated under reflux, with stirring, for seven hours, it was decomposed with ice and dilute sulfuric acid. The organic phase was separated and the aqueous phase extracted with two portions of benzene. The combined benzene extracts were extracted with a mixture of 200 cc. of water, 60 cc. of methanol, and 20 cc. of 6 *N* sodium hydroxide. Using the methods described above, neutral material was extracted from the alkaline solution, which was then acidified and worked up to yield 22.9 g. of crude acidic material. This contained only 15.6 g. (60% yield) of keto acids, as shown by the analysis below.

The crude acidic material was heated under reflux for one and one-half hours with 85.5 cc. (24 equivs.) of methanol and 3.5 cc. of concentrated sulfuric acid. There was no darkening of the solution during heating. The mixture was poured into 350 cc. of water and extracted with three portions of pentane. The pentane solution was worked up as described above under "Separation of Keto Esters" to yield neutral and acidic fractions. The neutral fraction, on distillation at 1.5 mm. pressure, gave 11.3 g. of keto ester, XIII, b.p. 130.5–133°, n_D^{30} 1.4501.

The crude acidic fraction (8.5 g.) containing XVI, was subjected to the standard Wolff-Kishner reduction, and there was obtained 4.2 g. of the trialkylacetic acid, XIV, b.p. 145.5–146.5° (1.5 mm.), n_D^{27} 1.4483. This is equivalent to 4.9 g. of keto acid, XVI, or 5.2 g. of the ester, XII. Thus, the keto acid obtained from the cadmium reaction with the anhydride consisted of 31.5% of keto acid, XVI, and 68.5% of keto acid, XVII.

SUMMARY

1. The melting points of branched-chain acids are discussed and evidence is presented that no acid, except the iso acid, which contains a single branching methyl group can melt less than 10° below the normal isomer. Other branched-chain types which may be relatively high-melting are discussed.

2. A new synthesis of quaternary-carbon acids is developed and applied to the synthesis of *n*-butylethyl-*n*-heptylacetic acid and 4-butyl-4-ethylnonanoic acid.

3. It is shown that either of the ester acid chlorides related to the two half esters of α-butyl-α-ethylglutaric acid rearranges, on standing, to a mixture of the two isomeric ester acid chlorides.

4. Evidence is presented that dialkylcadmium reagents do not react with anhydrides by addition to the carbonyl group.

Berkeley, California

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