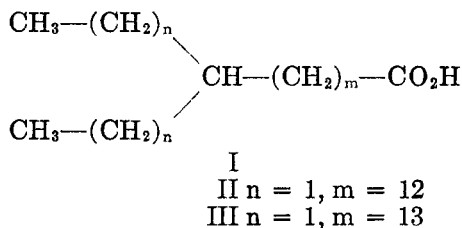


BRANCHED-CHAIN FATTY ACIDS. VIII. SYNTHESIS OF TWO ACIDS CONTAINING A 3-PENTYL SYMMETRICAL END-GROUPING

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In a previous publication (1), in which there was discussed the relationship of melting point to structure of branched-chain acids, it was shown that the iso acid is the only known type of high molecular weight branched-chain acid which has a melting point less than ten degrees below the melting point of the normal acid, with the same number of carbon atoms. Since the high melting point of the iso acid might be attributable to the symmetrical end-group, we have investigated this point by synthesis of acids with a structure such as indicated in formula I.



In the present paper is reported the synthesis of two such acids, 14-ethylhexadecanoic acid (II) and 15-ethylheptadecanoic acid (III). Each of these acids, whose branching end-groups are ethyl, has a melting point far below that of the normal isomer. The C₁₈ acid (II) melts at 42.0–42.9°, and the C₁₉ acid (III) melts at 36.7–37.4°. Thus, the latter melts even lower than 16-methyloctadecanoic acid, m.p. 49.9–50.6° (2), which has the same molecular weight and a methyl group in the same position relative to the end of the chain. It is also of interest that the C₁₈ acid (II), which has an even-carbon straight chain, melts 5.5° above the C₁₉ acid (III), which has an odd-carbon straight chain. This is reasonable, in view of the known relationship between the melting points of normal acids with odd- and even-carbon chains; however, this relationship does not hold for the iso acids. An even-carbon iso acid (3), which has an odd-carbon straight chain, melts at nearly the same place as the normal acid with the same number of carbon atoms, therefore higher than the odd-carbon normal acid corresponding to the straight chain in the iso acid.

Thus, the high melting points of iso acids must be attributed to some factor other than the symmetrical end-grouping. Velick's study (4) of the X-ray diffraction patterns exhibited by iso acids appears to offer a reasonable explanation³ of the remarkably high melting points exhibited by the iso acids. The

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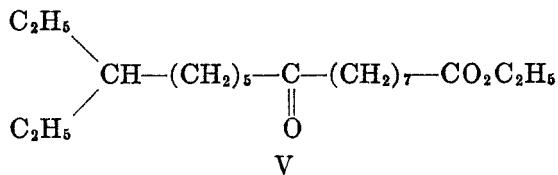
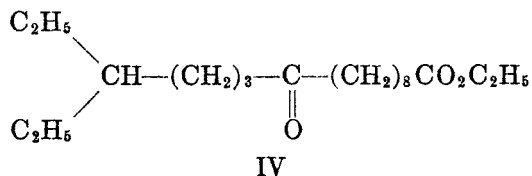
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³ This interpretation was suggested to the authors in a private communication from Dr. A. W. Weitkamp of the Standard Oil Company of Indiana, Whiting, Indiana.

crystal structures of the iso acids appear to be similar to those of the normal acids except for a large angle of tilt of the axis of the acid chain relative to the planes between the layers. This tilting may permit accommodation in the crystal lattice of the branching group, provided that the branching group is at the end of the chain and no larger than methyl. When the branching group is larger or not at the end of the chain, such a crystal structure is not possible, hence other crystal structures resulting in lower melting points are adopted.

The melting-point pattern exhibited by acids with symmetrical end-groups larger than ethyl is reported in the following paper of this series.

The starting material for synthesis of acids, II and III, was 2-ethyl-1-butanol. For synthesis of 14-ethylhexadecanoic acid (II), the chain of this alcohol was extended by means of the Grignard reaction with ethylene oxide, and ethyl 10-keto-14-ethylhexadecanoate (IV) was prepared by reaction of the cadmium reagent from 1-bromo-4-ethylhexane with ω -carbethoxynonyl chloride.



Clemmensen reduction of the keto ester in alcohol, followed by saponification, yielded the desired acid. 15-Ethylheptadecanoic acid (III) was prepared by a similar sequence of reactions, proceeding by way of ethyl 9-keto-15-ethylheptadecanoate (V). The 2-ethyl-1-butanol was purified by careful fractionation through a 3-foot column, and it was converted to the bromide or chloride by methods which avoid rearrangement; so the final acids were purified without difficulty.

EXPERIMENTAL

All melting points are corrected. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with heated jacket and partial reflux head.

1-Bromo-2-ethylbutane (5). Two liters of commercial 2-ethyl-1-butanol was distilled through a 3-foot column packed with glass helices, and equipped with heated jacket and total reflux head. After three passes, collecting successively narrower cuts, there was obtained 355 g. of alcohol of b.p. 148.3–148.5° (753 mm.). Higher-boiling fractions contained *n*-hexyl alcohol. The bromide was prepared from 255 g. (2.5 moles) of the pure 2-ethyl-1-butanol and 248 g. (0.91 mole) of phosphorus tribromide, essentially according to the method of Noller and Dinsmore (6). Distillation through the 3-foot packed column yielded 196.6 g. (47.6%) of bromide boiling at 73.8–74.7° (70 mm.).

1-Chloro-2-ethylbutane. Employing the method of Whitmore and Karnatz (7), in order to avoid rearrangement, a solution of 55.3 g. (0.54 mole) of pure 2-ethyl-1-butanol in 44

ml. of dry pyridine was treated during two hours with 90 g. (0.76 mole) of purified thionyl chloride. After heating at 70–80° for three hours, the mixture was diluted with water and hydrochloric acid. The chloride layer was washed with 3 *N* hydrochloric acid, water, and saturated sodium chloride solution, then dried and distilled; yield, 37.5 g. (55%), b.p. 126.5–127.6° (753 mm.).

4-Ethyl-1-hexanol. A Grignard reagent was prepared from 82.5 g. (0.5 mole) of 1-bromo-2-ethylbutane in 400 ml. of ether, in an atmosphere of nitrogen. Ethylene oxide (0.75 mole) was then passed into the solution during about two hours, at –6 to –10°. The mixture was then heated, first in ether, then in benzene, according to the usual published procedures (8). After decomposition of the organometallic complex and separation of the benzene solution, the aqueous phase was extracted twice with benzene. After the extracts had been washed with water, sodium carbonate solution, water, and saturated sodium chloride solution, solvent was removed and the residue distilled. After a fore-run of 18.1 g. (b.p. 53–93° at 20 mm.) the product was collected at 93–97° (20 mm.), 90% boiling at 96°; yield, 23.4 g. (37.5%). A center cut was used for analysis.

Anal. Calc'd for $C_8H_{18}O$: C, 73.79; H, 13.93.

Found: C, 73.78; H, 14.16.

4-Ethyl-1-hexanol was also prepared from 2-ethylbutylmagnesium chloride and ethylene oxide, but the yield (39%) was essentially the same as that obtained with the bromide. This is consistent with the report of Huston and Langham (9) that the reaction of isobutylmagnesium chloride with ethylene oxide gives a much lower yield than obtained with the straight-chain chlorides.

1-Bromo-4-ethylhexane was prepared from 23.0 g. (0.177 mole) of the alcohol with gaseous hydrogen bromide by the usual procedure (10). Distillation of the product yielded 28.2 g. (83%), b.p. 83–84° (17 mm.). A center cut was used for analysis. The analytical figures indicate a small impurity, probably 3,6-diethyloctane from coupling of the Grignard reagent used in preparing 4-ethyl-1-hexanol. The high carbon content of the alcohol prevents detection of this impurity by analysis of that compound. This hydrocarbon is easily removed at the next stage of the synthesis.

Anal. Calc'd for $C_8H_{17}Br$: C, 49.73; H, 8.87; Br, 41.41.

Found: C, 50.86; 50.75; H, 9.04, 9.25; Br, 40.44.

6-Ethyl-1-octanol was prepared as described for 4-ethyl-1-hexanol. From 27.9 g. of 1-bromo-4-ethylhexane, the yield of alcohol of b.p. 121–123.5° (18 mm.) was 9.85 g. (43%). For analysis there was used a center cut of b.p. 122.5° (18 mm.).

Anal. Calc'd for $C_{10}H_{22}O$: C, 75.87; H, 14.01.

Found: C, 75.40; H, 14.10.

1-Bromo-6-ethyloctane, prepared by the method used for 1-bromo-4-ethylhexane, was obtained in 71% yield, b.p. 121–123° (19 mm.). For analysis there was used a center cut of b.p. 121–121.8° (19 mm.).

Anal. Calc'd for $C_{10}H_{21}Br$: Br, 36.13. Found: Br, 36.37.

Ethyl 10-keto-14-ethylhexadecanoate (IV). A solution of cadmium reagent in 60 ml. of benzene was prepared in the manner previously described (11) from 14 g. (0.0725 mole) of 1-bromo-4-ethylhexane. After treatment of the boiling solution with 14.4 g. (0.058 mole) of ω -carbethoxynonyl chloride in 30 ml. of benzene, the mixture was refluxed for two hours, then worked up in the usual fashion (11) for keto esters. Distillation gave 1.20 g. of fore-run, b.p. 90–192° (5–1 mm.), and 10.6 g. (45% yield, based on bromide) of keto ester, IV, b.p. 192–196° (1 mm.).

Anal. Calc'd for $C_{20}H_{38}O_2$: C, 73.57; H, 11.73.

Found: C, 72.64; H, 11.80.

The corresponding *keto acid*, obtained by saponification of the ester with alcoholic potassium hydroxide, was obtained as fine plates, m.p. 45.8–47.4°, after three crystallizations from ligroin (b.p. 36–38°).

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 72.43; H, 11.48.

Found: C, 72.33; H, 11.49.

Ethyl 9-keto-15-ethylheptadecanoate (V) was prepared as described for keto ester, IV. From 9.54 g. (0.043 mole) of 1-bromo-6-ethyloctane and 8.10 g. (0.0345 mole) of ω -carbethoxycaprylyl chloride (12), the yield of keto ester, V, was 7.13 g. (48.5%, based on bromide), b.p. 175–181° (ca. 0.5 mm.).

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.

Found: C, 72.65, 72.88; H, 11.67, 11.81.

The *keto acid* was obtained from ester, V, by saponification with alcoholic potassium hydroxide. After three crystallizations from ligroin (b.p. 34–40°), it separated as blades of m.p. 43.6–44.2°.

Anal. Calc'd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.62.

Found: C, 73.21; H, 11.31.

Reduction of the keto esters was accomplished by Schneider and Spielman's modification (13) of the Clemmensen method. For 0.027 mole of keto ester in 200 ml. of absolute alcohol there was used 100 g. of amalgamated mossy zinc, and refluxing was continued for 36 hours, the solution being saturated at 0° with dry hydrogen chloride at the beginning of the reaction and after 14 hours under reflux. The products were isolated by dilution of the reaction mixture with water and extraction with benzene. The yield of *ethyl 14-ethylhexadecanoate* was 85.5%, b.p. 168–173° (ca. 0.5 mm.). An analytical sample was taken at 170–171°.

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

Found: C, 76.14; H, 12.60.

The yield of *ethyl 15-ethylheptadecanoate* was 62%, b.p. 157–165° (ca. 0.5 mm.).

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.

Found: C, 77.34; H, 12.89.

In this distillation, there was a relatively large forerun (more than half the weight of the ester fraction), which may have arisen in part from impurities in keto ester, V, for the analysis of this keto ester (*cf.* above) was in rather poor agreement with theory.

14-Ethylhexadecanoic acid (II). Saponification of 6.98 g. of ethyl 14-ethylhexadecanoate by heating under reflux for one hour with 50 ml. of 8% alcoholic potassium hydroxide gave a quantitative yield of crude acid, m.p. 38.8–41.4° (cloudy). After one crystallization from acetone, there was obtained 4.92 g. of fine lustrous needles, m.p. 41.8–42.9°. After two additional crystallizations from methanol, the m.p. was essentially the same, 42.0–42.9°.

Anal. Calc'd for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76; mol. wt., 284.5.

Found: C, 76.15; H, 12.43; mol. wt., 284.1.

The *amide* was prepared by dropping a dioxane (4 ml.) solution of acid chloride from 0.5 g. of acid into 12 ml. of cold concentrated ammonium hydroxide; crude yield, 0.49 g., m.p. 73–79°. After three crystallizations from ligroin, there was obtained 0.35 g. of fine blades, m.p. 78.8–79.9°.

Anal. Calc'd for $C_{18}H_{37}NO$: C, 76.26; H, 13.16.

Found: C, 76.04; H, 13.26.

The *tribromoanilide*, prepared as previously described (8b), was obtained in 81% yield, m.p. 86–95°, after one crystallization from ligroin (b.p. 80–96°). After successive crystallizations from ethanol, ligroin, and acetone, soft short needles were obtained melting at 100.2–101.0°.

Anal. Calc'd for $C_{24}H_{39}Br_3NO$: C, 48.33; H, 6.42.

Found: C, 48.31; H, 6.93.

15-Ethylheptadecanoic acid (III) was prepared as described for II by saponification of 3.67 g. of the corresponding ester; yield 3.17 g. (95%), m.p. 31–35°. After three crystallizations from methanol there was obtained 1.35 g. of acid as clusters of fine needles, m.p. 36.7–37.4°.

Anal. Calc'd for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; mol. wt., 298.5.

Found: C, 76.94; H, 12.60; mol. wt., 299.3, 298.9.

Derivatives of this acid were prepared as described for the homolog. The crude amide, obtained in 98% yield, melted at 72–75°. After three crystallizations from ligroin,

one from methanol, and one from acetone (m.p. not changing during latter crystallizations), this *amide* melted at 79.0–81.1°, after softening at 76°. It appears to be polymorphic, for it melts completely at once when placed in a bath preheated to 80°.

Anal. Calc'd for $C_{15}H_{29}NO$: C, 76.71; H, 13.21.

Found: C, 76.25; H, 13.16.

The *tribromoanilide* was obtained in 94% yield of m.p. 89–95°, and after three crystallizations from ethanol it was obtained as rosettes of needles melting at 101.5–102.2°.

Anal. Calc'd for $C_{25}H_{46}Br_3NO$: C, 49.21; H, 6.60.

Found: C, 49.44; H, 6.78.

SUMMARY

14-Ethylhexadecanoic acid and 15-ethylheptadecanoic acid have been prepared. Although these acids have symmetrical end-groups, they do not have relatively high melting points, as do the iso acids, but melt more than twenty-five degrees below the normal isomers of the same molecular weights.

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