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

BRANCHED-CHAIN FATTY ACIDS. XX. SYNTHESIS OF COMPOUNDS USEFUL FOR RELATING MELTING POINT TO STRUCTURE[1]

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In a previous paper (1) of this series, in which there was discussed the relationship of the melting point of high molecular weight branched-chain acids to structure, it was pointed out that there appears to be an "excluded region" of at least ten degrees below the melting point of the normal isomer, wherein do not occur the melting points of branched-chain isomers except for the iso acid. In later papers (2) the synthesis of additional acids has added evidence in support of this principle. As previously mentioned (1), completion of the data by synthesis of a DL-anteiso acid with twenty-four or more carbons is desirable. In the present work, DL-21-methyltricosanoic acid (XII) has been synthesized, and it melts at 66.5–67.5°, which is about 16.5° below the melting point of the normal isomer. We have also prepared (+)-21-methyltricosanoic acid by chain extension of the (+)-20-methyldocosanoic acid (3) isolated by Weitkamp.[2] It melts at 64.7–65.7°, slightly below the melting point of the DL-isomer and in reasonable agreement with the melting point reported by Ställberg-Stenhagen (4) for the (−)-isomer. In all other cases in the branched-chain acid series where DL- and optical isomers have been made the optical isomer has melted below the DL-isomer (*Cf.* also acid XI, Experimental).

It has previously been commented that 15-methylheptadecanoic acid (X) (5) melts about 26° below the normal isomer, whereas numerous odd-carbon anteiso acids melt 16–18° below the normal isomer. This raised the possibility that melting points of branched-chain acids should be related to the normal acid corresponding to the straight-chain portion of the molecule rather than the total number of carbons. This proposition is no longer tenable, however, since 21-methyltricosanoic acid (XII), containing an even number of carbons, melts about 16.5° below *n*-tetracosanoic acid. Also, 14-methylhexadecanoic acid (XI), with only seventeen carbons, has been prepared in the present work, and it melts about 21.5° below *n*-heptadecanoic acid. Thus, the value reported for the melting point of 15-methylheptadecanoic acid seems out of line with some fifteen other anteiso acids which have been reported; so we have again prepared 15-methylheptadecanoic acid by a route entirely different than that used by Ställberg-Stenhagen (5). As in other instances where we have compared data with that of Ställberg-Stenhagen, the agreement is excellent; so it seems established that the melting point of anteisostearic acid is abnormally low.

In order to complete the general picture of the melting point pattern in the

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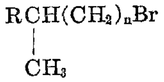
series of methyltetracosanoic acids, 18-methyltetracosanoic acid (XIV) has been prepared. This makes available from our syntheses data for the 3-, 6-, 10-, 14-, and 18-methyltetracosanoic acids, and other workers have reported the 2-, 12-, 21-, and 22-methyl isomers. From these data, assembled in Table I, it may be seen that the pattern is similar to that observed in the C_{19} series (12). For the acids, as the methyl group becomes more remote from the ends of the chain the melting point drops off in a fairly regular manner, but with minor irregularities, and reaches a minimum when the branch is near the middle of the chain. For the amides, there is little regularity, and the melting point of this derivative is generally less useful for characterization than the melting point of the acid itself.

TABLE I
METHYLTETRACOSANOIC ACIDS

POSITION OF METHYL[a]	M.P. OF ACID, °C.	M.P. OF AMIDE, °C.	REFERENCE
2-	72.0–72.5	111.5	6
3-	68.0–69.1	99.5–101	7, 8
3-Optical Isomers	65.4–65.6	102–102.3	8
6-	55.8–56.6	83.9– 85.3	9
10-	50.5–51.5	77.5– 78.5	6, 9
12-	43.8–44.6[b]	86.7– 86.9	10
14-	57.9–58.5	80.2– 81.0	11
18-	55.6–55.8	86.5– 87.5	
21-(−)-isomer	60.3–60.8	92.8– 93.0	4
22-(+)-isomer	67.8	101.5	3

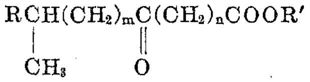
[a] Unless otherwise specified, the data apply to the DL-isomer. [b] Polymorphic. Samples crystallized from the melt had m.p. 51.8–52.2°.

The acids (X–XIV) prepared in this work were obtained by reduction of appropriate keto esters (V–IX). The keto esters were obtained by reaction of dialkylcadmium reagents in the usual manner (9, 13) with appropriate ester acid chlorides. Bromides (I–IV) used for making the cadmium reagents were obtained from the corresponding branched-chain alcohols. Synthesis of some of the al-



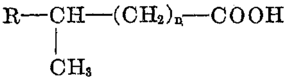
$$R\underset{\displaystyle CH_3}{\underset{|}{CH}}(CH_2)_nBr$$

I $R = C_2H_5, n = 3.$
II $R = C_2H_5, n = 13.$
III $R = n\text{-}C_6H_{13}, n = 3.$
IV $R = n\text{-}C_6H_{13}, n = 7.$



$$R\underset{\displaystyle CH_3}{\underset{|}{CH}}(CH_2)_m\underset{\displaystyle O}{\underset{\|}{C}}(CH_2)_nCOOR'$$

V $R = C_2H_5, m = 3, n = 9, R' = CH_3.$
VI $R = C_2H_5, m = 3, n = 8, R' = C_2H_5.$
VII $R = C_2H_5, m = 13, n = 5, R' = C_2H_5.$
VIII $R = n\text{-}C_6H_{13}, m = 3, n = 2, R' = CH_3.$
IX $R = n\text{-}C_6H_{13}, m = 7, n = 8, R' = C_2H_5.$



$$R\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}(CH_2)_n\text{—}COOH$$

X $R = C_2H_5, n = 13.$
XI $R = C_2H_5, n = 12.$
XII $R = C_2H_5, n = 19.$
XIII $R = n\text{-}C_6H_{13}, n = 6$ (isolated as ester).
XIV $R = n\text{-}C_6H_{13}, n = 16.$

cohols has been previously described (14); others were obtained by reduction of the esters of acids XI and XIII. These latter syntheses were required because two chain extensions were necessary for synthesis of 21-methyltricosanoic acid (XII) and 18-methyltetracosanoic acid (XIV).

The required dibasic acids were commercially available, except for hendecane-1,11-dioic acid required for synthesis of keto ester V. This acid was obtained by reduction of 6-ketohendecane-1,11-dioic acid. The keto dibasic acid was prepared by the recently described method of Sauer (15) for conversion of an acid chloride to a symmetrical ketone by proceeding through the ketene dimer. The method appears quite useful for making the higher odd-carbon dibasic acids.

EXPERIMENTAL

All melting points are corrected and all boiling points are uncorrected. Distillations were through a 2-foot column of the Podbielniak type (16). Analyses were by the Microanalytical Division of the Department of Chemistry and Chemical Engineering, University of California.

Hendecane-1,11-dioic acid. 6-Ketohendecane-1,11-dioic acid was prepared as described by Sauer (15), except for minor simplifications. The solution in anhydrous ether of 5-carbethoxyvaleryl chloride and triethylamine was heated under reflux with stirring for five hours, rather than by allowing it to stand for two days. Also the period of saponification of the dimer with 20% alcoholic potassium hydroxide was reduced from four hours to one-half hour. The yield of recrystallized keto acid, m.p. 109–111°, was 58–63%, in several runs of 0.1 mole to 0.8 mole. Following the exact procedure of Sauer, the yield was the same. Sauer reported m.p. 109°, yield 67%.

The keto acid was reduced by the method of Huang-Minlon (17) in 97% yield, m.p. 108–110°. The best sample obtained by recrystallization had m.p. 109–110°. From the literature (18), m.p. 111°.

Methyl hydrogen 1,11-hendecanedioate. Dimethyl 1,11-hendecanedioate was prepared in 98% yield by esterification with 20 equivalents of methanol in the presence of sulfuric acid. After extraction of acid with carbonate, the diester was saponified to the half ester with barium hydroxide in methanol by the procedure of Signer and Sprecher (19), but as previously reported (20) the pure half ester could not be obtained by crystallization. Rapid distillation through the column gave a 71% yield of half ester, b.p. 170–174° (2.5 mm.), m.p. 44–46°, equiv. wt., 230.6 (calc'd 230.3). In the literature (21), no m.p. is recorded.

14-Methyl-1-hexadecanol was prepared in 86% yield by reduction of ethyl 14-methylhexadecanoate with sodium and ethanol (22). It had b.p. 163–165° (3 mm.), m.p. 13.0–13.4°, n_D^{22} 1.4520.

Anal. Calc'd for $C_{17}H_{36}O$: C, 79.60; H, 14.15.
Found: C, 79.50; H, 14.27.

8-Methyl-1-tetradecanol, prepared in 87% yield as for the preceding alcohol, had b.p. 145–147° (4 mm.), n_D^{25} 1.4469.

Anal. Calc'd for $C_{15}H_{32}O$: C, 78.90; H, 14.13.
Found: C, 79.08; H, 13.89.

Bromides I–IV were prepared in 82–90% yields from the corresponding alcohols with anhydrous hydrogen bromide (23). Data are found in Table II.

Branched-chain keto esters V–IX were prepared by the cadmium reaction in essentially the manner which has been described (9, 13). Yields based on ester acid chloride were in the range 64–88%. Data on these esters are found in Table III, and in Table IV are found data on the keto acids obtained by saponification of the esters.

Reduction of the keto esters in 64–84% yields was by the Huang-Minlon modification (17) of the Wolff-Kishner reduction, except that VI was reduced in 90% yield by the modified Clemmensen method (6). Data on acids X, XI, and XIII are found below, while that on XII and XIV are found in Table V.

15-Methylheptadecanoic acid (X), after crystallization to constant m.p. from acetone, had m.p. 43.5–44.3°, equiv. wt. 285.4 (calc'd 284.5). Ställberg-Stenhagen (5) reported m.p. 43.5–43.7°.

Ethyl 14-methylhexadecanoate, obtained directly from the Clemmensen reduction in ethanol, had b.p. 169–174° (2–3 mm.), n_D^{22} 1.4417. A center cut was used for analysis.

Anal. Calc'd for $C_{19}H_{38}O_2$: C, 76.46; H, 12.83.

Found: C, 76.20; H, 12.72.

TABLE II

BRANCHED-CHAIN ALKYL BROMIDES

BROMIDE	B.P., °C. (MM.)	n_D^{22}	ANALYSES			
			Calc'd		Found	
			C	H	C	H
1-Bromo-4-methylhexane (I)[a]	74– 75 (28)	1.4515	46.94	8.49	46.43	8.44
1-Bromo-14-methylhexadecane (II)	163–165 (2.5)	1.4640	63.93	11.05	63.97	11.31
1-Bromo-4-methyldecane (III)	120–123 (15)	1.4575	56.16	9.85	56.42	10.09
1-Bromo-8-methyltetradecane (IV)	141–143 (3)	1.4611	61.87	10.73	61.94	10.90

[a] From the literature (24), b.p. 78° (44 mm.).

TABLE III

BRANCHED-CHAIN KETO ESTERS

ESTER	B.P., °C. (MM.)	n_D^{22}	ANALYSES			
			Calc'd		Found	
			C	H	C	H
Methyl 11-keto-15-methylheptadecanoate (V)	197–198 (4.5)	1.4495	73.03	11.61	72.59	11.32
Ethyl 10-keto-14-methylhexadecanoate (VI)	196–200 (4)	1.4478	73.03	11.61	72.75	11.65
Ethyl 7-keto-21-methyl-tricosanoate (VII)	225–250 (0.5)	[a]	76.05	12.27	74.54	12.08
Methyl 4-keto-8-methyltetradecanoate (VIII)	143–145 (1.5)	1.4458	71.06	11.19	72.15	11.45
Ethyl 10-keto-18-methyltetracosanoate (IX)	220–225[b] (0.3–0.5)	1.4535	76.34	12.35	76.65	12.64

[a] Waxy solid, m.p. 31°. [b] Freezing point, 12°.

14-Methylhexadecanoic acid (XI), obtained by saponification of the ester, was crystallized from acetone until the m.p. became constant at 39.2–39.7°.

Anal. Calc'd for $C_{17}H_{34}O_2$: C, 75.49; H, 12.67.

Found: C, 75.62; H, 12.89.

For the (+)-isomer, Weitkamp (3) reported m.p. 36.8°, while Velick and English (25) reported m.p. 37.3–37.6° for Weitkamp's sample and 36–36.8° for their synthetic sample. Thus, as in other instances, the DL-form is higher melting.

Ethyl 8-methyltetradecanoate, obtained by esterification of the liquid acid (XIII) obtained from the Wolff-Kishner reduction, had b.p. 143–145° (3 mm.), n_D^{20} 1.4392.

Anal. Calc'd for $C_{17}H_{34}O_2$: C, 75.49; H, 12.67.

Found: C, 75.52; H, 12.85.

(+)-*21-Methyltricosanoic acid* was prepared from (+)-20-methyldocosanoic acid (3) by use of the Arndt-Eistert reaction. In several trial runs with stearic acid, we were not able to get good yields, and purification was difficult. The following is the best procedure thus far developed by us. It is based partly on the procedures (26) for dodecane-1,12-dioic acid and *p*-homoanisamide.

TABLE IV

BRANCHED-CHAIN KETO ACIDS

ACID	M.P., °C. (SOLV. FOR CRYST.)	ANALYSES			
		Calc'd		Found	
		C	H	C	H
11-Keto-15-methyl-heptadecanoic..........	48.7–49.7 (hexane)	[a]			
10-Keto-14-methyl-hexadecanoic...........	45.0–45.4 (hexane)	71.80	11.34	71.95	11.41
7-Keto-21-methyl-tricosanoic.............	73.2–73.8 (acetone)	75.35	12.12	74.87	12.26
10-Keto-18-methyl-tetracosanoic...........	60.4–61.0 (acetone)	75.70	12.20	75.54	12.43

[a] Equiv. wt., 295 (calc'd 298.5).

TABLE V

BRANCHED-CHAIN ACIDS AND DERIVATIVES

	ACID		AMIDE			*p*-BROMOANILIDE		
	M.P., °C.	EQ. WT.[a]	M.P., °C.	Anal.[a]		M.P., °C.	Anal.[a]	
				C	H		C	H
21-Methyltri-cosanoic (XII).....	66.5–67.5	369.9 (368.6)	97.8–98.0	77.87 (78.40)	13.23[b] (13.43)	94.4–95.0	68.54 (68.93)	10.54 (10.03)
18-Methyltetra-cosanoic (XIV)....	55.5–55.8	382.3 (382.7)	86.5–87.5	78.68 (78.67)	13.20 (13.47)	81.6–82.3	69.45 (69.36)	10.11 (10.14)

[a] Calculated values are those in parentheses. [b] Analysis of this amide for N, 3.93 (calc'd: N, 3.81).

To a dried methylene chloride solution of three equivalents (titrated) of diazomethane prepared from N-nitrosomethylurea (26) was added the acid chloride prepared with thionyl chloride from 1.0 g. of (+)-20-methyldocosanoic acid (3), m.p. 62.0–62.3°. After removal of solvent at reduced pressure, the residual diazoketone was used directly for rearrangement (recrystallization was difficult and involved large losses).

The crude diazoketone was converted to the amide by following the procedure for *p*-homoanisamide (26). The crude amide, precipitated from the reaction mixture, melted at

70–95°. After passage through a column of Amberlite IRA-400 (27) to remove small amounts of acid, the recovered amide had m.p. 91.5–98°, wt. 0.63 g. A pure sample could not be obtained by crystallization. The total amide was saponified at 180–190°, for four hours, with 1.5 g. of potassium hydroxide in 40 ml. of diethylene glycol. The ammonia titrated corresponded to hydrolysis of 0.42 g. of amide. After dilution of the reaction mixture and acidification, the crude acid was extracted with ether and separated from neutral material by the use of Amberlite IRA-400 (27). After elution of the acid from the column and recrystallization (four times) to constant m.p. from acetone, there was obtained 260 mg. (25% over-all) of (+)-21-methyltricosanoic acid, m.p. 64.7–65.7°, α +0.117° ± 0.010°, $[\alpha]_D^{25}$ +2.95° ± 0.25° (c, 3.96 in chloroform), $[M]_D^{25}$ +10.85° ± 0.93°. Ställberg-Stenhagen (4) reported m.p. 67.8–68.1°, $[M]_D^{22}$ 12.6° or 13.0° for the (−)-isomer, and Weitkamp (3) reported $[M]_D^{26}$ 11.4° for anteiso acids. Our (+)-isomer mixed with about an equal amount of DL-isomer showed a depressed m.p. of 62.6–66.7°, thus the DL-isomer is a molecular compound.

Anal. Calc'd for $C_{24}H_{48}O_2$: Eq. wt., 368.6. Found: Eq. wt., 367.7.

SUMMARY

There are reported syntheses for the following branched-chain acids: 15-methylheptadecanoic acid, 14-methylhexadecanoic acid, 21-methyltricosanoic acid, (+)-21-methyltricosanoic acid, and 18-methyltetracosanoic acid.

The melting point patterns for methyltetracosanoic acids and amides are discussed.

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