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

BRANCHED-CHAIN FATTY ACIDS. XVII. SYNTHESIS OF TWO TRIMETHYLALKANOIC ACIDS. CERTAIN RELATIONSHIPS OF BOILING POINT AND INDEX OF REFRACTION TO STRUCTURE[1]

JAMES CASON, NORMAN L. ALLINGER, GENE SUMRELL, and
DAVID E. WILLIAMS

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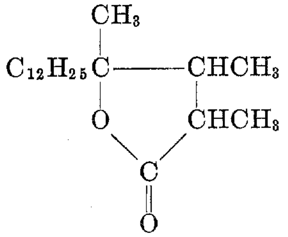
In connection with the syntheses reported in previous papers in this series, it has been noted that variations in the structures of branched-chain acids cause readily detectable changes in the boiling points of the esters, even for molecular weights above 325 (C_{21}). Also, Weitkamp (1) has published data on the boiling points of the esters of a series of iso acids, and found that, in the range from twelve to twenty-six carbons, an iso ester boils 3–4° below the corresponding normal isomer at 1.95 mm. pressure. In the present paper are reported data on the effects on boiling point of several variations in structure. Although additional variations in structure might permit a more detailed analysis, the available data should permit a reasonably reliable estimate to be made of the boiling point of an ester of any given structure. In a later paper of this series (XXII) will be reported a specific use of this information as an aid in determining molecular weight. These data also indicate the extent to which fractional distillation may be applied to separation of fatty acids.

Although most of the acids needed for this investigation had been previously prepared, no trimethylalkanoic acids were available. 2,3,4-Trimethylhexadecanoic acid was prepared from α,β,γ-trimethyl-γ-palmitolactone (I) by ring-opening with thionyl chloride, as previously described (2). The lactone was prepared from the appropriate γ-keto ester by the method previously used. Steric influence of the substituent methyl groups interfered with these reactions to only a minor extent.



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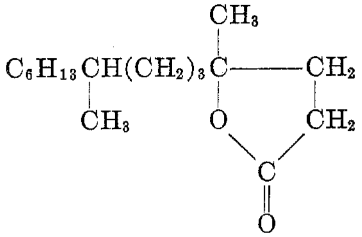

II

4,8,12-Trimethyloctadecanoic acid was prepared by a series of chain extensions starting with the reaction between n-hexylmagnesium bromide and ethyl levulinate, to give γ-methyl-γ-caprilactone. This was hydrogenated, as previously described (3), to 4-methyl-1-decanol. The Grignard reagent from the

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corresponding bromide was used for the synthesis of 4,8-dimethyl-1,4-tetradecanolide (II). After extension of the chain with one additional unit of ethyl levulinate, ring-opening with thionyl chloride gave the desired trimethylalkanoic acid, with the branches distributed along the chain.

TABLE I

BOILING POINTS OF ESTERS

NO. OF CARBONS	ESTER	B.P. AT 3.75 MM.,[a] °C.	DEGREES BELOW *n*-ISOMER
16	Methyl *n*-pentadecanoate (E)[b]	153.5	
	Methyl 2-*n*-butyl-2-ethylnonanoate	129–130.5	23
	Methyl 4-*n*-butyl-4-ethylnonanoate	130–132	21.5
17	Methyl palmitate	163–163.5	
19	Methyl stearate	181–181.5	
20	Methyl *n*-nonadecanoate (E)	190.5	
	Methyl 2,3,4-trimethylhexadecanoate	179.5–180	10.5
21	Ethyl *n*-nonadecanoate	198–198.5	
	Ethyl 4-methyloctadecanoate	194–194.5	4
22	Methyl *n*-heneicosanoate (E)	207	
	Methyl 4,8,12-trimethyloctadecanoate	193.5–194	13
23	Methyl *n*-docosanoate (E)	215.5	
25	Methyl *n*-tetracosanoate (E)	232.0	
	Methyl 12-*n*-hexyloctadecanoate	224.5–225	7
26	Ethyl *n*-tetracosanoate	240.0–240.5	
27	Methyl *n*-hexacosanoate (E)	248.0	
	Ethyl 10-methyltetracosanoate	241.5–242	6

[a] For a discussion of the precision of the data, and extrapolations used, refer to text.
[b] (E) means extrapolated. Refer to text.

GENERAL RELATIONSHIPS BETWEEN BOILING POINT AND STRUCTURE

The essential data obtained are listed in Table I. The following relationships, applied to methyl or ethyl esters,[2] seem of significance.

(a) A branching methyl group lowers the boiling point (below that of the

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[2] Although the methyl ester boils a few degrees higher than the ethyl ester with the same total number of carbons, for lower molecular weight esters (*Cf.* Ref. 5, p. 502), this difference appears to become very small when the total number of carbons reaches seventeen or more. For example, at 3.75 mm., methyl octadecanoate and ethyl nonadecanoate differ in boiling point by 17°, whereas methyl octadecanoate and methyl hexadecanoate differ in boiling point by 18°. The effect of branching in the alcohol moiety of the ester has not been included in the present investigation.

normal isomer) by about 5°. A branch near the middle of the chain may cause a slightly greater lowering than one near the end of the chain. Weitkamp's data (1) on esters of iso acids are consistent with our data.

(b) A larger branch (*n*-hexyl) lowers the boiling point by about 7°, only slightly more than a branching methyl.

(c) Three branching methyls lower the boiling point about twice as much as does one branch. If the methyls are grouped near carboxyl or distributed along the chain, the effect on boiling point is about the same.

(d) The largest effect in lowering the boiling point (22–23°) is that exerted by a quaternary carbon. The effect of an α- or γ-quaternary carbon is about the same.

(e) These generalizations fit only moderately well with the simple concept that more compact molecules exhibit lower boiling points.

Precision of the data. Extrapolations used. Boiling points were reproducible to ±0.5°. The thermometer was calibrated, with a precision of ±0.2°, against a set calibrated by the Bureau of Standards. Pressure was read on a McLeod gage and was controlled by a barostat depending on actuation of an electronic relay by a mercury switch. Fluctuation in pressure was ±0.05 mm., and a given pressure could be obtained with a precision of ±0.05 mm. A Podbielniak type of column, with partial reflux head, was used. It was similar to that which has been described in detail (4), except that the fractionating zone was 1.5 meters in length and the power input to the head was controlled with greater precision.

Most of the data presented were obtained directly at 3.75 mm., but a few values were extrapolated from 2.0 mm. or 3.0 mm. Numerous esters were distilled at these pressures, and extrapolation between these pressures is more accurate than a single determination at any of these pressures. Of various data obtained for variation of boiling point of esters with pressure, the following are pertinent: (a) a rise in pressure from 2.0 to 3.0 mm. causes a rise of 7.2° in boiling point; (b) a rise in pressure from 3.0 to 3.75 mm. causes a rise in boiling point of 4.3°; (c) below 10 mm., multiplying the pressure by two causes the boiling point to rise approximately 13°.

From the considerable data obtained on normal esters with 17, 19, and 21 carbons, extrapolation to other molecular weights [as indicated by (E) in Table I] can be made with about the same precision with which the boiling point may be determined. If all errors in extrapolation should be additive in a single determination at the C_{23} level, the maximum error would be about 1.0°.

GENERAL RELATIONSHIPS BETWEEN INDEX OF REFRACTION AND STRUCTURE

Index of refraction is a less reliable criterion than boiling point on account of the possible interference of small amounts of impurities; however, the index of refraction is easily obtained, in sharp contrast to a reliable boiling point at reduced pressure. Unfortunately, it also develops that most structural variations have relatively little effect on the index of refraction. Of the numerous values available, those regarded as most reliable and representative of the various structures are assembled in Table II. Variations of less than 0.001 in index are not regarded as reliably attributable to structural differences. The following relationships seem to be the ones of significance.

(a) Number of branches and size of branching group are of little, if any, significance for compounds containing no quaternary carbons.

TABLE II

INDICES OF REFRACTION OF ESTERS

NO. OF CARBONS	ESTER	n_{D}^{25}[a]
16	Ester with single branch near center of chain	1.4340[b]
	Methyl 2-*n*-butyl-2-ethylnonanoate	1.4388
	Methyl 4-*n*-butyl-4-ethylnonanoate	1.4450
17	Ethyl 8-methyltetradecanoate	1.4370
19	Ethyl 14-methylhexadecanoate	1.4404
20	Methyl 2-methyloctadecanoate	1.4408
	Methyl 3-methyloctadecanoate	1.4423
	Methyl 4-methyloctadecanoate	1.4442
	Methyl 5-methyloctadecanoate	1.4442
	Methyl 13-methyloctadecanoate	1.4438
	Methyl 15-methyloctadecanoate	1.4440
	Methyl 16-methyloctadecanoate	1.4431
	Methyl 2,3,4-trimethylhexadecanoate	1.4448
21	Ethyl 10-methyloctadecanoate	1.4447
	Methyl 2,2-dimethyloctadecanoate	1.4434
	Methyl 3,3-dimethyloctadecanoate	1.4449
	Methyl 17,17-dimethyloctadecanoate[c]	1.4478
22	Ester with single branch near center of chain	1.4458[a]
	Methyl 4,8,12-trimethyloctadecanoate	1.4461
26	Ethyl 12-*n*-hexyloctadecanoate	1.4486
27	Ethyl 10-methyltetracosanoate	1.4488

[a] Several of these values were determined at other temperatures than 25°. The temperature coefficient, as determined on several esters is 0.00045 per degree. This is slightly higher than the coefficient for acids, which is 0.0004 per degree for various branched-chain acids and also for normal acids (5). The index increases by 0.0009 per carbon atom, in the range of 20 to 27 carbon atoms. Below C_{20}, the rate of change is greater, *cf.* (*b*), also ref. 5. [b] In the range of C_{17} to C_{20}, the average increase in index per carbon atom is 0.0023, so the value for the C_{16} ester was estimated as 0.0030 below the value of C_{17}. [c] The value for this acid was taken from the literature (6).

(b) Position of a branch has no effect except for positions near the end of the chain. For branches only two or three carbons from the end of the chain, there is a small effect in lowering the index of refraction.

(c) The only large effect is that exerted by a quaternary carbon atom bearing substituent groups larger than methyl. This, again, is smaller when the quaternary carbon atom is near the end of the chain. A 4-*n*-butyl-4-ethyl substitution raises the index of refraction by about 0.01.

EXPERIMENTAL

All melting points are corrected. All boiling points, except those in Table I, are uncorrected. All distillations, unless otherwise specified, were through a 2-foot column of the Podbielniak type (4). Analyses are by the Microanalytical Division of the Dept. of Chemistry and Chemical Engineering, University of California.

α,β,γ-Trimethyl-γ-palmitolactone (I). The Grignard reagent from 0.3 mole of magnesium and excess methyl bromide was converted to the cadmium reagent in the usual manner (7) and allowed to react with the ester acid chloride (8) obtained from 0.15 mole of *sym*-dimethylsuccinic anhydride. The procedure was essentially that which has been described for ethyl 10-ketohendecanoate (9). Fractionation of the product obtained after the usual work-up yielded 12.8 g. (54%, based on anhydride) of *methyl 2,3-dimethyl-4-ketopentanoate*, b.p. 86.5–88.5° (15 mm.). This presumably contains dimethyl (and methyl ethyl) *sym*-dimethylsuccinate, but is satisfactory for preparation of lactone I. Larger runs gave similar results.

The above-described keto ester (0.081 mole) in 70 ml. of benzene was treated, at 0°, with the Grignard reagent from 0.105 mole of fractionated *n*-dodecyl bromide, according to the procedure which has been described for the synthesis of γ-alkyl-γ-lactones (2). Fractionation of the product yielded 12.6 g. (52.5%) of semi-solid lactone I, b.p. 202–207° (5.5 mm.). For analysis, there was used a center cut, b.p. 203° (5.5 mm.).

Anal. Calc'd for $C_{19}H_{36}O_2$: C, 76.96; H, 12.24.
Found: C, 76.62; H, 12.33.

2,3,4-Trimethylhexadecanoic acid. Following the published procedure (2), 11.9 g. (0.04 mole) of lactone I was heated in benzene solution with 3 mole-equivalents of purified thionyl chloride, and the mixture was poured into 30 ml. of absolute ethanol. Fractionation of the product yielded 7.8 g. (60%) of *ethyl 2,3,4-trimethylhexadecenoate*, b.p. 184–187° (5.5 mm.), an intermediate fraction of 1.7 g., and 1.0 g. of recovered lactone I, b.p. 202–207° (5.5 mm).

The unsaturated ester could not be completely hydrogenated, in ethanol solution, even with large quantities of platinum oxide catalyst; so it was saponified with alcoholic potassium hydroxide and the acid was separated from any neutral material by the use of Amberlite IRA-400 strong anion exchange resin, according to the procedure which has been described (8). The partially unsaturated acid was not distilled on account of the likelihood of converting the γ-substituted unsaturated acid to lactone (10). Hydrogenation of the acid was completed rapidly with 0.2 g. of platinum oxide catalyst in 50 ml. of glacial acetic acid. Complete hydrogenation was assured by rehydrogenation with another similar portion of catalyst and allowing hydrogenation to proceed for 24 hours. The second hydrogenation did not significantly alter the ultraviolet absorption spectrum (to be published in the next paper of this series). Distillation gave a 75% yield of 2,3,4-trimethylhexadecanoic acid, b.p. 194.5–196° (3.5 mm.).

Anal. Calc'd for $C_{19}H_{38}O_2$: Equiv. wt., 298.5. Found: Equiv. wt., 302.8.

The *methyl ester* was prepared by heating the acid under reflux for 24 hours with 50 equivalents of methanol in the presence of sulfuric acid. Fractionation gave an 87% yield of material of b.p. 179.5–180° (3.75 mm.), n_D^{25} 1.4448.

The *amide* was prepared by the usual procedure (11) for later use in studying the rate of its hydrolysis, although its m.p. is of little use for characterization since the molecule contains three asymmetric carbons. After two crystallizations from acetone, the m.p. was 55–60°.

Anal. Calc'd for $C_{19}H_{39}NO$: N, 4.71. Found: N, 4.63.

4,8-Dimethyl-1,4-tetradecanolide (II) was prepared from 4-methyl-1-decylmagnesium bromide and ethyl levulinate according to the general procedure which has been described for γ-alkyl-γ-valerolactones (2). The yield in a 1-mole run was 88%, b.p. 150–151° (1 mm.), n_{D}^{25} 1.4523.

Anal. Calc'd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89.

Found: C, 76.33; H, 12.24.

4,8-Dimethyl-1-tetradecanol was obtained in 81% yield by hydrogenation (3) of lactone II, using 25 g. of copper chromite catalyst per mole of lactone. There was less than 1% of tetrahydrofuran formed. The alcohol boiled at 133–134.5° (1.5 mm.), n_{D}^{23} 1.4496.

Anal. Calc'd for $C_{16}H_{34}O$: C, 79.27; H, 14.14.

Found: C, 79.58; H, 14.00.

1-Bromo-4,8-dimethyltetradecane, prepared with anhydrous hydrogen bromide, was obtained in 89.3% yield, b.p. 141–142° (2 mm.), n_{D}^{25} 1.4618.

Anal. Calc'd for $C_{16}H_{33}Br$: Br, 26.17. Found: Br, 26.56.

4,8,12-Trimethyl-1,4-octadecanolide. Reaction of 4,8-dimethyltetradecylmagnesium bromide with ethyl levulinate, in the usual manner (2), gave 73.5% yield of the lactone, b.p. 188–190° (1 mm.), n_{D}^{23} 1.4604.

Anal. Calc'd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.43.

Found: C, 77.93; H, 12.46.

7,11,18,22-Tetramethyloctacosane was obtained from the distillation residue from the above lactone. After washing with concentrated sulfuric acid, the hydrocarbon was distilled, b.p. 256–257° (3 mm.), n_{D}^{27} 1.4523. Recovery corresponded to 8.1% of the bromide used.

Anal. Calc'd for $C_{32}H_{66}$: C, 85.24; H, 14.76.

Found: C, 85.24; H, 14.72.

Methyl 4,8,12-trimethyloctadecanoate. The ring of the trimethyloctadecanolide was opened with thionyl chloride, and the reaction mixture treated with ethanol, according to the previously-used procedures (2). Persistent frothing prevented fractional distillation of the ethyl 4,8,12-trimethyloctadecenoate, so it was distilled in a Claisen flask to give a yield of 86% of unsaturated ester, b.p. 200–204° (3 mm.). This could not be hydrogenated with platinum oxide in ethanol, so it was saponified, and the acid distilled; yield 77%, b.p. 218.5–219° (4 mm.). Hydrogenation of 36 g. of the unsaturated acid in acetic acid proceeded rapidly, in the presence of 1.3 g. of platinum oxide catalyst, to yield 29.7 g. of saturated acid, b.p. 221–221.5° (3 mm.). Titration of this acid indicated about 15% of neutral impurity, which proved to be the starting lactone. The mixture of acid and lactone (26.1 g.) was esterified with methanol and sulfuric acid. Fractionation through the 1.5-meter column yielded 21 g. (85%) of pure ester, b.p. 193.5–194°, n_{D}^{25} 1.4461. Three grams of the lactone was also recovered.

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

Found: C, 77.41; H, 12.92.

4,8,12-Trimethyloctadecanoic acid was obtained from the ester by saponification, b.p. 220.0–220.5° (5 mm.), n_{D}^{20} 1.4550.

Anal. Calc'd for $C_{21}H_{42}O_2$: Equiv. wt., 326.5. Found: Equiv. wt., 323.7.

Sources of esters in Tables I and II. 2-*n*-Butyl-2-ethyl-nonanoic acid was esterified with diazomethane, and the ester was saponified for 90 minutes with 0.5 equivalent of boiling 0.5 *N* propanolic potassium hydroxide in order to insure removal of any admixed 4-*n*-butyl-4-ethylnonanoic acid. The resultant mixture of ester and acid was fractionated.

Methyl palmitate and methyl stearate were purified samples of esters prepared from commercial acids. Synthesis of methyl 8-methyltetradecanoate will be reported in a future paper in this series (No. XX). The remaining esters or the corresponding acids have been reported in previous papers of this series.

SUMMARY

The relationship of boiling point and of index of refraction to structures of the esters of fatty acids is discussed, and tables of values are given.

Synthesis of 2,3,4-trimethylhexadecanoic acid and of 4,8,12-trimethyloctadecanoic acid is reported.

BERKELEY, CALIFORNIA

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