[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. XXXII. SYNTHESIS AND ISOMERIZATION OF α,γ-DIALKYL-α,β-UNSATURATED ESTERS[1]

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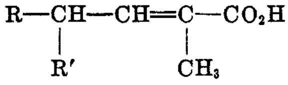
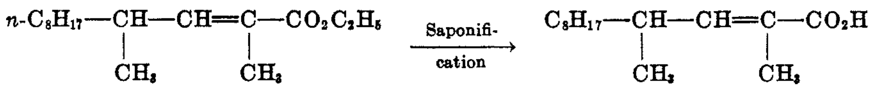
Received July 20, 1955

During the course of recent work concerned with the elucidation of the structure of C_{27}-phthienoic acid and with a study of the properties of compounds



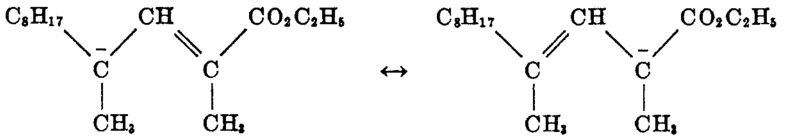
$$\underset{R'}{R-\underset{|}{C}H}-CH{=}\underset{CH_3}{\underset{|}{C}}-CO_2H$$

I



$$n\text{-}C_8H_{17}-\underset{CH_3}{\underset{|}{C}H}-CH{=}\underset{CH_3}{\underset{|}{C}}-CO_2C_2H_5 \xrightarrow[\text{cation}]{\text{Saponifi-}} C_8H_{17}-\underset{CH_3}{\underset{|}{C}H}-CH{=}\underset{CH_3}{\underset{|}{C}}-CO_2H$$

II IIa



IIi

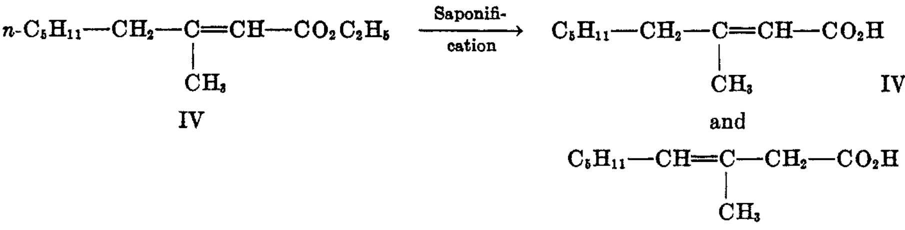
$$n\text{-}C_5H_{11}-CH_2-CH{=}CH-CO_2C_2H_5 \xrightarrow[\text{cation}]{\text{Saponifi-}} C_5H_{11}-CH_2-CH{=}CH-CO_2H$$

III IIIa

and

$$C_5H_{11}-CH{=}CH-CH_2-CO_2H$$

IIIb



$$n\text{-}C_5H_{11}-CH_2-\underset{CH_3}{\underset{|}{C}}{=}CH-CO_2C_2H_5 \xrightarrow[\text{cation}]{\text{Saponifi-}} C_5H_{11}-CH_2-\underset{CH_3}{\underset{|}{C}}{=}CH-CO_2H \quad \text{IVa}$$

IV

and

$$C_5H_{11}-CH{=}\underset{CH_3}{\underset{|}{C}}-CH_2-CO_2H$$

IVb

containing the known structural features (I) of this physiologically corrosive acid, Cason and Allen (1) observed that the saponification of synthetic optically active ethyl L(+)-2,4-dimethyl-2-dodecenoate (II) proceeds with essentially no

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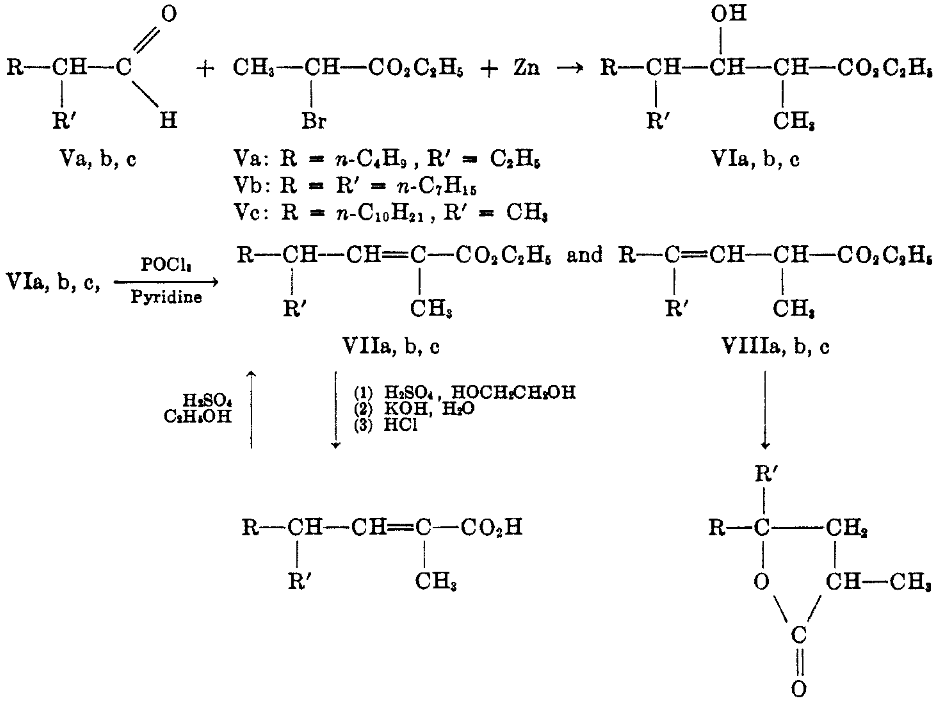
[1] This investigation was supported in part by a research grant (E-86) from the National Institutes of Health, U. S. Public Health Service. It has been presented, in part, at the 126th Meeting of the American Chemical Society, New York, Sept. 12-17, 1954.

[2] National Science Foundation Fellow, 1952-1954.

racemization of the asymmetric γ-carbon. Failure to racemize indicates a lack of equilibration with the corresponding β,γ-unsaturated ester during hydrolysis. This behavior is in direct contrast to that observed by Cason and Sumrell (2) during similar treatment of the unsubstituted ethyl 2-nonenoate (III) and the β-substituted ethyl 3-methyl-2-nonenoate (IV), both of which became equilibrated with their unconjugated β,γ-unsaturated isomers. Linstead (3), as well as Cason, Allinger, and Sumrell (4), have found that acids such as IIIa do not undergo significant isomerization under the conditions that were used for saponification; equilibration occurs at a significant rate only under more strenuous conditions (3). It follows, therefore, that equilibration of the esters, III and IV, must have occurred prior to saponification, and the resonance-stabilized enolate ion (4) seems a plausible intermediate in the equilibration of the esters.



Va, b, c VIa, b, c

Va: R = n-C_4H_9, R′ = C_2H_5
Vb: R = R′ = n-C_7H_{15}
Vc: R = n-$C_{10}H_{21}$, R′ = CH_3

VIIa, b, c VIIIa, b, c

IXa, b, c Xa, b, c

Equilibration of α,β-unsaturated acids and esters has been studied by Linstead and co-workers (5). In the case of an unsubstituted acid, the alkali-equilibrated mixture contains about 75% of the conjugated isomer, IIIa, whereas introduction of an α-methyl substituent increases the equilibrium concentration of the α,β-unsaturated isomer to about 90%. In contrast, introduction of a γ-methyl substituent reduces the equilibrium concentration of conjugated isomer to about 20%. Equilibration of an α,γ-dimethyl-α,β-unsaturated acid or ester appears not to have been studied, but the work of Linstead and co-workers supports the reasonable prediction that these two substituents would tend to counteract each other. Lack of racemization of the L(+)-2,4-dimethyl-2-dodecenoate (II) can hardly be attributed, however, to an equilibrium highly unfavorable to the β,γ-unsaturated isomer, for formation of the resonance-stabilized enolate ion, IIi, should result in racemization of the asymmetric center, regardless of the final equilibrium between the two isomeric esters (dependent on relative rate of attack of the proton at the *alpha* or *gamma* position). If the enolate ion is indeed the intermediate responsible for equilibration, the most plausible explanation for failure of II to racemize is a very slow rate of formation of the enolate ion, IIi. This would allow time for saponification to the acid, which is known to form enolate ion at an insignificant rate under the conditions of saponification. Presence of the 4-methyl substituent would be expected to reduce the acidity of the hydrogen at position-4, and this is consistent with a reduction in rate of formation of enolate ion. Results of the investigation of isomerization of 2,4-dialkyl-2-alkenoic esters, reported in the present paper, are entirely consistent with these views concerning the mechanism of equilibration.

SYNTHESIS

Compounds which were used for the equilibration studies were synthesized by the sequence outlined in the equations containing formulas V–X.

This synthetic sequence was chosen because it yields the two isomeric unsaturated esters, VII and VIII, desired as reference compounds for use in analysis of mixtures of unsaturated esters. The isomeric ethyl 2-methyl-4-ethyloctenoates (VIIa and VIIIa) were separated by fractional distillation. This separation is difficult, since the boiling points differ by about eight degrees, but there was obtained a sample of the β,γ-unsaturated isomer (VIIIa) containing only about 4% of the conjugated isomer. The conjugated isomer is more readily obtained by treatment of the mixture of unsaturated esters with acid in a high-boiling solvent, as shown in the reaction sequence. The resultant mixture of lactone and unsaturated acid is readily separated either by distillation or chemical means. Esterification of the α,β-unsaturated acid in boiling ethanol yields ester VIIa, not contaminated with the isomeric ester, VIIIa (*cf.* below for discussion of equilibration). Properties of the 2-methyl-4-ethyl acids and esters are assembled in Table I.

TABLE I

PROPERTIES OF α-METHYL-γ-ETHYL UNSATURATED ESTERS AND ACIDS

Compound	B.P., °C/mm.	n_D^{25}	λ_{max}, mμ	ϵ_{max}	ϵ'[a]
Ethyl 2-methyl-4-ethyl-2-octenoate	102–103/4.8	1.4478	216	13,400	13,300
Ethyl 2-methyl-4-ethyl-3-octenoate	94–95/4.8	(1.4387)[b]	—	—	(2,700)[b]
2-Methyl-4-ethyl-2-octenoic acid	141–142/4.6	1.4628	219	14,100	14,000
2-Methyl-4-ethyl-3-octenoic acid	106–107.5/0.9	(1.4515)[b]	—	—	(2,100)[b]

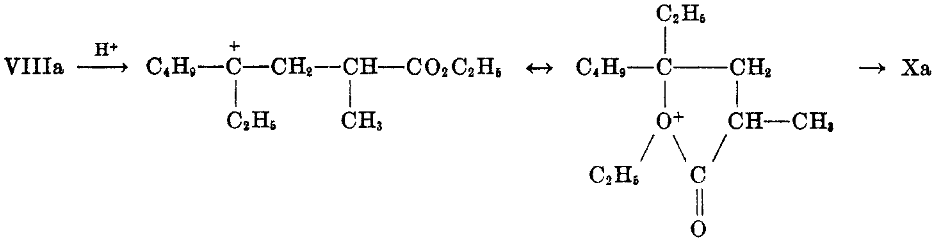
[a] Extinction coefficient at the wave length where the spectra of the isomeric esters (or acids) are most widely separated. This is at 217 mμ for the esters, 220 mμ for the acids.

[b] Estimated by extrapolation of the properties of the best sample of Δ^3-isomer (containing 4- 6% of Δ^2-isomer).

Although the presently utilized synthetic sequence was chosen because it yields the isomeric unsaturated esters, it constitutes a method of synthesis of α,β-unsaturated acids which compares favorably with the previously used (12) method depending on α-bromination of the saturated acid, followed by dehydrohalogenation. When the mixture of unsaturated esters obtained directly from dehydration was equilibrated with sodium glycolate (*cf.* below), then converted to lactone and conjugated acid, there was obtained an over-all yield of pure 2-methyl-4-ethyl-2-octenoic acid (IXa) amounting to 44%. If non-conjugated ester is separated prior to conversion to lactone and re-equilibrated with conjugated ester, the over-all yield of IXa may be raised to 65%.

Of the aldehydes required as starting materials for the synthetic scheme, 2-ethylhexanal (Va) is commercially available and the other two were satisfactorily prepared by Rosenmund reduction of the corresponding acid chlorides. 2-Methyldodecanal (Vc) proved to be unstable in presence of air, presumably on account of polymerization (6). Distillation of old samples of aldehyde gave moderately good recovery of pure aldehyde, but some acid was also obtained. Polymerization of the aldehyde is inhibited by storage under nitrogen or addition of traces of hydroquinone (7).

The Reformatsky reaction, followed by dehydration, gave excellent yields (85–90%, based on aldehyde), when an excess of α-bromo ester and zinc was used. Excess bromo ester is required because of the formation of ethyl α-propionylpropionate, which was isolated as a by-product. Although the hydroxyl group has a tertiary carbon in each adjacent position, direct dehydration was not readily accomplished. Treatment of the ester, VIa, with boiling anhydrous formic acid yielded the formate ester, ethyl 2-methyl-4-ethyl-3-formoxyoctanoate; while treatment of the corresponding acid with acetic anhydride yielded the acetate, 2-methyl-4-ethyl-3-acetoxyoctanoic acid.



XI

Dehydration of ester VIa could also be accomplished with thionyl chloride and quinoline at elevated temperature; however, this procedure is of less synthetic utility than that shown in the reaction sequence. The total yield of dehydration products was 64%, and the yield of unsaturated esters (about two-thirds the conjugated isomer, VIIa) was only 24%. The remaining products of this dehydration consisted of the saturated γ-lactone, Xa, and the α,β-unsaturated γ-lactone, XIII. Formation of the saturated γ-lactone, Xa, may be reasonably formulated as proceeding *via* protonation (quinoline hydrochloride would

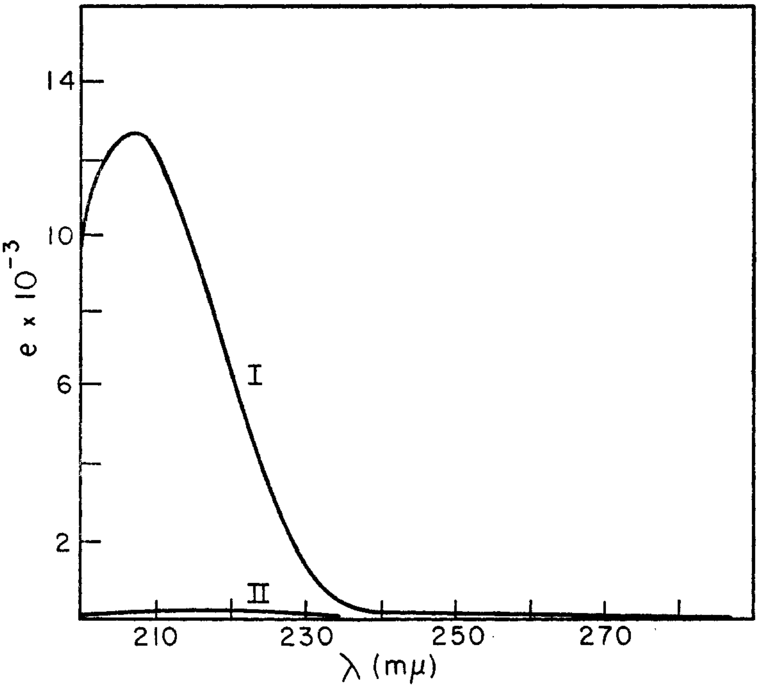


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF γ-LACTONES. Curve I, 2-methyl-4-ethyl-4-hydroxy-2-octenoic acid, γ-lactone; Curve II, 2-methyl-4-ethyl-4-hydroxyoctanoic acid, γ-lactone.

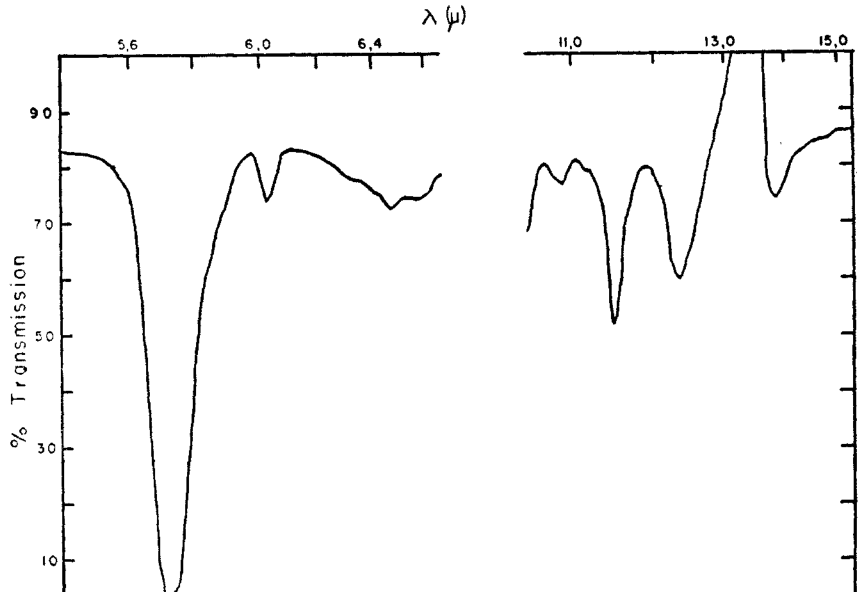
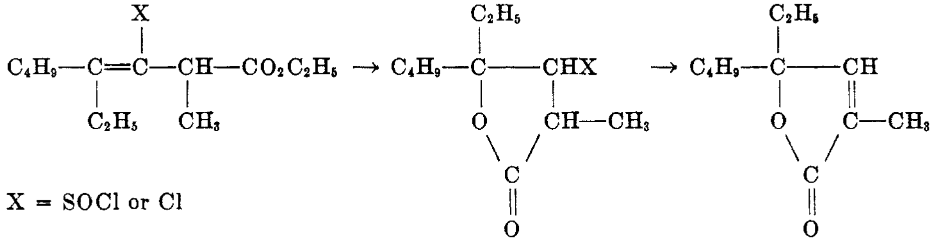


FIG. 2. INFRARED ABSORPTION SPECTRUM OF 2-METHYL-4-ETHYL-4-HYDROXY-2-OCTENOIC ACID, γ-LACTONE. Determined in carbon tetrachloride solution with a Perkin-Elmer Model 21 infrared spectrophotometer.

supply a low concentration of protons) of the β,γ-unsaturated ester to give the resonance-stabilized intermediate, XI. The intermediate, XI, is the same type of cyclic resonance hybrid which has been used successfully to correlate rearrangements (8) of alkoxy acid chlorides and ester acid chlorides. The origin of the unsaturated lactone, XIII, is less clear, but it may have arisen *via* sulfinylation or chlorination (9) of the double bond to give the intermediate, XII, which could lactonize by the mechanism shown for XI, then give XIII by elimination of the β-substituent. The unsaturated lactone (XIII) has been characterized, in part, by comparison of its ultraviolet and infrared spectra (Fig. 1 and 2) with those published (10) for α,β-unsaturated γ-lactones. The remote possibility that the unsaturated lactone might be the isomeric methylene lactone was eliminated by Kuhn-Roth determination of terminal methyl (11); the saturated and unsaturated lactones gave nearly identical values in this analysis.



X = SOCl or Cl

XII XIII

INFRARED AND ULTRAVIOLET SPECTRA

The infrared spectra of the three α,β-unsaturated acids prepared for the present work show the features previously cited (13) as characteristic of acids of the *trans* series. In particular, each spectrum includes very strong bands at about 7.05 and 7.8 μ, very weak bands or shoulders at 6.85 and 8.0 μ (*cis* acids show the stronger bands at the latter locations). The ultraviolet spectra (Fig. 3) also show molar extinction coefficients near 14,000, about 5,000 higher than the extinctions shown by the *cis* isomers. There appears to be no reasonable doubt that these acids have the *trans* configuration.

As has previously been discussed by Freeman (14) and by Cason and Kalm (15), the positions of the long wavelength unsaturation bands in the infrared are influenced markedly by the substituents near the double bond. In particular, most of the α,β-unsaturated acids have a band at about 10.35 μ (or else no absorption in the 10.0–10.4 μ region), and have a band at about 15.5 μ. The 2,4-dimethyl-2-alkenoic acids, alone among those acids thus far examined, show no absorption in these regions but have instead bands at about 10.1 μ and at about 15 μ. As shown in Table II, 2,4-dimethyl-2-tetradecenoic acid shows bands in these regions; however, the two acids having larger groups than methyl in the 4-position do not show bands just above 10 μ, but have bands just below 10 μ instead. Furthermore, a re-examination of the spectra previously published (13) for a series of lower molecular weight *trans*-2-methyl-2-alkenoic acids has revealed

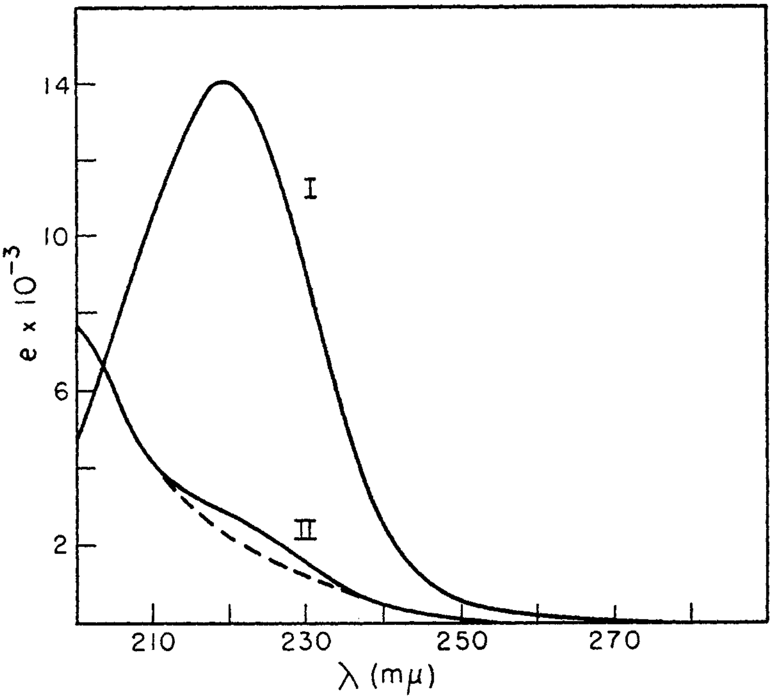


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRA OF ISOMERIC UNSATURATED ACIDS. Curve I, 2-methyl-4-ethyl-2-octenoic acid; Curve II, 2-methyl-4-ethyl-3-octenoic acid. The broken line is the theoretical curve for pure Δ^3-acid. The sample shown contains about 6% of Δ^2-acid.

that the only acid exhibiting a band just above 10 μ is *trans*-2-methyl-2-hexenoic acid (terminal methyl is at the 4-position). These data raise the possibility that the band at about 10.1 μ is characteristic of a methyl group at the 4-position. Since C_{27}-phthienoic acid has the band at 10.06 μ, and there appears to be no reliable evidence that the 4-alkyl group in this acid is methyl, further investigation of the spectral properties of 4-alkyl-2-alkenoic acids seems desirable. It is of particular interest that the positions of the long wavelength unsaturation bands are nearly identical for 2,4-dimethyl-2-tetradecenoic acid and 2,4-dimethyl-2-pentacosenoic acid, yet C_{27}-phthienoic acid shows slightly different positions for three of these bands.

Mixtures of the 2- and 3-alkenoic acids and esters obtained in equilibration studies were analyzed by means of the ultraviolet absorption at the region of maximum difference in absorption of the two isomers (*cf.* Fig. 3). Although a relatively pure sample of the β,γ-unsaturated isomer was obtained only in the case of the 2-methyl-4-ethyl-3-octenoic acid and ester, application of these data to the other acids appears sufficiently accurate for these studies. The absorption of the other two α,β-unsaturated acids agrees within 3% with that of the 2-methyl-4-ethyl-2-octenoic acid. It is of interest that the molar extinction coefficients of the α,β-unsaturated esters differ considerably more than do those

TABLE II

LONG WAVELENGTH UNSATURATION BANDS FOR α,β-UNSATURATED ACIDS

Acid	Absorption Bands (μ)				
2,4-Dimethyl-2-tetradecenoic		10.08	12.38	13.33	15.03
2-Methyl-4-ethyl-2-octenoic	9.86		12.24	13.30	15.01
2-Methyl-4-*n*-heptyl-2-hendecenoic	9.91		12.42	13.29	15.01
2,4-Dimethyl-2-pentacosenoic[a]		10.08	12.40	13.36	15.10
C_{27}-Phthienoic[b]		10.06	12.50	13.26	14.92

[a] Data from ref. 15. [b] Data from ref. 14.

of the acids. Whereas the values for ϵ_{max} of acids IXa, b, and c are respectively 14,100, 13,800, and 13,700; the corresponding values for the esters are 13,400, 12,800, and 13,800. It may be noted that as the γ-substituent in the esters becomes larger, the molar extinction coefficient becomes smaller. Steric interference between the α-methyl and the branch in the γ-position might be expected to give a small decrease in extinction coefficient as the size of the γ-substituent increases; however, if this be the explanation it is unclear why the effect is not observed in the case of the acids, for the functional group is *trans* to the terminal chain.

ISOMERIZATION STUDIES

Equilibration of 2- and 3-alkenoic acids or esters of the type included in this study does not occur under acid catalysis. The β,γ-unsaturated isomer goes to lactone in presence of acid, as previously mentioned, while the α,β-unsaturated isomer is essentially unaffected by prolonged heating in presence of mineral acid. The latter observation is consistent with the very slow rate of thermal racemization of active 2,4-dimethyl-2-alkenoic acids (1). This behavior may be reasonably attributed to the fact that tertiary carbonium ions (*alpha* or *gamma* positions) are formed in preference to the higher energy secondary carbonium ion that would be formed in the *beta* position. The *gamma* carbonium ion (*cf.* formula XI) then may go to lactone by elimination of alkyl from the ester or hydrogen from the acid. In acids having no γ-substituent, there is little tendency for lactone formation, and equilibration with the α,β-unsaturated isomer does occur (2, 16). The *alpha* carbonium ion may only generate the starting α,β-unsaturated acid or the methylene acid, which is of higher energy; and previous studies (1) have shown that the equilibrium mixture contains only a small percentage of methylene acid.

Isomerization catalyzed by alkali is believed dependent on formation of the resonance-stabilized enolate ion (IIi), which is formed slowly because both ionizable hydrogens are tertiary ones. In addition, a steric factor is probably important in developing an equilibrium unfavorable to enolate ion formation. The resonance-stabilized enolate ion, IIi, must be planar, with the substituents on the *alpha* and *gamma* carbons in the plane of the three atoms involved with the π-orbital (the plane at right angles to the π-orbital). Since there are two substituents on both the *alpha* and *gamma* carbon atoms, this geometry of the

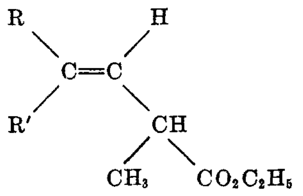
TABLE III

EQUILIBRATION OF ETHYL 2-METHYL-4-ETHYL-2 (AND -3)-OCTENOATES

Conditions	Time (hrs.)	Δ^2-Isomer	
		Starting material, %	Product, %
2.0 *N* sodium ethoxide in refluxing ethanol	9	6	34
3.0 *N* sodium ethoxide in refluxing ethanol	90	6	49
2.4 *N* sodium glycolate in refluxing glycol	11	35	60
3.4 *N* sodium glycolate in refluxing glycol	27	12	68
3.3 *N* sodium glycolate in refluxing glycol	60	100	66

enolate ion causes serious steric interference between these substituents, hence decreases the stability of the ion. The data assembled in Table III show that equilibrium between the 2- and 3-alkenoates is reached only after long heating in boiling ethylene glycol. These data are consistent with failure of the ester to equilibrate (1) in the brief interval prior to saponification in boiling ethanolic potassium hydroxide.

It is of interest that the equilibrated mixture of the 2-methyl-2-heptylhendecenoates contains about 60% of the 2-isomer, a value in reasonable agreement with that shown in Table III for the 2-methyl-4-ethyloctenoates; however, the equilibrated mixture of 2,4-dimethyltetradecenoates contains only about 44% of the 2-isomer. Both Ingold (17) and Alexander (18) have attributed to hyperconjugation the lower energy of a double bond attached to a carbon bearing an alkyl branch. According to this idea, the *gamma* methyl substituent would favor the β,γ-unsaturated isomer more than would a larger alkyl on account of the larger number of hydrogens available for hyperconjugation in the case of methyl. Since there is much evidence (19) of the significantly different steric requirements of methyl and a larger group, we prefer to ascribe the difference in position of equilibrium to steric factors; however, the analysis is not a simple one. Nothing is known about the geometry of the β,γ-multiple bond, but it seems reasonable to assume that the larger groups would assume *trans* positions during the equilibration (XIV, $R >$ or $= R'$). With the double bond in the β,γ-position, the strain



XIV

between R and R′ would be relieved somewhat, as compared with the α,β-position for the double bond, for the normal sp^2 bond angle is about 120°, as compared to about 109° for the sp^3 bond angle. On the other hand, the group denoted by R′ is thrown into the co-planar *cis* position with the bulky branched group on the adjacent doubly bonded carbon. This would appear to result in a more significant steric strain than could be balanced by relief in strain resulting from the slight spread of the bond angle between R and R′. It follows that as R′ becomes larger than methyl, the β,γ-isomer is less favored on account of the increase in steric strain.

EXPERIMENTAL[3]

2-Heptylnonanal (Vb) was prepared by the Rosenmund reduction (22) of 2-heptylnonanoyl chloride, b.p. 161–164°/4.0 mm., n_D^{25} 1.4477, prepared in 97% yield by the procedure of Bishop (23) from commercial 2-heptylnonanoic acid [Lit. (24), b.p. of 2-heptylnonanoyl chloride 178–180°/14 mm.]. Hydrogenation of 95.3 g. of the acid chloride in presence of 6.8 g. of commercial palladium-barium sulfate catalyst and 0.7 ml. of sulfur-quinoline poison (22) in 240 ml. of purified xylene required seven hours; yield 62.2 g. (75%) of 2-heptylnonanal, b.p. 128–131°/1.5 mm., n_D^{25} 1.4397.

Anal. Calc'd for $C_{16}H_{32}O$: C, 79.95; H, 13.42.
Found: C, 79.85; H, 13.20.

The *semicarbazone*, after two crystallizations from methanol, from which it separates as small white needles, melted at 43–49.5°. A sample placed in a bath at 47° melts completely at once. Further recrystallization did not alter this behavior, thus the substance appears to be polymorphic.

Anal. Calc'd for $C_{17}H_{35}NO_3$: C, 68.64; H, 11.86.
Found: C, 68.34; H, 11.82.

2-Methyldodecanal (Vc) was prepared by the procedure described above for 2-heptylnonanal. From 88.6 g. of 2-methyldodecanoyl chloride [b.p. 126–128°/4.5 mm., n_D^{26} 1.4435, prepared in 98% yield from 2-methyldodecanoic acid (11)], there was obtained 53.6 g. (71%) of 2-methyldodecanal, b.p. 119–121°/4.5 mm., n_D^{25} 1.4332.

Anal. Calc'd for $C_{13}H_{26}O$: C, 78.70; H, 13.21.
Found: C, 78.70; H, 13.35.

The aldehyde should be distilled as soon as reduction has been completed and should be employed directly in the Reformatsky reaction; however, the refractive index of pure aldehyde did not change during storage for several days under nitrogen or in contact with a catalytic amount of hydroquinone. A sample left standing in contact with air had n_D^{25} 1.4386 after one day and n_D^{25} 1.4453 after seven days. Redistillation of this material gave mostly regenerated aldehyde, together with some of the corresponding acid.

Ethyl 2-methyl-3-hydroxy-4-ethyloctanoate (VIa) was the only one of the hydroxy esters conveniently isolated by fractional distillation, without significant cracking to unsaturated esters. It was prepared by a Reformatsky procedure essentially that previously described in detail (25), except that there was used a ratio of 1 mole of aldehyde to 3 moles each of zinc and ethyl α-bromopropionate. The yield of ester VIa was 87%, b.p. 122–124°/4.9 mm., n_D^{25} 1.4414.

Anal. Calc'd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38.
Found: C, 67.51; H, 11.09.

There was also obtained from the distillation a lower-boiling fraction, amounting to about one-third the weight of the desired product, of b.p. 64–77°/8 mm., n_D^{25} 1.4241, which gave a blue-violet ferric chloride test (26) and probably consists largely of ethyl α-propionylpropionate [Lit. (27), b.p. 88–90°/12 mm.].

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[3] All melting points are corrected, all boiling points are uncorrected. Distillations, unless otherwise specified, were through an 18-inch column of the simple Podbielniak type (20). Microanalyses are by the Microanalytical Division, Dept. of Chemistry, Univ. of California. Ultraviolet spectra were determined on a Beckman model DU quartz spectrophotometer, in specially purified (21) heptane or hexane at concentrations such that optical densities were in the range 0.15–1.5.

In runs in which the ratio of aldehyde, zinc, and bromoester was 1:2:3, yields of 64–71% were obtained.

Saponification of the hydroxy ester gave *2-methyl-4-ethyl-3-hydroxyoctanoic acid,* b.p. 154–156°/2.6 mm., n_{D}^{25} 1.4553.

Anal. Calc'd for $C_{11}H_{22}O_3$: C, 65.30; H, 10.96; Eq. wt., 202.3.

Found: C, 65.87; H, 11.02; Eq. wt., 201.

Ethyl 2-methyl-4-ethyl-3-octenoate (VIIIa) was separated from the mixture of unsaturated esters resulting from dehydration of ester VIa. To a solution of 20.0 g. of ester VIa in 123 g. of pyridine, cooled in ice, was slowly added 26.6 g. of phosphorus oxychloride. After the resultant mixture had stood for 8 hours at room temperature, it was heated for 90 minutes on the steam-bath (omission of the final heating period lowered the yield by about 15%). The cooled reaction mixture was decanted into cracked ice, and the product was extracted with hexane. The extracts were washed with 2 *N* hydrochloric acid and water, then were dried and distilled. The total yield of unsaturated esters, b.p. 95–108°/4.5 mm., n_{D}^{25} 1.4427, was 16.0 g. (87%). From the ultraviolet spectrum (ϵ_{217} 7,200), the product was estimated (*cf.* below) to contain about 58% of β,γ-unsaturated ester. Fractional distillation of the mixed esters through a 4-ft. Podbielniak type column (28), and systematic redistillation of lower-boiling fractions (b.p. in range 94–99°/4.8 mm., n_{D}^{25} in range 1.4402–1.4411) gave a best sample of ester VIIIa of b.p. 94–95°/4.8 mm., n_{D}^{25} 1.4393. The ultraviolet absorption of this sample (no maximum above 200 mμ, ϵ_{208} 7,800, ϵ_{216} 3,300) shows it to contain about 4% of the α,β-unsaturated isomer. The pure β,γ-unsaturated isomer is estimated to have n_{D}^{25} 1.4387.

Anal. Calc'd for $C_{13}H_{24}O_2$: C, 73.55; H, 11.40.

Found: C, 73.31; H, 11.38.

2-Methyl-4-ethyl-3-octenoic acid was obtained by saponification at room temperature of a sample of ester VIIIa having n_{D}^{25} 1.4396. The sample of acid so obtained had b.p. 106–107.5°/0.9 mm., n_{D}^{25} 1.4523; the ultraviolet spectrum is shown in Fig. 3 (no maximum above 200 mμ, ϵ_{200} 7,700, ϵ_{219} 2,900).

Anal. Calc'd for $C_{11}H_{20}O_2$: C, 71.66; H, 10.93; Eq. wt., 184.3.

Found: C, 72.01; H, 11.21; Eq. wt., 186.

Since a sample of acid taken prior to distillation had n_{D}^{25} 1.4528, there is no evidence of isomerization during heating required for distillation. This is consistent with previous experiments (2) on heat equilibration of another β,γ-unsaturated acid.

2-Methyl-4-ethyl-4-hydroxyoctanoic acid, γ-lactone (Xa). *A.* A solution of 2.0 g. of ethyl 2-methyl-4-ethyl-3-octenoate (n_{D}^{25} 1.4396) in 20 ml. of 10% ethanolic hydrochloric acid was heated for 70 hours at 75°, then diluted with water and extracted with hexane. Work-up and fractionation gave 0.3 g. of fore-run and 1.3 g. (75%) of the γ-lactone, b.p. 115–117°/4.3 mm., n_{D}^{25} 1.4462, $\lambda_{\max}$ 213 mμ, ϵ 188, ϵ_{208} 174.

Anal. Calc'd for $C_{11}H_{20}O_2$: C, 71.66; H, 10.93; C—CH_3, 24.5.

Found: C, 71.76; H, 10.54; C—CH_3, 15.5.

The value for terminal methyl (63% of theory) is only slightly below the range usually found for higher molecular weight branched-chain acids (29).

B. A solution of 0.5 g. of 2-methyl-4-ethyl-3-octenoic acid (n_{D}^{25} 1.4521), 10 ml. of ethylene glycol, and 0.61 ml. of concentrated sulfuric acid was heated under reflux for 14 hours, then cooled, diluted with water, and extracted with hexane. Work-up and fractionation gave 0.4 g. (80%) of the γ-lactone, b.p. 118–119°/4.9 mm., n_{D}^{25} 1.4477.

2-Methyl-4-ethyl-4-hydroxy-2-octenoic acid, γ-lactone (XIII); *dehydration with quinoline and thionyl chloride.* In an adaptation of methods previously described (2, 30), a solution of 50 g. of β-hydroxy ester, VIa, in 56 g. of quinoline was treated during 40 minutes with 52 g. of thionyl chloride. The resultant mixture was heated for 2 hours at 165°, then cooled and decanted into cracked ice. After addition of hexane, the two-phase mixture was filtered with suction through a layer of Supercel, and the tarry material on the Supercel was extracted alternately with hexane and 5% hydrochloric acid. The total hexane extracts were separated and washed with water, sodium bicarbonate, and water, then dried over sodium sulfate. After distillation of solvent, the residue was distilled in a Claisen flask in order to separate tarry material. The Claisen distillate was fractionated through the 4-foot column (28) to yield, besides intermediate fractions, the following: (a) 3.0 g. of β,γ-unsaturated ester, VIIIa, b.p. 94.5–99°/5.1 mm., contaminated with a small amount of impurity from the technical quinoline (1); (b) 7.5 g. (16%) of α,β-unsaturated ester, VIIa, b.p. 103–105.5°/5.1 mm., n_D^{25} 1.4489; (c) 11.5 g. (29%) of a mixture of the saturated lactone, Xa, and the unsaturated lactone, XIII. The mixed lactones had b.p. 116–118.5°/5.1 mm., n_D^{25} 1.4509, λ_{max} 206.5 mμ, ϵ 3,750. A comparison of the ultraviolet spectrum to those of the pure compounds (*cf.* Fig. 1) indicates about 30% of the unsaturated lactone, 70% of the saturated one.

When intermediate fractions are included, the total yield of dehydration products amounts to about 64%.

For separation of the unsaturated lactone, the mixture of lactones was heated under reflux for 8 hours with excess aqueous 2 *N* sodium hydroxide. The insoluble layer consisted largely of unsaturated lactone, while acidification of the alkaline solution yielded the saturated lactone, b.p. 119–122°/5.4 mm., n_D^{25} 1.4480, containing about 8% of the unsaturated lactone estimated from the U. V. spectrum). To obtain a pure sample of the unsaturated lactone, the insoluble layer from the first saponification was again saponified in a similar fashion. Distillation of this final unsaponified lactone yielded the pure unsaturated γ-lactone, XIII, b.p. 111°/3.8 mm., n_D^{25} 1.4592.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.95; C—CH_3, 24.7.
Found: C, 72.26; H, 10.10; C—CH_3, 16.4.

The ultraviolet spectrum of this lactone (*cf.* Fig. 1) has a broad maximum at 207.5 mμ ϵ 12,700. The infrared spectrum (*cf.* Fig. 2) shows a very strong carbonyl stretching band at 5.71 μ and the weaker olefin stretching band at 6.02 μ, together with long wavelength unsaturation bands at 10.89, 11.47, and 12.33 μ.

Heating of the unsaturated lactone in boiling ethanolic sodium hydroxide, followed by dilution with water and acidification, yielded recovered lactone with properties essentially identical to those of the starting material.

Attempts at direct dehydration of β-hydroxy acid or ester. A. Formic acid. In accordance with the procedure of Bachmann (31), 3.0 g. of β-hydroxy ester (VIa) and 15 ml. of anhydrous formic acid were heated under reflux for 25 minutes. After work-up and fractionation, there was isolated 3.3 g. (98%) of *ethyl 2-methyl-4-ethyl-3-formoxyoctanoate*, b.p. 119–120°/2.8 mm., n_D^{25} 1.4377.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14.
Found: C, 65.23; H, 10.16.

When heating under reflux was continued for 69 hours, only a small amount of unsaturated ester was formed.

B. Acetic anhydride. According to the procedure described by Wallach (32), 3.0 g. of hydroxy acid and 6 ml. of acetic anhydride were heated under reflux for 4 hours. Work-up and fractional distillation yielded 2.0 g. of *2-methyl-4-ethyl-3-acetoxyoctanoic acid*, b.p. 159–160°/3 mm., n_D^{25} 1.4446.

Anal. Calc'd for $C_{13}H_{24}O_4$: C, 63.92; H, 9.90.
Found: C, 63.91; H, 10.05.

α,β-Unsaturated acids were most conveniently prepared by direct dehydration of the crude β-hydroxy esters, followed by alkali-catalyzed equilibration of the two isomers and conversion of the β,γ-unsaturated isomers to γ-lactones (X). Preliminary separation of the β,γ-unsaturated isomer and re-equilibration gives maximum yield of the α,β-unsaturated isomer, and this procedure is described for preparation of acid IXa. Direct isolation without equilibration is described for acids IXb and IXc.

2-Methyl-4-ethyl-2-octenoic acid (IXa). Hydroxy ester, VIa, was prepared as described above from 38.4 g. of 2-ethylhexanal (Va). The crude hydroxy ester was dehydrated as described for preparation of the β,γ-isomer, VIIIa, to yield 81 g. of crude reaction product. The undistilled dehydration product was equilibrated by heating for 16 hours under reflux in a solution of 34.5 g. of sodium and 450 ml. of ethylene glycol (prepared as described below for equilibration). For saponification of the glycol esters, the solution was diluted with water and heated under reflux for 30 minutes. Acidification, extraction, and distillation yielded 49.8 g. of mixed unsaturated acids.

In order to facilitate separation of the β,γ-unsaturated isomer, the mixture was partially esterified. For this purpose, the mixed acids were allowed to stand in a solution of 15.2 ml. of concentrated sulfuric acid and 350 ml. of commercial absolute alcohol for 7 hours at room temperature, then the mixture was heated under reflux for 30 minutes. Work-up and fractionation of the total acidic and neutral product through the 4-foot column yielded the following fractions:

(a) 26.2 g. of a mixture of α,β- and β,γ-unsaturated esters boiling below 101.5°/4.9 mm.;

(b) 14.7 g. (23%) of α,β-unsaturated ester (VIIa), b.p. 101.5–102.5°/4.9 mm., n_D^{25} 1.4480;

(c) 11.6 g. (21%) of α,β-unsaturated acid (IXa), b.p. 138–141°/4.9 mm., n_D^{25} 1.4627.

Fraction (a) was again subjected to the equilibration process described above, then the equilibrated acids were heated under reflux for 10 hours in a solution of 6.8 ml. of concentrated sulfuric acid and 124 ml. of ethylene glycol. Saponification of the glycol esters, followed by work-up and fractionation of the product yielded 5.6 g. of lactone Xa, b.p. 117–119°/4.8 mm., n_D^{25} 1.4471, and 11.8 g. (21%) of α,β-unsaturated acid (IXa), b.p. 141–142°/4.8 mm., n_D^{25} 1.4626.

The total yield of α,β-unsaturated acid (IXa) or the corresponding ester obtained by these procedures amounts to 65%, calculated on the basis of aldehyde used in the Reformatsky reaction.

For analysis, there was used a redistilled sample of 2-methyl-4-ethyl-2-octenoic acid (IXa), b.p. 141–142°/4.6 mm., n_D^{25} 1.4628. The ultraviolet spectrum of this sample is shown in Fig. 3., λ_{max} 219 mμ, ϵ 14,100.

Anal. Calc'd for $C_{11}H_{20}O_2$: C, 71.66; H, 10.93; Eq. wt., 184.3.

Found: C, 71.81; H, 10.79; Eq. wt., 185.6.

Esterification of isomeric unsaturated acids. A. A 1.0-g. sample of 2-methyl-4-ethyl-2-octenoic acid (n_D^{25} 1.4623) was esterified by heating under reflux for 7 hours with a solution of 1.2 g. of concentrated sulfuric acid in 10 g. of absolute ethanol. *Ester VIIa* (1.0 g.), obtained after work-up and distillation, had b.p. 104–105°/5.0 mm., n_D^{25} 1.4479, λ_{max} 216 mμ, ϵ 13,350, in agreement with the properties observed for the sample obtained under milder conditions of esterification (preceding section) and also the sample obtained by direct fractional distillation of the product from dehydration of the β-hydroxy ester with quinoline and thionyl chloride.

Anal. Calc'd for $C_{13}H_{24}O_2$: C, 73.55; H, 11.40.

Found: C, 73.78; H, 11.31.

B. When 0.5 g. of 2-methyl-4-ethyl-3-octenoic acid (n_D^{25} 1.4524) was allowed to stand at room temperature for 20 hours in a solution of 10 ml. of absolute ethanol and 0.44 ml. of concentrated sulfuric acid, the product (VIIIa) obtained after workup and distillation weighed 0.55 g. and had b.p. 94–96°/4.9 mm., n_D^{25} 1.4384, in agreement with the previously described sample obtained by direct fractionation of the product of dehydration of the β-hydroxy ester.

2-Methyl-4-n-heptyl-2-hendecenoic acid (IXb). The Reformatsky reaction was carried out as described for preparation of ester VIa, starting with 24.0 g. of 2-heptylnonanal (Vb). Dehydration of the crude hydroxy ester with pyridine and phosphorus oxychloride, according to the procedure described previously, and distillation yielded 3.9 g. of ethyl α-propionyl propionate, b.p. 48–55°/1.3 mm., and 29.1 g. (90%) of a mixture of unsaturated esters and γ-lactone, b.p. 159–173°/1.5 mm. From the ultraviolet spectrum, this mixture was estimated by Method *B* (*cf.* below) to contain about 58% α,β-unsaturated ester; so equilibration is unprofitable.

The mixture of unsaturated esters was converted directly to lactone, Xb, and α,β-unsaturated acid, IXb, by heating under reflux for 10 hours with a solution of 13 g. of concentrated sulfuric acid in 117 g. of ethylene glycol, followed by saponification of the glycol esters. Distillation yielded 9.4 g. (32%) of γ-lactone, Xb, b.p. 148–161°/0.5 mm., n_D^{25} 1.4565;

3.8 g. of intermediate fraction; and 11.1 g. (37%) of α,β-unsaturated acid IXb, b.p. 183–184°/0.5 mm., n_D^{25} 1.4643.

An analytical sample of *2-methyl-4-n-heptyl-4-hydroxyhendecanoic acid, γ-lactone* (Xb), obtained after extraction with sodium carbonate solution and distillation, had b.p. 160–163°/0.5 mm., n_D^{25} 1.4547. It absorbed no base on titration.

Anal. Calc'd for $C_{19}H_{36}O_2$: C, 76.96; H, 12.24.
Found: C, 77.01; H, 12.44.

An analytical sample of *2-methyl-4-n-heptyl-2-hendecenoic acid* (IXb), purified by way of the insoluble barium salt, had b.p. 184°/0.5 mm., n_D^{25} 1.4645, λ_{max} 219 mμ, ε 13,800.

Anal. Calc'd for $C_{19}H_{36}O_2$: C, 76.96; H, 12.24; Eq. wt., 296.
Found: C, 76.68; H, 12.15; Eq. wt., 292.

Ethyl 2-methyl-4-n-heptyl-2-hendecenoate (VIIb), prepared by esterification of the acid as described for preparation of ester VIIa, had b.p. 164–167°/1.5 mm., n_D^{25} 1.4548, λ_{max} 216 mμ, ε 12,800.

Anal. Calc'd for $C_{21}H_{40}O_2$: C, 77.73; H, 12.43.
Found: C, 77.75; H, 12.32.

2,4-Dimethyl-2-tetradecenoic acid (IXc) was prepared from 47.7 g. of freshly distilled 2-methyldodecanal (Vc) by the same sequence of procedures as described for acid IXb, except that 0.42 g. of hydroquinone was added to the Reformatsky reaction as inhibitor to oxidation and polymerization of the aldehyde. The final products obtained were 17.1 g. (28%) of 2,4-dimethyl-4-hydroxytetradecanoic acid, γ-lactone (Xc), b.p. 157–162°/1.5 mm., n_D^{25} 1.4533; and 22.2 g. (36%) of 2,4-dimethyl-2-tetradecenoic acid (IXc), b.p. 170–176°/1.5 mm., n_D^{25} 1.4635.

An analytical sample of *2,4-dimethyl-4-hydroxytetradecanoic acid, γ-lactone,* (Xc) secured after extraction with carbonate solution, had b.p. 157–158°/1.5 mm., n_D^{25} 1.4507. It absorbed no base on titration.

Anal. Calc'd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89.
Found: C, 75.96; H, 11.59.

An analytical sample of *2,4-dimethyl-2-tetradecenoic acid* (IXc) was purified by extraction of a sodium carbonate solution counter-currently with hexane. The recovered acid had b.p. 176–177°/1.5 mm., n_D^{25} 1.4634, λ_{max} 219 mμ, ε 13,700.

Anal. Calc'd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89; Eq. wt., 254.
Found: C, 75.82; H, 11.68; Eq. wt., 254.

Ethyl 2,4-dimethyl-2-tetradecenoate (VIIc), prepared by esterification of the acid, as described for ester VIIa, had b.p. 147–148.5°/1.5 mm., n_D^{25} 1.4520, λ_{max} 216 mμ, ε 13,800.

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13.
Found: C, 76.59; H, 12.37.

Estimation of the composition of mixtures of α,β- and β,γ-unsaturated esters and acids. A. The composition of a mixture such as ethyl 2-methyl-4-ethyl-2-octenoate (VIIa) and ethyl 2-methyl-4-ethyl-3-octenoate (VIIIa) is best calculated from the ultraviolet absorption of the mixture at the wavelength where the maximum difference is observed between the extinction coefficients for the two esters. The pure conjugated ester has ϵ_{217} 13,300, while the pure unconjugated isomer has been estimated to have ϵ_{217} 2,700. The composition of an unknown mixture may be determined from the relation:

$$27(1 - X) + 133X = \epsilon'_{217} \text{ or } 106X = \epsilon'_{217} - 27,$$

where $\epsilon'_{217} = \epsilon_{217} \times 10^{-2}$ for the mixture, and X is the fraction of α,β-unsaturated ester. Similarly, for the acids:

$$119X = \epsilon'_{220} - 21$$

where X is the fraction of α,β-unsaturated acid, 4-ethyl-2-methyl-2-octenoic acid (IXa).

B. Another method for determining the composition of mixtures of unsaturated esters depends on the preparation of a series of theoretical absorption curves by calculations from the spectra of the pure isomers. The *shapes* of curves for unknown mixtures of isomeric esters then may be compared to the shapes of these calculated curves. This method has proved especially useful for analyzing crude mixtures from dehydration, containing optically inert diluents, for which the above formulas are no longer valid. A similar series of calculated spectra were prepared for mixtures of 4-ethyl-2-methyl-2-octenoic acid and the corresponding 3-octenoic acid. The success of this method of analysis depends on the fact that the curve for the 2-alkenoic acid rises very steeply in the region where the curve for the 3-alkenoic acid drops equally steeply.

While both Methods *A* and *B* are specifically valid only for mixtures of the two esters or acids in the *a* series, for which complete data are presented, the accuracy is adequate for present purposes when the same data are applied to mixtures of other α,γ-dialkyl-α,β- and β,γ-unsaturated acids, for their ultraviolet absorptions have been found to differ only slightly. Since the esters show greater differences, acids were used for determination of the composition of equilibrated mixtures in the *b* and *c* series of compounds.

Alkali-catalyzed equilibrations. Data included in Table III for the *2-methyl-4-ethyl esters* were secured with sodium ethoxide according to the representative procedure under Method *A*, below, or with sodium glycolate according to the representative procedure under Method *B* below.

A. Sodium ethoxide. In 15 ml. of dried ethanol, distilled from sodium ethoxide and diethyl phthalate, was dissolved 0.69 g. of sodium, followed by 2.0 g. of ethyl 2-methyl-4-ethyl-3-octenoate (n_D^{25} 1.4396). After the solution had been heated under reflux for 9 hours, it was cooled, diluted with water, and extracted with hexane. From the hexane phase, after washing and fractional distillation, there was obtained a mixture of unsaturated esters of b.p. 93-98°/3.5 mm., n_D^{25} 1.4416, ϵ_{217} 6,300.

B. Sodium glycolate. Ethylene glycol was dried by distillation from sodium, then redistillation until 25 ml. of glycol (less than half that distilled from sodium) remained. In this residual glycol, protected from moisture, was dissolved 1.4 g. of sodium, followed by 1.6 g. of mixed unsaturated esters (n_D^{25} 1.4419, 35% α,β-unsaturated isomer). After the anhydrous mixture had been heated under reflux for 11 hours, it was diluted with water and heating was continued for an additional 30 minutes in order to hydrolyze the glycol esters. The solution was acidified and worked up to yield 1.0 g. of mixed acids, b.p. 135-138°/4.0 mm., n_D^{25} 1.4574, ϵ_{220} 9,300.

Equilibration of the 2-methyl-4-n-heptyl esters was accomplished according to Method *B*, by heating under reflux for 24 hours a solution of 5.8 g. of sodium in 75 ml. of anhydrous glycol containing 9.3 g. of ethyl 2-methyl-4-heptyl-2-hendecenoate (n_D^{25} 1.4548). The mixed acids (7.5 g.) finally isolated had b.p. 168-188°/0.5 mm., n_D^{25} 1.4620, ϵ_{220} 9,250. Calculation of isomer content by use of the formula presented previously gives 60% of the α,β-unsaturated isomer.

Equilibration of the 2,4-dimethyl esters was also accomplished according to Method *B*, by heating under reflux for 22 hours a solution of 5.8 g. of sodium in 75 ml. of anhydrous glycol containing 14.6 g. of ethyl 2,4-dimethyl-2-tetradecenoate (n_D^{25} 1.4520). The mixed acids finally obtained weighed 12.7 g. and had b.p. 152-163°/0.4 mm., n_D^{25} 1.4591, ϵ_{220} 7,300. Calculation gives the content of α,β-unsaturated isomer as 44%.

SUMMARY

In order to carry out equilibration studies between Δ^2- and Δ^3-isomers, there have been synthesized three 2-methyl-4-alkyl-2-alkenoic acids and the corresponding esters. One 3-alkenoic acid and ester were also separated in reasonably pure condition.

2,4-Dimethyl-2-tetradecenoic acid showed an infrared absorption band at 10.08 μ, as have other 2,4-dimethyl-2-alkenoic acids; however, the two other similar acids containing a group larger than methyl at the 4-position showed no band at 10.08 μ, but exhibited instead a band at about 9.9 μ.

The ultraviolet spectra of mixtures were used to determine isomer content, by

reference to spectral data obtained on the pair of pure α,β- and β,γ-unsaturated acids.

In acidic media, the α,β-unsaturated ester does not equilibrate at a significant rate with the non-conjugated isomer, while the β,γ-unsaturated ester goes slowly to γ-lactone. Esterification of the β,γ-unsaturated acid under mild conditions gives an excellent yield of the corresponding ester.

In alkaline media, the conjugated and non-conjugated esters do equilibrate, but sufficiently slowly to allow normal saponification of esters without change in isomer composition.

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