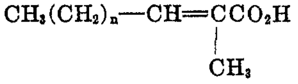
[Contribution from the Chemical Laboratory of the University of California]

BRANCHED-CHAIN FATTY ACIDS. XXX. THE SYNTHESIS OF THREE HIGHER MOLECULAR WEIGHT 2-METHYL-2-ALKENOIC ACIDS[1]

JAMES CASON and MAX J. KALM

Received July 26, 1954

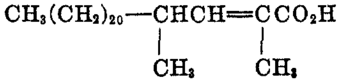
The physiologically active (1) C_{27}-phthienoic acid, isolated in these laboratories (2) from the fatty acids of the tubercle bacillus, has been shown (3) to have a structure represented by 4,x-dialkyl-2-methyl-2-tetracosenoic acid. This finding has led to a continuing investigation of the synthesis of 2-methyl-2-alkenoic acids for several reasons. It would appear that completion of the elucidation of the structure of C_{27}-phthienoic acid will require a classical degradation, and this acid is very difficult indeed to secure in appreciable quantity; therefore, preliminary degradation of model compounds seems indicated. Model compounds are also desired for a study of the geometrical isomerism at the double bond (4). Finally, 2-methyl-2-alkenoic acids of the molecular weight of C_{27}-phthienoic acid are desired for biological testing, for it is of interest to learn how many of the structural features of the natural acid are required in order to give the characteristic lesions in test animals (1).



$CH_3(CH_2)_n{-}CH{=}\underset{CH_3}{C}CO_2H$

I n = 16

II n = 22



$CH_3(CH_2)_{20}{-}\underset{CH_3}{C}HCH{=}\underset{CH_3}{C}CO_2H$

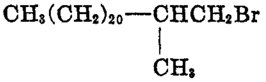
III

Acids whose syntheses are reported in the present paper are 2-methyl-2-eicosenoic acid (I), 2-methyl-2-hexacosenoic acid (II), and 2,4-dimethyl-2-pentacosenoic acid (III). Acids II and III have the same molecular weight as C_{27}-phthienoic acid and contain progressive additions of the known structural features of this acid. Acids I, II, and III have been synthesized by α-bromination of the corresponding saturated acid, followed by dehydrobromination, according to the methods previously reported (3, 5). No great difficulties were encountered in these conversions, but the isolations were complicated by the troublesome properties of the high molecular weight acids, and yields of pure products were lowered. The syntheses reduce, therefore, to preparation of the saturated analogs of I, II, and III.

Synthesis of 2-methyleicosanoic acid and 2-methylhexacosanoic acid (saturated analogs of I and II) was accomplished by alkylation of diethyl methylmalonate, the procedure previously used by Schneider and Spielman (6). Preparation of 2,4-dimethylpentacosanoic acid (saturated analog of III) by alkylation of diethyl methylmalonate required 2-methyl-1-tricosyl bromide (IV), a com-

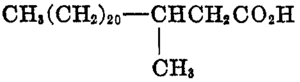
[1] This investigation was supported in part by a grant (E-86) from the National Institutes of Health, U. S. Public Health Service.

pound previously prepared (7) from reaction of bromine with the silver salt of 3-methyltetracosanoic acid (V). The bromine analysis reported for IV by Ställberg-Stenhagen was about one per cent high, and we also encountered this difficulty, which probably results from free radical bromination in the chain (8). As a consequence of the intractable properties of this high molecular weight branched-chain bromide, all efforts to remove the small amounts of polybrominated contaminants were unsuccessful. Furthermore, the 2,4-dimethylpentacosanoic acid obtained from the crude IV could not be obtained in a pure condition by fractional distillation of the ester or by crystallization. Attempted crystallization was defeated by the presence of two asymmetric carbons. Fortunately, the unsaturated acid, III, which contains only one asymmetric carbon, was readily purified by crystallization, and there was no difficulty in obtaining a final product whose analytical and physical properties indicate a high degree of purity.



$$CH_3(CH_2)_{20}—\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Br$$

IV



$$CH_3(CH_2)_{20}—\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CO_2H$$

V

Infrared spectra of the three α,β-unsaturated acids prepared in this work are quite characteristic of acids of the *trans* configuration (*cf.* ref. 4). In particular, there are strong bands at 7.05 μ and very strong bands at 7.8 μ, while much weaker bands or shoulders occur at 6.85 and 8 μ. Freeman (9) has discussed the occurrence and position of unsaturation bands beyond 10 μ as a function of substituents on or near the double bond, and he has pointed out that the positions of these bands in 2,4-dimethyl-2-dodecenoic acid correspond well with those in C_{27}-phthienoic acid. The same relationship holds for 2,4-dimethyl-2-pentacosenoic acid, as shown by the data in Table I. Further, the bands found in the two presently reported 2-methyl-2-alkenoic acids agree well with those reported (9) for 2-methyl-2-dodecenoic acid and 2,5-dimethyl-2-heptadecenoic acid, except for the absence of anything more than a shoulder to represent the 10.35 μ band reported for 2-methyl-2-dodecenoic acid. Such a band near 10.35 μ is also consistently absent from another series (4) of 2-methyl-2-alkenoic acids, although the bands at 12.5, 13.5, and 15.5 μ are present. Appearance of the band near 10.4 μ may well depend on whether its exact position is such that it can be re-

TABLE I

LONG WAVELENGTH UNSATURATION BANDS FOR α,β-UNSATURATED ACIDS

Acid	Absorption Bands (μ)[a]					
2-Methyl-2-dodecenoic	10.35	12.45		13.30		15.30
2-Methyl-2-eicosenoic			12.60	13.52		15.50
2-Methyl-2-hexacosenoic	(10.43)	12.42	12.65	13.50	(14.95)	15.55
2,4-Dimethyl-2-pentacosenoic	10.08	12.40		13.36	15.10	
C_{27}-Phthienoic	10.06	12.50		13.26	14.92	

[a] Numbers in parentheses are positions of shoulders on the curve.

solved from the very strong carboxyl band occurring at about 10.7 μ. In most of the 2-methyl-2-alkenoic acids, the 10.7 μ band has become rather unsymmetrical (4, 9). The bands near 12.5 μ are of interest since some of the 2-methyl-2-alkenoic acids have two bands, respectively above and below this wave length, while others have one or the other band (*cf.* also ref. 4). The appearance of bands at about 10 μ and 15 μ (possibly a shift of the bands normally at about 10.5 and 15.5 μ) has occurred, thus far, only in acids substituted with methyl groups at the 2- and 4-positions.

EXPERIMENTAL[2]

2-Methyleicosanoic acid was prepared by alkylating 191.5 g. (1.1 moles) of diethyl methylmalonate with 333 g. (1.00 mole) of *n*-octadecyl bromide in the presence of sodium ethoxide. The malonic acid resulting from the saponification of diethyl methyl-*n*-octadecylmalonate was precipitated by the addition of water and was dried in a vacuum desiccator. Decarboxylation followed by esterification with 24 mole-equivalents of methanol containing 10% by weight of concentrated sulfuric acid yielded 158 g. (46.5%) of *methyl 2-methyleicosanoate*, b.p. 192–194° (2.25 mm.). Saponification of this ester gave a 94% yield of 2-methyleicosanoic acid which, after recrystallization from acetone, had m.p. 61.5–62.0°, equiv. wt., 328 (Calc'd 326.6). The literature (6) value is m.p. 61.7–62.0°.

2-Methylhexacosanoic acid. n-Tetracosanoic acid (10) was esterified with methanol and concentrated sulfuric acid to yield *methyl n-tetracosanoate*, b.p. 223–225° (3.2 mm.), m.p. 56.2–57.9°; literature (11), m.p. 58.4°.

The reduction of 133.1 g. (0.349 mole) of methyl *n*-tetracosanoate with 13.3 g. of copper chromite catalyst (12) at 250° and a maximum pressure of 4000 p.s.i. of hydrogen gas yielded *n*-tetracosanol. The crude alcohol was converted to the corresponding bromide with hydrogen bromide gas (13). Distillation yielded 91.2 g. (62%) of *n*-tetracosyl bromide, b.p. 229–232° (3.8 mm.), m.p. 49–50°.

Methyl 2-methylhexacosanoate was prepared *via* alkylation of 41.7 g. (0.239 mole) of diethyl methylmalonate with 90.3 g. (0.217 mole) of *n*-tetracosyl bromide in the presence of sodium ethoxide. Hydrolysis, decarboxylation, esterification, and fractional distillation yielded 50.4 g. (54.8%) of *methyl 2-methylhexacosanoate*, b.p. 238–240° (1.7 mm.).

Anal. Calc'd for $C_{28}H_{56}O_2$: C, 79.18; H, 13.30.
Found: C, 79.36; H, 13.28.

Saponification of the ester gave a 95% yield of 2-methylhexacosanoic acid which, after recrystallization from acetone, had m.p. 73.5–75.0°; literature (6) m.p. 75.5–76.0°.

2,4-Dimethylpentacosanoic acid. 3-Methyltetracosanoic acid (V), prepared by Wolff-Kishner reduction of the keto ester resulting from the reaction between the cadmium reagent from *n*-nonadecyl bromide and β-methyl-γ-carbomethoxybutyryl chloride (14), was converted to 2-methyl-1-tricosyl bromide (IV) by use of the silver salt and bromine reaction. The procedure employed was a modification developed by Stenhagen (7) which is adapted to recovery of unreacted starting material. 2-Methyl-1-tricosyl bromide (IV) was prepared in 46.7% yield from 115.7 g. (0.303 mole) of 3-methyltetracosanoic acid (V), and this yield was increased to 82% by recyclization of recovered starting material. Distillation of

---

[2] All melting points are corrected, and all boiling points are uncorrected. Unless otherwise specified, distillations were through a half-meter column with heated jacket and partial reflux head, and containing a tantalum wire spiral of the simple Podbielniak design. Ultraviolet spectra were determined on a Beckman Model DU quartz spectrophotometer, following the precautions previously described (5). Spectroscopically pure hexane was used as solvent. Infrared spectra were recorded on a Perkin Elmer Model 21 double beam recording spectrophotometer, using carbon tetrachloride and carbon disulfide as solvents. Analyses are by the Microanalytical Division, Dept. of Chemistry, Univ. of California.

the bromide was prevented by thermal decomposition; recrystallization from acetone yielded material of m.p. 35–37°. Analysis gave Br, 20.33 (Calc'd for $C_{24}H_{49}Br$: Br, 19.15). Stenhagen (7) reports m.p. 34–36° and similar analytical figures, Br, 20.07.

Methyl 2,4-dimethylpentacosanoate was prepared in 44% over-all yield *via* alkylation of 51.1 g. (0.293 mole) of diethyl methylmalonate with 111.2 g. (0.267 mole) of 2-methyl-1-tricosyl bromide (IV) in the presence of sodium ethoxide in the same manner described for the preparation of methyl 2-methyleicosanoate. The mono-ester was twice fractionally distilled, b.p. 237–239° (1.7 mm.).

Anal. Calc'd for $C_{28}H_{56}O_2$: C, 79.18; H, 13.30.
Found: C, 77.74; H, 13.59.

Saponification followed by recrystallization from acetone yielded 2,4-dimethylpentacosanoic acid with the constant m.p. 44.5–46.0°.

Anal. Calc'd for $C_{27}H_{54}O_2$: C, 78.96; H, 13.25; Equiv. wt., 410.7.
Found: C, 77.99; H, 12.70; Equiv. wt., 416.0.

Various attempts at further purification failed to improve this analysis.

2-Methyl-2-alkenoic acids. The 2-methylalkanoic acids were converted to their α,β-unsaturated analogs (I, II, III) by α-bromination withphosphorus tribromide and bromine, followed by quinoline dehydrohalogenation (3, 5). The unsaturated esters were isolated from the reaction mixture by addition of water and precipitation of the crude material. Purification and conversion to the acids are described for the individual compounds.

2-Methyl-2-eicosenoic acid (I). Fractional distillation gave methyl 2-methyl-2-eicosenoate in 62.8% yield, b.p. 203–205° (2.5 mm.). Saponification of this material gave 86.5% of 2-methyl-2-eicosenoic acid which, after recrystallization from acetone, had m.p. 66.3–67.6°, λ_{max} 217 mμ, ϵ_{max} 13,490.

Anal. Calc'd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42; Equiv. wt., 324.5.
Found: C, 77.21; H, 12.37; Equiv. wt., 326.

Low values for carbon and hydrogen were obtained for this and the other unsaturated acids unless a slow combustion and a high furnace temperature were used.

2-Methyl-2-hexacosenoic acid (II). The crude ester was Claisen-distilled at 1 mm. and saponified to give the crude unsaturated acid. Three recrystallizations from acetone, followed by evaporative distillation, gave a 20.1% yield of pure 2-methyl-2-hexacosenoic acid, m.p. 85.4–86.2°, λ_{max} 217 mμ, ϵ_{max} 14,000.

Anal. Calc'd for $C_{27}H_{52}O_2$: C, 79.34; H, 12.83; Equiv. wt., 408.7.
Found: C, 79.10; H, 12.98; Equiv. wt., 410.

2,4-Dimethyl-2-pentacosenoic acid (III). The crude ester was Claisen-distilled and saponified. After the acid had been crystallized three times from acetone, there was obtained, in 19.1% yield, pure 2,4-dimethyl-2-pentacosenoic acid, m.p. 69.5–70.3°, λ_{max} 218 mμ, ϵ_{max} 14,550.

Anal. Calc'd for $C_{27}H_{52}O_2$: C, 79.34; H, 12.83; Equiv. wt., 408.7.
Found: C, 79.33; H, 12.80; Equiv. wt., 410.6.

SUMMARY

2-Methyl-2-eicosenoic, 2-methyl-2-hexacosenoic, and 2,4-dimethyl-2-pentacosenoic acids have been prepared from the corresponding saturated acids. The saturated acids were prepared by alkylation of diethyl methylmalonate with the appropriate alkyl bromides. Infrared spectra of these acids are compared with those of other 2-methyl-2-alkenoic acids.

BERKELEY 4, CALIF.

REFERENCES

(1) HUSSEINI AND ELBERG, *Am. Rev. of Tuberculosis*, **65**, 655 (1952).
(2) CASON AND SUMRELL, *J. Biol. Chem.*, **192**, 405 (1951).

(3) CASON AND ALLEN, *J. Biol. Chem.*, **205**, 449 (1953).
(4) To be published in a succeeding paper in the *Journal of Organic Chemistry*.
(5) CASON, ALLINGER, AND ALLEN, *J. Org. Chem.*, **18**, 857 (1953).
(6) SCHNEIDER AND SPIELMAN, *J. Biol. Chem.*, **142**, 345 (1942).
(7) STÄLLBERG-STENHAGEN, *Arkiv. Kemi*, **1**, 18 (1949).
(8) CASON, KALM, AND MILLS, *J. Org. Chem.*, **18**, 1670 (1953).
(9) FREEMAN, *J. Am. Chem. Soc.*, **75**, 1059 (1953).
(10) CASON, ALLINGER, AND SUMRELL, *J. Org. Chem.*, **18**, 850 (1953).
(11) RALSTON, *Fatty Acids and Their Derivatives*, John Wiley and Sons, New York, 1948, p. 503.
(12) LAZIER AND ARNOLD, *Org. Syntheses*, Coll. Vol. II, 142 (1948).
(13) REID, RUHOFF, AND BURNETT, *Org. Syntheses*, Coll. Vol. II, 246 (1948).
(14) CASON, WOLFHAGEN, TARPEY, AND ADAMS, *J. Org. Chem.*, **14**, 147 (1949).