Thermal Reactions of Methyl Linoleate. II. The Structure of Aromatic C18 Methyl Esters

William R. Michael, The Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio

ABSTRACT

This second report describes the characterization of C₁₈ aromatic esters from the heated linoleate and the independent synthesis of two of them. The esters were isolated by a combination of molecular distillation, urea adduction, column chromatography, and gas chromatography. They were characterized by infrared, ultraviolet, NMR, and mass spectroscopy. The analytical data for the isolated esters were compared with the data for the synthetic esters, methyl 11-(2'-methylphenyl)undecanoate, methyl 7-(2'-pentylphenyl)heptanoate, and methyl 8-(2'-butylphenyl) octanoate. The latter two compounds were found to be components of the aromatic fraction isolated from heated linoleate, and their synthesis is described in detail.

INTRODUCTION

ETHYL LINOLEATE was heated at 200C for M_{200} hr and the reaction mixture was separated by a combination of molecular distillation, urea adduction, column chromatography, and gas chromatography (1). As reported previously, a fraction whose infrared spectrum showed it to be rich in aromatic compounds was concentrated from the urea filtrate monomers by column chromatography. The quantity of this fraction isolated corresponded to about 0.6% of the methyl linoleate heated. This fraction was further purified by preparative gas chromatography. The analytical data were consistent with the empirical formula, C₁₇H₂₇CO₂CH₃. The NMR, mass spectroscopy, and infrared data indicated that the material was a mixture of isomers different from methyl 11-(2'-methylphenyl)undecanoate (I) described by Hutchinson and Alexander (2). On this basis the following structure was proposed:



where n = 3-4 and n + m = 10

The two compounds postulated to be present in the mixture, methyl 7-(2'-pentylphenyl) (IIa) and methyl 8-(2'-butylheptanoate phenyl)octanoate (IIb), were independently synthesized. Figure 1 is an outline of the synthetic scheme, which comprised the following steps. Butyl bromide was allowed to react with magnesium, and the resulting Grignard reagent was treated with cadmium chloride to give dibutyl cadmium (IIIa). 2-Bromobenzoyl chloride was added to the cadmium reagent to yield a ketone (IVa) which was reduced by the Haung-Minlon (3) modification of the Wolff-Kishner reaction to 2amvlbromobenzene (Va). The bromide was converted to the corresponding cadmium reagent (VIa) which, upon interaction with the ester chloride of pimelic acid (VIIa) (4) a1forded the keto-ester (VIIIa). The keto-ester was reduced to the acid by the Wolff-Kishner reaction. The acid was esterified by the Fisher procedure (5) to give methyl 7-(2'-pentylphenyl)heptanoate (IIa). Methyl 8-(2'-butylphenyl)octanoate (IIb) was made by following the same procedure but using propyl bromide and suberic acid in place of butyl bromide and pimelic acid. The aromatic esters were hydrogenated to cyclohexane derivatives (IXa, IXb) with a platinum oxide catalyst and a trace of acid (6). The mixture of esters isolated from heated methyl linoleate was similarly hydrogenated. Comparison of the physical properties of the synthetic material IIa and b, and IXa and b, with the properties of the isolated material before and after hydrogenation, respectively, confirmed that the isolated esters consisted largely of IIa and b, with possibly small traces of IIc.

The synthesis of methyl 11-(2'-methylphenyl)undecanoate was reported previously (2,7). Comparison of its properties with those of the isolated mixture showed that the mixture contained none of this substance.

EXPERIMENTAL

Isolation of Aromatic Esters

The preparation of the methyl linoleate, the heating conditions, and the isolation procedures used in this investigation were described previously (1). The fractions from the silicic acid—silver nitrate columns which were richest



FIG. 1. Syntheses of aromatic esters.

in aromatic compounds were combined. The aromatic components were purified by preparative gas chromatography. The materials collected from the gas chromatograph were again injected, fractionated, and collected until the final product showed only one peak upon reinjection.

The instrument used for the gas chromatography was an Aerograph Model A-90-P. The column was a $\frac{3}{8}$ in. (O.D.) \times 5 ft copper tube packed with Chromosorb W (30-60 mesh) containing 25% ethylene glycol adipate. The following operating conditions are representative: helium pressure 60 psi; helium flow rate, 200 ml/min; oven temperature 205C; injection temperature 295C; detector temperature 350C; injection volumes 50-100 μ l. The aromatic component of the mixture had a retention time of about 70 minutes. The material was collected in a 16-mm tube containing glass wool wet with methanol.

Absorption bands were observed in the infrared spectrum of the isolated material at LIPIDS, VOL. 1, NO. 5 the following wavelengths: 3.21, 6.22, 6.70 μ (aromatic); 13.34 μ (1,2-disubstituted benzene); 5.72, 8.50 μ (ester); 13.75 μ (tetramethylene). The ultraviolet spectrum showed absorption maxima at 263, 267, and 270 m μ ; this spectrum was consistent with an *ortho* substitute benzene (8). The NMR spectra were obtained on a Varian A-60 spectrometer. The NMR spectrum gave the following τ values: 3.02 ppm (aromatic protons); 6.40 ppm ($-\text{OCH}_{s}$); 7.20–8.00 ppm (α -methylene protons);¹ 8.20–8.90 ppm (methylene protons); 8.90–9.30 ppm (terminal methyl protons).

Anal. Cale. for C₁₈H₃₀O₂: C, 78.6; H, 10.4. Found: C, 78.2; H, 10.7.

2-Amylbromobenzene (Va)

To a suspension of 7.5 g (0.30 g-atom) of magnesium and 20 ml of dry ether was added slowly with stirring 52 g (0.37 mole) of *n*-butyl bromide in 200 ml of dry ether. When

 $^{{}^1\}alpha\text{-Methylene}$ designates methylene protons α to an electron withdrawing substituent.

the addition of the *n*-butyl bromide was complete, the reaction was stirred at reflux temperature for an additional 15 min. The reaction was carried out in a nitrogen atmosphere.

The reaction flask was cooled in an ice bath and 30 g (0.26 mole) of cadmium chloride was added over a period of 5–10 min. The reaction mixture was stirred and heated under reflux for 3 hr. The ether was distilled and 300 ml of anhydrous benzene was added. A solution of 58 g of 2-bromobenzoyl chloride (prepared from 2-bromobenzoic acid and thionyl chloride at 60C) in 100 ml of anhydrous benzene was added over a period of 5 min. The reaction mixture was then heated under reflux for 4 hr. Approximately 300 g of crushed ice and 100 ml of ice-cold 20% sulfuric acid were added to the reaction mixture. The benzene and aqueous layers were separated and the aqueous layer was extracted with 100 ml of benzene. The benzene layers were combined and washed with water, 20% sodium carbonate, water, and saturated sodium chloride solution. The benzene layer was dried over anhydrous sodium sulfate and the benzene was removed by distillation. The 2-bromovalerophenone (IVa) distilled at 124-134C (4.5-5 mm). The yield was 40 g (62% based on 2-bromobenzoyl chloride).

The ketone (IVa) (65 g) was heated under reflux with 80 g of potassium hydroxide and 60 ml of 85% hydrazine hydrate in 600 ml of ethylene glycol for 1 hr. The water formed was removed by distillation and the temperature of the solution was allowed to rise to 175C; after 16 hr at this temperature, the reaction mixture was poured into one liter of ether and the layers were separated. The ether layer was washed with water. The solvent was removed on a rotary evaporator to leave a light yellow liquid. The 2-amylbromobenzene (Va) was collected by distillation at 80–120C (0.3-0.5 mm). The yield was 28 g (45% based on the ketone (IVa)).

Anal. Cale. for $C_{11}H_{15}Br$: C, 58.2; H, 6.6; Br, 35.2 Found: C, 58.8; H, 6.9; Br, 31.8.

Methyl 7-(2'-Pentylphenyl)heptanoate (IIa)

Twenty-eight grams (0.123 mole) of 2amylbromobenzene (Va) in 200 ml of dry ether was added slowly to a flask containing 4 g (0.162 g-atom) of magnesium in 20 ml of dry ether under a nitrogen atmosphere. When the addition of the 2-amylbromobenzene was complete, the reaction mixture was stirred at reflux temperature for an additional 15 min.

The reaction flask was cooled in ice and 12 g (0.108 mole) of cadmium chloride was added over a period of 5–10 min. The reaction mix-

ture was stirred and heated under reflux for 3 hr. The ether was distilled off and 300 ml of anhydrous benzene was added. A solution of 4 g (0.194 mole) of monoethyl pimeloyl chloride [prepared by the method of Cason and Rapoport (4)] in 100 ml of anhydrous benzene was added over a period of 5 min. The reaction mixture was heated under reflux for 4 hr. The reaction work-up was identical with that described for 2-bromovalerophenone. The resulting keto-ester (VIIIa) was distilled at 155– 165C (0.1–0.2 mm), and 21.7 g of product was obtained.

The keto-ester (VIIIa) (21.7 g) was reduced by the Wolff-Kishner method described above with 40 g of potassium hydroxide, and 30 ml of 85% hydrazine hydrate in 200 ml of ethylene glycol. After the initial one-hour heating, water was removed by distillation and the temperature was allowed to rise to 175C where it was maintained for 16 hr. The product obtained from the reaction was heated under reflux with 100 ml of methanol and 600 mg of sulfuric acid for 3 hr. The yield of ester (IIa) was 15.2 g (42% based on 2-amylbromobenzene). A 1.25 g portion of the product was chromatographed on silicic acid (20 g, $\frac{1}{2}$ in. column). Elution with benzene: hexane (1:1)vol) afforded a product having n_D^{25} 1.4882.

Anal. Calc. for C₁₉H₃₀O₂: C, 78.6; H, 10.4. Found: C, 78.7; H, 10.7.

Absorption bands were observed in the infrared spectrum of the isolated material at the following wavelengths: 3.21, 6.22, 6.71 μ (aromatic); 13.40 μ (1,2-disubstituted benzene); 5.72, 8.50 μ (ester); 13.80 μ (tetramethylene). The ultraviolet spectrum gave absorption maxima at 263, 267, and 270 m μ . The NMR spectrum gave the following τ values: 3.02 ppm (aromatic protons); 6.40 ppm ($-\text{OCH}_3$); 7.20-8.00 ppm (a-methylene protons); 8.20-8.90 ppm (methylene protons); 8.90-9.30 ppm (terminal methyl protons).

2-Butylbromobenzene (Vb)

This intermediate was prepared using the same reaction sequence and conditions described above for 2-amylbromobenzene.

2-Bromobutyrophenone (IVb) was synthesized from 58.9 g (0.475 mole) of propyl bromide, 12 g (0.50 g-atom) of magnesium, 45 g (0.25 mole) of cadmium chloride, and 83.4 g (0.368 mole) of 2-bromobenzoyl chloride. The ketone IVb (62.5 g) was distilled at 115–120C (4.5–5 mm).

The ketone (IVb) (62 g) was reduced by the Wolff-Kishner procedure with 40 g of potassium hydroxide and 30 ml of 85% hydrazine

hydrate in 300 ml ethylene glycol. The product was distilled at 74–84C (0.5 mm). The yield was 18 g (23% based on 2-bromobenzoyl chloride). The refractive index was $n_{\rm E}^{\rm m}$ 1.5313.

Anal. Calc. for C₁₀H₁₃Br: C, 56.4; H, 6.1; Br, 37.5. Found: C, 56.7; H, 6.3; Br, 35.1.

Methyl 8-(2'-Butylphenyl)octanoate (IIb)

The aromatic-keto ester VIIIb was prepared from 13 g (0.061 mole) of 2-butylbromobenzene, 1.5 g (0.0625 g-atom) of magnesium, 6 g (0.033 mole) of cadmium chloride, and 19.7 g (0.0895 mole) of monoethyl suberyl chloride. The ester (3.5 g) was purified by distillation at 180–195C (0.25 mm).

Methyl 8-(2'-butylphenyl)octanoate (IIb) was prepared from 3.5 g (0.0124 mole) of the keto-ester (VIIIb) by the Wolff-Kishner procedure with 20 g of potassium hydroxide and 20 ml of 85% hydrazine hydrate in 100 ml ethylene glycol. The isolated acid was esterified and the resulting 2.75 g (15% based on 2butylbromobenzene) of methyl 8-(2'-butylphenyl)octanoate (IIb) was purified by distillation at 155-165C (0.20 mm). The refractive index was n⁵⁵ 1.4888.

Anal. Cale. for $C_{10}H_{s0}O_2$: C, 78.6; H, 10.4. Found: C, 78.6; H, 10.7.

The infrared and NMR spectra were identical with those of methyl 7-(2'-pentylphenyl) heptanoate.

Hydrogenation of Aromatic Esters

A 124 mg quantity each of the synthetic esters and the isolated esters was hydrogenated by the method of Brown, Durand, and Marvel (6). Three moles of hydrogen were consumed per mole of ester. The molecular weights of the hydrogenated materials as determined by mass spectroscopy were 296.

Mass Spectroscopy

Mass spectra of the isolated and synthetic esters were obtained on a Bendix Time-of-Flight mass spectrometer. The spectra are reproduced in Figure 2.

All of the spectra showed parent peaks at m/e 290, as expected for aromatic C_{1s} methyl esters, as well as the expected peaks at m/e 259, corresponding to loss from the molecule of the elements CH_sO .

The following peaks were ascribed to loss of part or all of the hydrocarbon side chain (C_nH_{2n+1}) from the molecule: for IIa, 233 (corresponding to n = 4) and 219 (n = 5); for IIb, 247 (n = 3) and 233 (n = 4); and for the isolated ester, 247, 233, and 219 (n = 3, 4, 5, respectively). The following peaks were LIPIDS, Vol. 1, No. 5

attributed to loss both of the hydrocarbon side chain and of the elements CH₄O from the ester group: for IIa, 201 and 187 (n = 4, 5); for IIb, 215 and 201 (n = 3,4); and for the isolated esters, 215, 201, 187 (n = 3, 4,5). Additional peaks apparently arose from loss of the hydrocarbon side chain, the elements CH₄O, and the elements H₂O as follows: for IIa, 183, 169 (n = 4,5); for IIb, 197, 183 (n = 3,4); for the isolated esters 197, 183, 169 (n = 3,4,5).

Another series of peaks in each spectrum was attributed to the loss of part or all of the ester chain, $C_nH_{2n}CO_2CH_3$, as follows: for IIa, 175, 161 and 147 (corresponding to n = 4,5,6, respectively); for IIb, 161, 147, 133 (n = 5,6, 7); for the isolated esters, 175, 161, 147, 133 (n = 4,5,6,7).

Intense peaks at m/e 91 and 105 were seen in all three spectra. These peaks are common to the mass spectra of dialkylbenzenes, and correspond to the ions $C_7H_7^+$ and $C_8H_9^+$.

Figure 3 shows the mass spectra of the hydrogenated esters. Parent peaks at m/e 296 and peaks corresponding to loss of CH_*O at 265 were seen as expected.

Peaks apparently related to the loss of hydrocarbon side chain (C_nH_{2n+1}) from the ring were the following: for IXa, 225 (corresponding to n = 5), for IXb, 239 (n = 4); for the isolated esters, 253, 239, 225, (n = 3, 4, 5). The following peaks were attributed to loss of the side chain plus the elements CH₄O: for IXa, 193 (n = 5); for IXb, 207 (n = 4); for the



FIG. 2. Mass spectra of synthetic esters and isolated mixture.

isolated esters, 221, 207, 193 (n = 3, 4, 5). Peaks which apparently arose from loss of the hydrocarbon side chain, the elements CH₄O, and the elements H₂O were these: for IXa, 175 (n = 5); for IXb, 189 (n = 4); and for the isolated esters, 203, 189, 175 (n = 3, 4, 5). Note that the hydrogenated synthetic esters, unlike their aromatic counterparts, did not give peaks corresponding to fragmentation within the hydrocarbon chain. Peaks resulting from the loss of the hydrocarbon side chain, therefore, gave an indication of the length of the chain and of the numbers of components in the isolated mixture.

Peaks which apparently arose through the loss of the ester chain; $C_nH_{2n}CO_2CH_3$, were the following: for IXa, 153 (n = 6); for IXb, 139 (n = 7), for the isolated esters, 153, 139, 125 (n = 6, 7, 8). Again it appeared that fragmentation did not occur within the ester side chain, and that the peaks seen for the mixture indicate the number of components in the mixture and the lengths of their side chains.

Bioassay of Aromatic Esters

The toxicity of IIa was checked by the bioassay method described previously (1). One-half milliliter per day for 3 days was administered by stomach tube to 5 weanling rats. All rats died on the third day.



FIG. 3. Mass spectra of hydrogenated synthetic esters and isolated mixture.



FIG. 4. Possible mechanism for formation of eyclic esters.

DISCUSSION

The analytical data for the isolated ester fraction are consistent with the empirical formula for the proposed structure $C_{17}H_{37}CO_2CH_3$. The final determination of structure for the fraction depends upon the interpretation of the infrared, ultraviolet, NMR, and mass spectral data. The spectra of the synthetic compounds methyl 11-(2'-methylphenyl)undecanoate (I), methyl 7-(2'-pentylphenyl)heptanoate (IIa), and methyl 8-(2'-butylphenyl)octanoate (IIb) were compared with the spectra obtained from the isolated mixture.

The infrared spectra and ultraviolet spectra of the synthetic materials were indistinguishable from the spectrum of the isolated material.

The NMR spectra for all four materials showed peaks at 3.02 ppm corresponding to the 4 protons on the aromatic nucleus. Each compound and the isolated material showed a peak at 6.40 ppm which corresponded to the three protons of the methyl ester. Compound I differed from compounds IIa and IIb and from the mixture in the regions 7.20–8.00 ppm and 8.90–9.30 ppm. For Compound I a strong peak at 7.68 ppm corresponding to the methyl protons adjacent to the benzene ring was found. The other two synthetic compounds (IIa and IIb) and the isolated mixture showed only peaks of low intensity which would be expected for the a-methylene protons adjacent to the benzene ring and adjacent to the carboxyl group. In the 8.90-9.30 ppm region each of the latter compounds showed a triplet corresponding to the three methyl protons. This triplet was not present in the spectrum of compound I. A triplet at 8.90-9.30 ppm corresponds to a terminal methyl group of a hydrocarbon chain, as would be expected if the proposed structure (II) were correct. Thus it was apparent from the infrared and NMR data that the isolated ester fraction was a 1.2-disubstituted benzene with an ester chain of more than two and less than 11 carbons and a hydrocarbon chain of more than one and less than 10 carbons.

The mass spectra of the four materials were compared to determine the chain lengths of the radicals attached to the benzene ring. The spectrum of the isolated fraction was much more complex than the spectra of the three synthetic materials (Fig. 2). It was immediately apparent that this was not one pure compound but a mixture of isomers differing from each other by the length of the chains attached to the benzene ring. Comparisons of the mass spectra of synthetic IIa and IIb with the mass spectra of the isolated mixture strongly indicated that IIa and IIb were components of the mixture. Comparions of the mass spectra of IXa and IXb with the mass spectrum of the hydrogenated mixture confirmed that conclusion. The peaks at m/e 253, 221, 203, and 125 in the mass spectrum of the hydrogenated mixture suggested the presence of IXe; from this it was concluded that methyl

9-(2'-propylphenyl)nonanoate (IIc) was a component of the mixture of aromatic esters isolated from heated methyl linoleate.

Aromatic esters have not hitherto been isolated from the reaction products of heated fats. A mechanism based upon a single ring closure via a free radical allylic proton abstraction (Fig. 4) may account for the presence of these esters in the urea filtrate monomers. This mechanism, in part, predicts that nonaromatic cyclic compounds should be formed during the heating process. Indeed, this does happen, and the isolation and characterization of such materials are reported in a subsequent paper in this series.

In an earlier paper (1), the urea filtrate monomers were reported to be toxic to weanling Methyl 7-(2'-pentylphenyl)heptanoate, rats. shown to be a component of these monomers, was found to be toxic when administered to weanling rats at a level of 25 g/kg.

REFERENCES

1. Michael, W. R., J. C. Alexander and N. R. Artman,

Michael, W. R., J. C. Alexander and N. R. Artinal, Lipids 1, 353-358 (1966).
 Hutchison, R. B., and J. C. Alexander, J. Org. Chem. 28, 2522-2526 (1963).
 Huang-Minlon, J. Am. Chem. Soc. 68, 2487-2488

(1946).

4. Cason, J., and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., Englewood Prentice-Hall, Inc., Englewood

Cliffs, N. J., 1962, p 419. 5. Fischer, E., and Speier, Chem. Ber. 28, 3252-3258 (1958).

6. Brown, J. H., H. W. Durand and C. S. Marvel,
J. Am. Chem. Soc. 58, 1594-1596 (1936).
7. Michael, W. R., J. Chem. Eng. Data 11, 134-135

(1966).

8. Tunnicliff, D. D., R. R. Brattain and L. R. Zumwalt, Anal. Chem. 21, 890-894 (1949).

[Received March 28, 1966]