Methyl 9-(2-(2,5-Dihydro-5-pentylfuryl))-nonanoate in the Copper-catalyzed Decomposition Products of Methyl Linoleate Hydroperoxides and Some Other Products

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The hydroperoxide of methyl linoleate containing 95% 13-hydroperoxide and 5% 9-hydroperoxide was decomposed in benzene with 10^{-4} M cupric naphthenate at $75\sim 80^{\circ}\text{C}$ under degassed conditions. The decomposition products were fractionated by Sephadex LH-20 column chromatography with chloroform-hexane (2:1, v/v) and the fractions were purified by HPLC. In addition to the known products, three compounds were identified as methyl 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate, methyl 8-(2-furyl)-octanoate, and methyl 9(13)-hydroperoxy-12,13-(9,10)-epoxy-10(12)-octadecenoate as minor decomposition products by MS and IR spectrophotometry.

Transition metal ions have dual effects on the decomposition of hydroperoxide.¹⁾ In the lower valence state, they reduce hydroperoxide to $\text{RO}\cdot$ and in the higher valence state, oxidize it to $\text{ROO}\cdot$. However in the case of copper, it seems unlikely that the reaction of $\text{Cu}^{2+} + \text{ROOH} \rightarrow \text{Cu}^{+} + \text{ROO}\cdot + \text{H}^{+}$ (1) occurs because Cu^{2+} is stable and its oxidizing power is low. O'Brien reported that Cu^{2+} was more effective than Cu^{+} for the decomposition of hydroperoxide of linoleate²⁾. Therefore, some mechanism other than reaction 1 by which Cu^{2+} acts on the hydroperoxide is necessary, but what it is isn't clear. Elucidation of the products of copper-catalyzed decomposition will give a clue.

Schieberle *et al.* identified the decomposition products of 13-hydroperoxide of linoleate arising from the system catalyzed by copper-(II) palmitate³⁾. They reported oxooctadecadienoate, oxoepoxyoctadecenoate, hydroxyoctadecadienoate, hydroxyepoxyoctadecenoate, and dioctadecadienoate peroxides as the decomposition products in an atmosphere of nitrogen. In our laboratory, 13-hydroperoxide of linoleate was decomposed by cupric naph-

thenate under degassed conditions and 8-phenyloctanoate and a carbon-carbon linked dimer were identified.⁴⁾ In this paper, a novel product of methyl 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate (compound I), and two compound of methyl 8-(2-furyl)-octanoate (compound II) and methyl 9(13)-hydroperoxy-12,13(9,10)-epoxy-10(12)-octadecenoate (compounds III) are reported.

MATERIALS AND METHODS

Materials. Hydroperoxide of methyl linoleate containing 95% 13-hydroperoxide and 5% 9-hydroperoxide was prepared by lipoxygenase oxidation as described by Hamberg *et al.*⁵⁾ The hydroperoxide was purified by Sephadex LH-20 column chromatography and thin layer chromatography as previously described.⁶⁾

Decomposition of the hydroperoxide. The purified hydroperoxide (300 mg) was decomposed in benzene solution of cupric naphthenate (10^{-4} M, 50 ml) under degassed conditions at $75\sim 80^{\circ}\text{C}$ overnight.

Sephadex LH-20 column chromatography. Decomposition products were fractionated by Sephadex LH-20 column chromatography. The column was 1.5×72 cm and the products were eluted with chloroform-hexane (2:1,

v/v). The fractions eluted in elution volume of 30~50 ml (A) and 100~150 ml (B) were collected. Fraction A contained low polar compounds (A-1), oxo compound, and dimers. Fraction B contained an *N,N'*-*p*-phenylenediamine sensitive product (B-1) which had a peroxy group but was much more polar than intact hydroperoxide. Fraction A was put on a silica gel column and eluted stepwise with hexane-ether (97:3 and 95:5, v/v) to collect fraction A-1. Fraction B was purified on a silica gel column by stepwise elution of hexane-ether (95:5, 90:10, 85:5, 80:20, and 60:40, v/v). Fraction B-1 was eluted with hexane-ether (3:2, v/v) after intact hydroperoxide was eluted.

HPLC. Each fraction was injected into a liquid chromatograph (Shimadzu LC-3A) on a Zorbax SIL column (0.46 × 15 cm, DuPont). Compounds I and II were isolated from fraction A-1. The eluent was 3% ether in hexane and the flow rate was 1.5 ml/min. A refractive index detector (Shimadzu RID-2A) was used. Compounds III were isolated from fraction B-1 with hexane-ether (4:1, v/v). The flow rate was 2.9 ml/min and the refractive index detector was used. Compounds III consisted of four peak materials.

GLC. Compound I isolated by HPLC was further purified by GLC. The conditions of GLC were the same as previously reported⁶⁾ except that the oven temperature was programmed from 100 to 270°C at a rate of 8°C/min.

Spectrophotometry. Mass spectra were obtained with a mass spectrometer (JEOL JMS DX-300). The GC columns were 3 mm × 2 m and 3 mm × 1 m glass columns packed with 3% Silar 10C on Diasolid L-1. The temperature was elevated from 100 to 270°C at a rate of 8°C/min. The ionization potentials were 70 eV for EI method and 300 eV for CI. The reaction gas of CI was isobutane. IR spectra were obtained with a Hitachi 285 spectrophotometer.

Synthesis of compound I (methyl 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate). *cis*-2-Butene-1,4-diol (15 g) was allowed to react with triphenylchloromethane (123 g) in dehydrated pyridine to prepare 4-triphenylmethoxy-2-buten-1-ol. 4-Triphenylmethoxy-2-buten-1-ol was oxidized with MnO₂⁷⁾ in hexane. 4-Triphenylmethoxy-2-butenal was produced, and it was purified by column chromatography on silica gel with hexane-ether (9:1, v/v), with a yield of 1.91 g. *R*_f = 0.34 (silica gel GF₂₅₄, hexane-ether, 2:1). A Grignard reagent was prepared by the reaction of 1-bromopentane (1.1 ml) with Mg (0.24 g) in anhydrous ether with refluxing. The reagent was allowed to react with 4-triphenylmethoxy-2-butenal (0.99 g). Produced 1-triphenylmethoxy-2-nonen-4-ol was purified by column chromatography on silica gel with hexane-ether (90:10 and 85:5, v/v) with a yield of 1.04 g and an

*R*_f = 0.28 (hexane-ether, 2:1, v/v). 1-triphenylmethoxy-2-nonen-4-ol (0.99 g) was acetylated with acetic anhydride-pyridine (1:2, v/v) with a yield of 1.03 g and an *R*_f = 0.59 (hexane-ether, 2:1, v/v). 4-Acetoxy-1-triphenylmethoxy-2-nonen-1-ol (1.00 g) was hydrolyzed with 0.01N HCl in acetone-water (9:1, v/v) with refluxing. The 4-acetoxy-2-nonen-1-ol produced was purified by column chromatography on silica gel with hexane-ether (80:20, 70:30 and 60:40, v/v) with a yield of 0.34 g and an *R*_f = 0.08 (hexane-ether, 2:1, v/v). MS (TMS derivative) *m/z*: 242, 213 (M-CH₃COO), 117 and 73. 4-Acetoxy-2-nonen-1-ol (0.33 g) was oxidized with MnO₂ (1.2 g) in hexane. 4-Acetoxy-2-nonenal was produced with a yield of 0.18 g and an *R*_f = 0.28 (hexane-ether, 2:1, v/v).

Nonane-1,9-diol was brominated by refluxing with HBr (1.5 fold the molar quantity of the diol) for 1 hr. 9-Bromononan-1-ol was purified on a silica gel column with hexane-ether (60:40 and 50:50, v/v). 9-Bromononan-1-ol (4.2 g) was allowed to react with triphenylchloromethane (6.6 g) in dehydrated pyridine, producing 1-bromo-9-triphenylmethoxynonane that was purified on a silica gel column with hexane with a yield of 3.8 g and an *R*_f = 0.62 (hexane-ether, 2:1, v/v). A Grignard reagent was prepared by the reaction of 1-bromo-9-triphenylmethoxynonane (3.7 g) with Mg (0.2 g) in anhydrous ether and the reagent was allowed to react with 4-acetoxy-2-nonenal (0.18 g) in ether. Produced 18-triphenylmethoxy-7-octadecene-6,9-diol was purified on a silica gel column with hexane-ether (3:2, 1:1, 1:2, v/v) and ether with a yield of 0.38 g and *R*_f = 0.35 and 0.23 (ether). 18-Triphenylmethoxy-7-octadecene-6,9-diol (0.37 g) was acetylated with acetic anhydride-pyridine (1:2, v/v) with a yield of 0.37 g and an *R*_f = 0.61 (hexane-ether, 2:1, v/v). 6,9-Diacetoxy-18-triphenylmethoxy-7-octadecene (0.45 g) was hydrolyzed by 0.01N H₂SO₄ in acetone-water (9:1) with refluxing. *R*_f = 0.09 (hexane-ether, 2:1, v/v). The reaction mixture was cooled in an ice-water bath and a reagent (0.2 ml) containing CrO₃ (2.67 g) and H₂SO₄ (2.3 ml) in 10 ml water was added to the reaction mixture with stirring, producing 10,13-diacetoxy-11-octadecenoic acid which was purified on a silica gel column with hexane-ether (90:10, 80:20, 60:40, 50:50, v/v) and ether with a yield of 0.88 g and an *R*_f = 0.27 (hexane-ether-acetic acid, 1:1:0.02, v/v). MS (methyl ester) *m/z*: 353 (M-CH₃COO), 310, and 169. 10, 13-Diacetoxy-11-octadecenoic acid (0.08 g) was saponified with 2N KOH in methanol. *R*_f = 0.30 and 0.22 (1% acetic acid in ether), producing 10,13-dihydroxy-11-octadecenoic acid (0.06 g) which was methylated with diazomethane. *R*_f = 0.42 and 0.24 (ether). MS (TMS derivative) *m/z*: 457 (M-CH₃), 441 (M-OCH₃), 401, 301, 273 and 173. Methyl-10, 13-dihydroxy-11-octadecenoate was dissolved in 2~3 ml of 1-butanol and 1 ml of water containing 100 mg HgO and 10 mg HNO₃ was added to the butanol solution with refluxing⁸⁾. The 2,5-dihydrofuran derivative produced was purified on a silica gel column with hexane-ether (95:5, v/v). MS *m/z*: 310 (M⁺), 297 (M-OCH₃),

239, 207, and 139.

RESULTS

Compounds I and II

Fraction A-1 was subjected to HPLC on a Zorbax SIL column and the fractions containing compounds I and II were isolated (Fig. 1). The other peak materials (a, b, and c) shown in Fig. 1 were identified by GC-MS as methyl 13-oxotridecadienoate, methyl oxooctadecadienoate, and 2,4-decadienal, respectively by comparing their mass spectra with those of library data. After purification by GLC ($t_R = 13.5$ min), compound I was injected into a mass spectrometer. Retention time on Silar

FIG. 1. High Performance Liquid Chromatogram of Fraction A-1.

I, methyl 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate (compound I); II, methyl 8-(2-furyl)-octanoate (compound II); a, methyl 13-oxotridecadienoate; b, methyl oxooctadecadienoate; c, 2,4-decadienal.

10C (1 m) of compound I was about 12 min. Figure 2A shows the EI mass spectrum of compound I. Fragment ions of m/z : 310 (M^+), 279 ($M - OCH_3$), 239 ($M - CH_3(CH_2)_4$), 207 ($239 - CH_3OH$) and 139 ($M - (CH_2)_8COOCH_3$) were shown. The CI mass spectrum showed intense $M+1$ ion of m/z : 311. Elemental compositions found by high resolution MS were as follows: m/z : 310.25376 ($C_{19}H_{34}O_3$), 279.23120 ($C_{18}H_{31}O_2$), 239.16711 ($C_{14}H_{23}O_3$), 207.14008 ($C_{13}H_{19}O_2$) and 139.11282 ($C_9H_{15}O$). A structure for compound I was postulated as shown in Fig. 2A from these MS results. After hydrogenation catalyzed by Pd black, the EI mass spectrum showed intense ions of m/z : 241 ($M - CH_3(CH_2)_4$), 223 ($241 - H_2O$), 209 ($241 - CH_3OH$), 141 ($M - (CH_2)_8COOCH_3$), and 123 ($141 - H_2O$) as shown in Fig. 2B. Though the molecular ion (m/z : 312) couldn't be detected, these results suggested that the hydrogenated compound I was 9-(2-(tetrahydro-5-pentylfuryl))-nonanoate. Since compound I was a minor product and a sufficient amount for IR or NMR spectrophotometry could not be obtained, 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate was synthesized to confirm the structure of compound I. Retention time of GC and the EI mass spectrum of synthesized 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate agreed with those of compound I. Accordingly, compound I was identified as 9-(2-(2,5-dihydro-5-pentylfuryl))-nonanoate.

Retention time of compound II on Silar 10C (1m) was about 8.3 min. The EI mass spectrum of compound II showed fragment ions nearly identical to those reported by Frankel *et al.*⁹⁾ for 8-(2-furyl)-octanoate; m/z : 224 (M^+), 193 ($M - OCH_3$), 137 ($M - (CH_2)_2COOCH_3$), 123 ($137 - CH_2$), 95 ($123 - (CH_2)_5COOCH_3$), and 81 ($M - (CH_2)_6COOCH_3$). The CI mass spectrum showed an intense ion of m/z : 225 ($M + 1$). High resolution MS indicated m/z of 224.13800 ($C_{13}H_{20}O_3$), 95.04836 (C_6H_7O), and 81.03248 (C_5H_5O). The mass spectra and GC retention time of compound II agreed with those of the authentic sample, therefore it was

confirmed that compound II was 8-(2-furyl)-octanoate.

Compounds III

Fraction B-1 was an *N,N'*-*p*-phenylenediamine sensitive material and separated into four peaks on HPLC (Fig. 3). Each peak material (compound III-1, III-2, III-3, or III-4) was isolated by HPLC and reduced to the corresponding hydroxy derivative with triphenylphosphine. The reduced products of compounds III were eluted much more slowly (14~17 min) than compounds I. They were converted into TMS derivatives and analyzed by GC-MS. The EI mass spectra of TMS derivatives of reduced compounds III-1, III-2, and III-4 were identical with those of 9-TMSO-12,13-epoxy-10-octadecenoate reported by Hamberg *et al.*¹⁰; m/z : 398 (M^+),

383 ($M - CH_3$), 367 ($M - OCH_3$), 259 ($CHO-TMS(CH_2)_7COOCH_3$), 241 ($M - (CH_2)_7COOCH_3$), and 99 ($CH_3(CH_2)_4CO$). High resolution MS revealed: 398.28642 ($C_{22}H_{42}O_4Si$), 383.26422 ($C_{21}H_{39}O_4Si$), 259.17225 ($C_{13}H_{27}O_3Si$), 241.16295 ($C_{13}H_{25}O_2Si$), and 99.08030 ($C_6H_{11}O$). The EI mass spectrum of the TMS derivative of reduced compound III-3 showed the fragment ions at m/z : 398 (M^+), 383 ($M - CH_3$), 367 ($M - OCH_3$), 327 ($M - CH_3 - (CH_2)_4$), 241 ($M - (CH_2)_7COOCH_3$), 185 ($CO(CH_2)_7COOCH_3$), and 173 ($CH_3(CH_2)_4CHOTMS$) as shown in Fig. 4. High resolution MS revealed: 383.25926 ($C_{21}H_{39}O_4Si$), 327.19800 ($C_{17}H_{31}O_4Si$), 241.16333 ($C_{13}H_{25}O_2Si$), 185.11617 ($C_{10}H_{17}O_3$), and 173.13575 ($C_9H_{21}OSi$). These MS results suggested that the reduced product of compound III-3 was 13-hydroxy-9,10-epoxy-11-octadecenoate. The IR spectrum of compounds III showed characteristic absorptions of *trans* epoxide at 880 cm^{-1} , *trans* double bond at 960 cm^{-1} , hydroxyl at 3450 cm^{-1} , and ester carbonyl at $1740\sim 1730\text{ cm}^{-1}$, which agreed with those of 13-hydroxy-9,10-epoxy-11-octadecenoate reported by Schieberle *et al.*¹¹) and Neff *et al.*¹²). These MS and IR results suggested that compounds III-1, III-2, and III-4 were 9-hydroperoxy-12,13-epoxy-10-octadecenoate and compound III-3 was 13-hydroperoxy-9,10-epoxy-11-octadecenoate.

FIG. 3. High Performance Liquid Chromatogram of Fraction B-1. III-1, III-2 and III-4, methyl 9-hydroperoxy-12,13-epoxy-10-octadecenoate; III-3, methyl 13-hydroperoxy-9,10-epoxy-11-octadecenoate.

FIG. 4. Mass Spectrum (EI) of Compound III-3.

DISCUSSION

Compound I is a novel product which has not been reported as a decomposition product of the hydroperoxide of linoleate. Though the mechanism of its formation is not clear, it seemed that the hydroperoxy group at carbon 13 underwent cyclization *via* $RO\cdot$.

Compound II was reported as a thermal decomposition product of 6-membered hydroperoxy epidioxide¹³) and hydroperoxyepoxyoctadecenoate¹⁴) (compounds III) which were secondary oxidation products of the hydroperoxide. Parson suggested¹⁵) a mechanism of formation of pentylfuran from the 9-hydroperoxide; the hydroperoxide de-

composed into a conjugated diene radical which was oxidized to vinyl hydroperoxide, and it cyclized. The formation of compound II would be explained by application of this mechanism to 13-hydroperoxide. However compound II has not been reported as a thermal decomposition product of the hydroperoxide of linoleate¹⁶⁾.

Compounds III were reported as a decomposition product of the 13-hydroperoxide allowed to react with a soybean extract or cysteine-FeCl₃ in an atmosphere of oxygen.¹⁷⁾ A mechanism of its formation was proposed; the RO· produced by decomposition of the hydroperoxide cyclized to α -unsaturation, and oxygen combined with produced epoxy radicals.¹⁷⁾ Evidently participation of oxygen is necessary to this mechanism. In our experiment, the hydroperoxide was decomposed under degassed conditions, so that the production of compounds III suggested that oxygen was generated in the process of the decomposition. Unpublished data of an other study indicated the generation of oxygen. Among the decomposition products, carbon-carbon linked dimer which we previously reported⁴⁾ was most abundant and occupied about 10% of all the products. Since this dimer lacks oxygen in comparison with the hydroperoxide, the generation of oxygen is expected to be accompanied by its production. There is another unpublished datum indicating the yield of the dimer tended to increase when the hydroperoxide was decomposed with a higher concentration of Cu²⁺. Thus, the mechanistic relation of the production of the dimer and oxygen to reduction of Cu²⁺ to Cu⁺ is an

interesting problem. The detailed study on this problem is in progress.

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