Allylic Halogenation and Oxidation of Long Chain α,β-Unsaturated Ester

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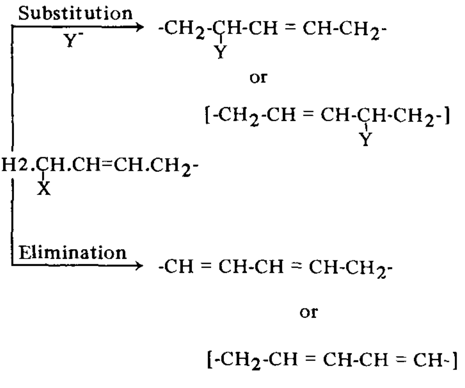
ABSTRACT

Methyl *trans*-2-hexadecenoate (*1b*) on allylic bromination with N-bromosuccinimide (NBS) (0.5 mole) yielded methyl 4-bromo-*trans*-2-hexadecenoate (*2b*) in 50% yield. Reaction with 2.0 moles of NBS afforded the allylic bromide (*2b*, δ 80%) as well as the dibromide (*3b*). Alkaline hydrolysis of the bromo ester (*2b*) yielded 4-hydroxy-*trans*-2-hexadecenoic acid (*4a*, δ 70%) and an unexpected product, 4-oxo-hexadecanoic acid (*5a*, δ 30%). A mechanism involving rearrangement is proposed to account for this unusual product. The effect of the ester carbonyl adjacent to the double bond in *2b* was found to suppress dehydrobromination (elimination) reaction and favors only substitution (S_N2), unlike the allylically brominated derivatives of internal olefinic compounds. The CrO_3-pyridine oxidation of *4b* yielded the corresponding unsaturated ketone (*7b*). The structures of individual reaction products were established by elemental analyses as well as by spectral studies.

INTRODUCTION

Reactions producing allylically substituted compounds are of considerable practical importance in fat chemistry; they increase the reactivity, and therefore the potential usefulness of such compounds. The allylic halogenation of fatty esters (1) containing internal double bonds has earlier been carried out in some detail. The products usually formed are mono allyl bromo-, diallyl bromo compounds with some bromine addition product. Allylically brominated esters readily undergo nucleophilic substitution as well as elimination reaction, and both reactions occur with double bond rearrangement.



$$-CH_2.\underset{X}{C}H.CH{=}CH.CH_2- \xrightarrow[Y^-]{\text{Substitution}} -CH_2\text{-}\underset{Y}{C}H\text{-}CH = CH\text{-}CH_2- \text{ or } [-CH_2\text{-}CH = CH\text{-}\underset{Y}{C}H\text{-}CH_2\text{-}]$$

$$-CH_2.\underset{X}{C}H.CH{=}CH.CH_2- \xrightarrow{\text{Elimination}} -CH = CH\text{-}CH = CH\text{-}CH_2- \text{ or } [-CH_2\text{-}CH = CH\text{-}CH = CH\text{-}]$$

Reaction of N-bromosuccinimide (NBS) with long chain α,β-unsaturated ester has received only limited attention (2). In continuation of our earlier work on the reactions of long chain α,β-unsaturated acids (3-5), the present work on allylic halogenation was undertaken for two reasons. First, there appeared to be no mention in the literature of a systematic study of allylic halogenation of these compounds. Second, it was considered desirable to study the influence of a carbomethoxy group adjacent to the double bond in the C-2, C-3 position on allylic bromination and the reactivity of the resulting allyl bromide toward substitution/elimination reactions.

EXPERIMENTAL PROCEDURES

Melting points were observed on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer in CCl_4 and ultraviolet (UV) spectra in methanol with a Beckman DK-2A spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A60 spectrometer. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS). The samples were run as 10% solution in chloroform-d. The abbreviations "s, d, m, br, and t" denote "singlet, doublet, multiplet, broad, and triplet," respectively. Mass spectra were measured with an AEI MS-9 mass spectrometer. Thin layer chromatographic (TLC) plates were coated with silica gel. Spots were detected by charring after spraying with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of bp 40-60 C.

MATERIALS AND METHODS

trans-2-Hexadecenoic acid, *1a*, (mp 54 C) was prepared from palmitic acid by the procedure of Palameta and Prostenick (6). The 2-enoic structure of this acid and its geometry was established by IR, NMR, and mass spectrometry (3).

NBS-bromination of *1b*

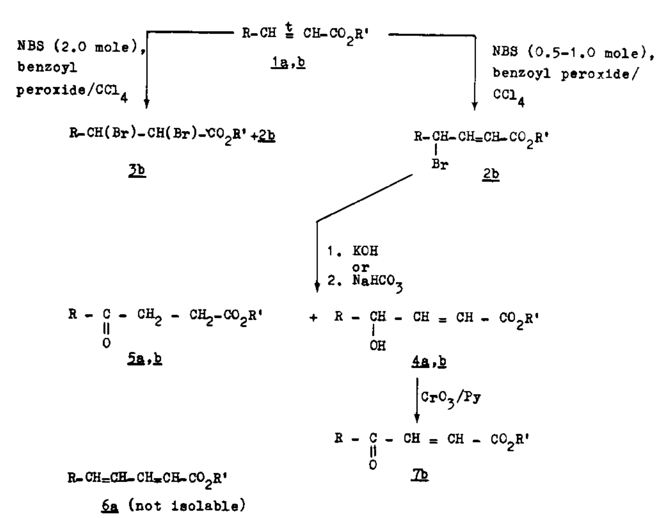
General procedure: To the solution of methyl *trans*-2-hexadecenoate, *1b*, (5.0 g, 0.018 mole) in 100 ml anhydrous CCl_4 (dried over P_2O_5), crystallized NBS (1.65 g, 0.5 mole) and benzoyl peroxide (80 mg) were added, and the mixture was refluxed for 3 hr. The progress of the reaction was followed by the change of the heavy NBS at the bottom of the flask and succinimide which rises to the surface (7). This process usually required about 3 hr. After cooling, the insoluble succinimide was filtered off, washed with the solvent, and the bulk of the solvent was removed under reduced pressure. The residue was poured into water, extracted with ether, and the ethereal solution was washed and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a dark brown liquid (8.0 g, positive Beilstein test) which showed two distinct spots on TLC (petroleum ether-ether-acetic acid, 80:20:1, v/v).

The crude product (8.0 g) was chromatographed over a column of neutral alumina (80 g). Elution with petroleum ether gave the starting material, *1b* (1.68 g) (each fraction of 15 ml was collected), and subsequent elution with a mixture of petroleum ether-ether (98:2, v/v) gave the reaction product. The TLC-monitored fractions which showed positive test for bromine were combined and rechromatographed to give a pure methyl 4-bromo-*trans*-2-hexadecenoate, *2b*, (3.22 g, ca. 50%) as a brown liquid. The yield of *2b* varied with the molar concentration of NBS. With 1.0 mole NBS, *2b* was obtained in about 75% yield together with a decreased quantity of *1b* (25%) whereas with 2.0 mole NBS it afforded *2b* (80%), *3b* (10%) (petroleum ether-ether, 96:4, v/v) together with unreacted *1b* (~ 10%).

Analysis (*2b*) Calc. for $C_{17}H_{31}O_2Br$: C, 58.78; H, 8.93; Br, 23.07. Found: C, 58.60; H, 8.70; Br, 22.70%.

Calc. for (*3b*) $C_{17}H_{32}O_2Br_2$: C, 47.66; H, 7.47; Br, 37.40. Found: C, 47.43; H, 7.20; Br, 37.10%.

TABLE I



1a $R = CH_3(CH_2)_{12}-$; $R' = H$
1b & 3b $R = CH_3(CH_2)_{12}-$; $R' = Me$
2b $R = CH_3(CH_2)_{11}-$; $R' = Me$
4a & 5a $R = CH_3(CH_2)_{11}-$; $R' = H$
4b, 5b & 7b $R = CH_3(CH_2)_{11}-$; $R' = Me$
6a $R = CH_3(CH_2)_{10}-$; $R' = H$

(Spectral values are recorded in the discussion part of the paper).

Alkaline Hydrolysis of *2b*

Compound 2b (3.5 g, 0.01 mole) was hydrolyzed by heating with KOH solution (2.5 g in 40 ml of ethanol-water in the ratio of 1:1) under reflux for 4 hr. The bulk of the solvent was removed under reduced pressure, and the residue was diluted with ice-cooled water, acidified with HCl, and extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. The yellow product (2.9 g) obtained after evaporation of the ether showed two distinct spots on TLC (petroleum ether-ether-acetic acid, 80:20:1, v/v) and was chromatographed over a column of Silica Gel G (60 g) and was eluted with a mixture of petroleum ether-ether (80:20, v/v). The TLC-monitored eluates were combined and crystallized from petroleum ether to give 4-oxo-hexadecanoic acid, *5a* (0.82 g, ca. 30%), mp 95-96 C. *Analysis.* Calc. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.80; H, 11.00%. Its methyl ester, *5b*, prepared with ethereal diazomethane, melted at 72 C. M^{+} 284 ($C_{17}H_{32}O_3$). *Analysis.* Calc. for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.59; H, 11.12%.

Subsequent elution with a mixture of petroleum ether-ether (70:30, v/v), followed by crystallization from petroleum ether gave 4-hydroxy-*trans*-2-hexadecenoic acid, *4a* (1.91 g, ca. 70%), mp 70-71 C. *Analysis.* Calc. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.83; H, 11.02%. Its methyl ester, *4b*, prepared with ethereal diazomethane, melted at 56-57 C. M^{+} 284 ($C_{17}H_{32}O_3$). *Analysis.* Calc. for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34. Found: C, 71.53; H, 11.13%.

Alkaline hydrolysis of *2b* with boiling 2M $NaHCO_3$ for 2 hr furnished the same reaction products, *4a* (mp and mixed mp 70-71 C) and *5a* (mp and mixed mp 95-96 C).

CrO_3-pyridine Oxidation of *4b*

The chromium (VI) oxide-pyridine complex was used as oxidizing agent, prepared by the general procedure of Holum (8). A slurry of the complex in anhydrous pyridine was prepared by adding chromium (VI) oxide (2.1 g, 2.1 x 10^{-2} mole) to vigorously stirred, chilled (ice bath) pyridine (80 ml) over a period of 15-20 min. *4b* (1 g, 3.5 x 10^{-3} mole) in pyridine (20 ml) was added to the slurry dropwise with continuous stirring for 30 min, and then it was allowed to stand at room temperature for 24 hr. The mixture was poured into water (250 ml) and was extracted with ether. The combined ether extracts were washed successively with 10% HCl (250 ml), 10% Na_2CO_3 (50 ml), and water (150 ml) and dried over anhydrous sodium sulfate. Evaporation of the ether gave a solid (0.9 g) which on crystallization from a mixture of petroleum ether-acetone (1:1) at low temperature yielded a white crystalline compound, *7b* (0.84 g, ca. 85%), mp 65-66C. M^{+} 282 ($C_{17}H_{30}O_3$). *Analysis.* Calc. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72,18; H, 10.50%. The 2,4-DNP derivative of *7b* melted at 126 C.

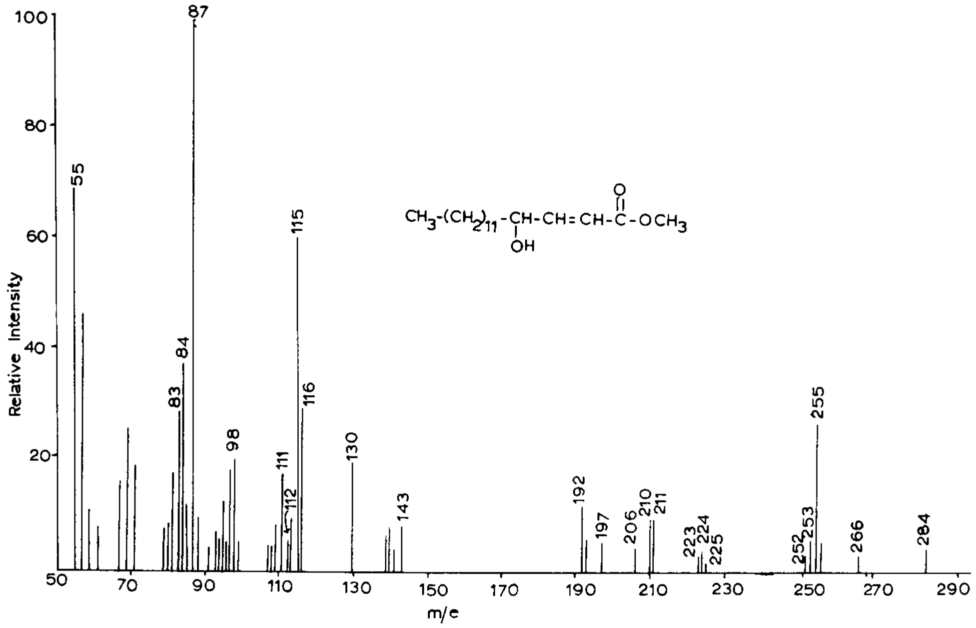
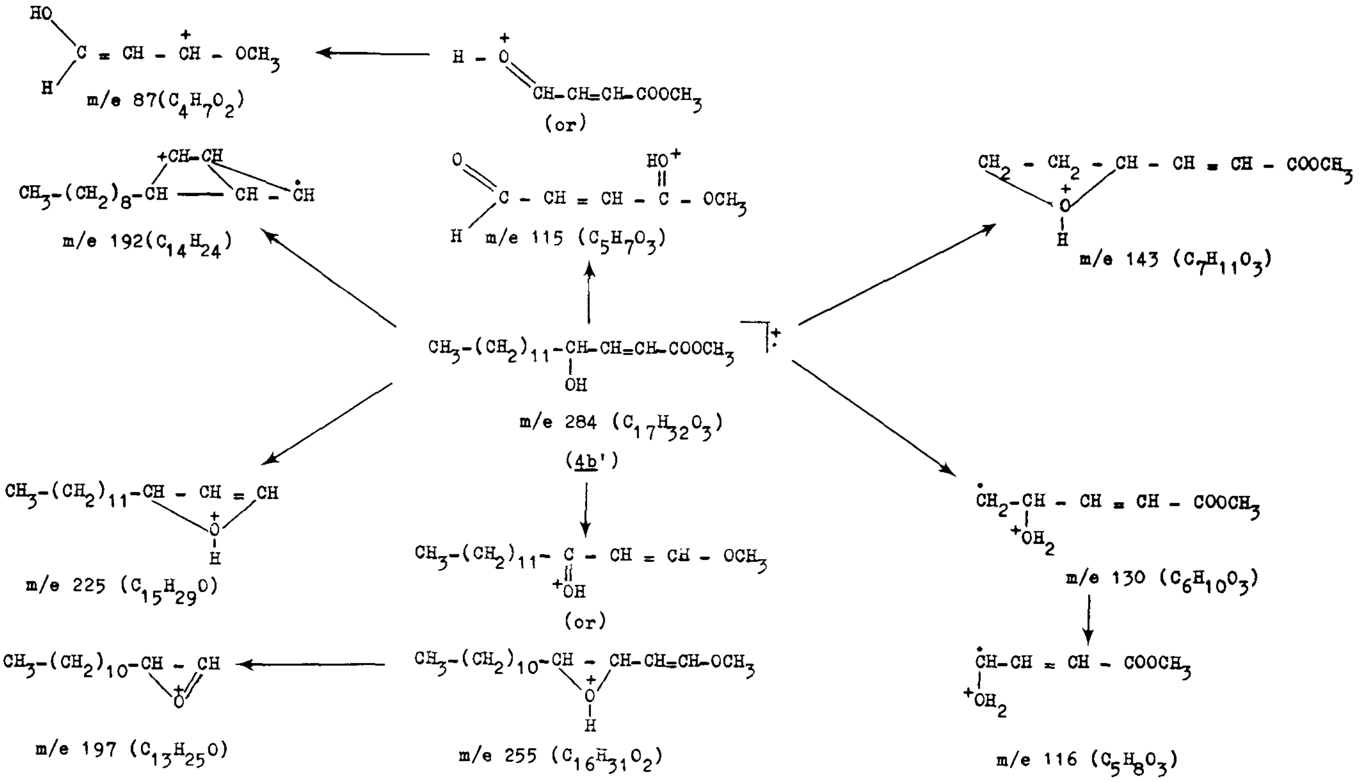


FIG. 1. Mass spectrum of methyl 4-hydroxy-*trans*-2-hexadecenoate.



SCHEME I.

RESULTS AND DISCUSSION

Table I outlines the results of the reaction of N-bromosuccinimide with methyl *trans*-2-hexadecenoate *1b*, isolation of the resulting mono allyl bromination product *2b*, its hydrolysis and oxidation reaction. The structures of the reaction products were established by combustion and spectroscopic data.

The two major reactions in the treatment of methyl *trans*-2-hexadecenoate, *1b*, with NBS are allylic bromination and addition of bromine to the double bond. When *1b* was treated with 0.5 mole of NBS, it gave mono allyl bromo compound, *2b* in about 50% yield; much of the starting material was recovered. NBS (1.0 mole) gave a mixture of *1b* and *2b* in the ratio of 25:75, respectively. With 2.0 moles of NBS a mixture of *1b, 2b,* and *3b* was obtained in the ratio of 1:8:1. Chromatographic resolution of the crude brominated methyl ester yielded the mono bromo compound (major, *2b*) and bromine addition product (minor, *3b*). The structure of *3b* was established as *vic*-dibromide on the basis of elemental analysis, IR, and co-chromatography on a TLC plate with an authentic sample prepared by direct bromination (9). Its IR spectrum gave bands at 1740 (*C*OOCH$_3$) and 720 cm^{-1} (C-Br).

The identity of methyl 4-bromo-*trans*-2-hexadecenoate, *2b*, is based upon its elemental analysis, spectral behavior, and chemical transformation. Elemental analysis of *2b* corresponded to formula $C_{17}H_{31}O_2Br$. Its IR spectrum gave bands at 1730(s) (C=C-*C*OOCH$_3$), 1640 (C=C), 967 (*trans* olefin), and 720 cm^{-1} (C-Br). The NMR spectrum gave signals at δ 6.2d,d (J= 15 and 5 Hz, 1H, β to ester carbonyl), 5.2d (J=12 Hz with small long range coupling, *trans* olefinic proton, 1H, α to ester carbonyl), 4.4m (1H, C*H*Br), 3.8s (3H, COOC*H*$_3$), 1.3br,s (chain-C*H*$_2$), and 0.9t (3H, terminal-C*H*$_3$). The signal for C*H*-Br appeared relatively downfield and this is probably due to its being allylic to C-2, C-3 double bond. It should be pointed out that the bromo compound *2b* is highly unstable under atmospheric condition and tends to decompose within 24 hr of its formation.

Alkaline hydrolysis of *2b* gave *4a* and *5a*. Structures of *4a* and *5a* were established by combustion data and IR, NMR, and mass spectra of their methyl esters, *4b* and *5b*, respectively.

The ester *4b* analyzed for $C_{17}H_{32}O_3$ and had IR bands at 3350-3270(OH), 1730 (C=C-*C*OOCH$_3$), 1660 (C=C), 1170, 1140, 1080, 1050 (C-O), and 980 cm^{-1} (*trans* olefin). The NMR spectrum gave a doublet of doublet centered at δ 6.9 (1H, J = 15 and 5 Hz) ascribable to proton β to ester carbonyl, a doublet at 6.0 (1H, J=15 Hz with a small long range coupling, *trans* olefinic proton) ascribable to a proton α to ester carbonyl, 4.2br (1H, C*H*-OH), 3.71s (3H, COOC*H*$_3$), 2.4br (1H, O*H*, disappeared on addition of D_2O), 1.26br,s (chain-C*H*$_2$), and 0.86t (3H, terminal-C*H*$_3$). The J values of vinylic protons strongly suggest *trans* configuration of the double bond. After D_2O exchange the signal at δ 2.4 disappeared with a small change in the signal at δ 4.2.

The above structure of *4b* was further supported by its mass spectrum. It (Fig. 1) gave the molecular ion peak at m/e 284 ($C_{17}H_{32}O_3$) followed by other salient ion peaks at m/e 266(M-H$_2$O), 255 (M-29), 253 (M-CH$_3$O), 252 (M-CH$_3$OH), 225 (M-COOCH$_3$), 224 (255-CH$_3$O), 223 (255-CH$_3$OH), 211, 210, 206, 197, 192, 143, 130, 116, 115, 112 (130-H$_2$O), 111 (143-CH$_3$OH), 98 (130-CH$_3$OH), 87 (base peak), 84 (115-CH$_3$O), 83 (115-CH$_3$OH), and other low mass ion peaks. The mass spectral fragmentation of *4b* is given in Scheme I.

Elemental analysis of *5a* corresponded to formula $C_{16}H_{30}O_3$. In the IR spectrum of its methyl ester, *5b*, two equally strong bands at 1750 (*C*OOCH$_3$) and 1725 cm^{-1} (C=O) were indicated. There was no evidence for the presence of an olefinic bond. The NMR spectrum likewise was devoid of any vinylic proton. It gave signals at δ 3.61s (3H, COOC*H*$_3$), 2.4m (6H, C*H*$_2$. CO.C*H*$_2$.C*H*$_2$.COOCH$_3$), 1.25br,s (chain-C*H*$_2$) and 0.83t (3H, terminal-C*H*$_3$). From these data *5b* was formulated as methyl 4-oxo-hexa-

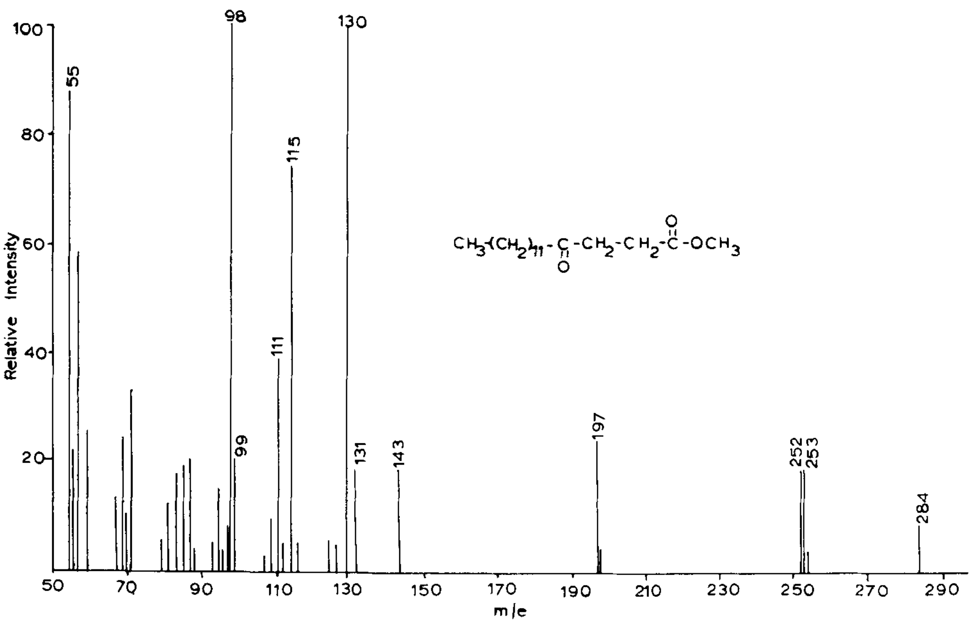
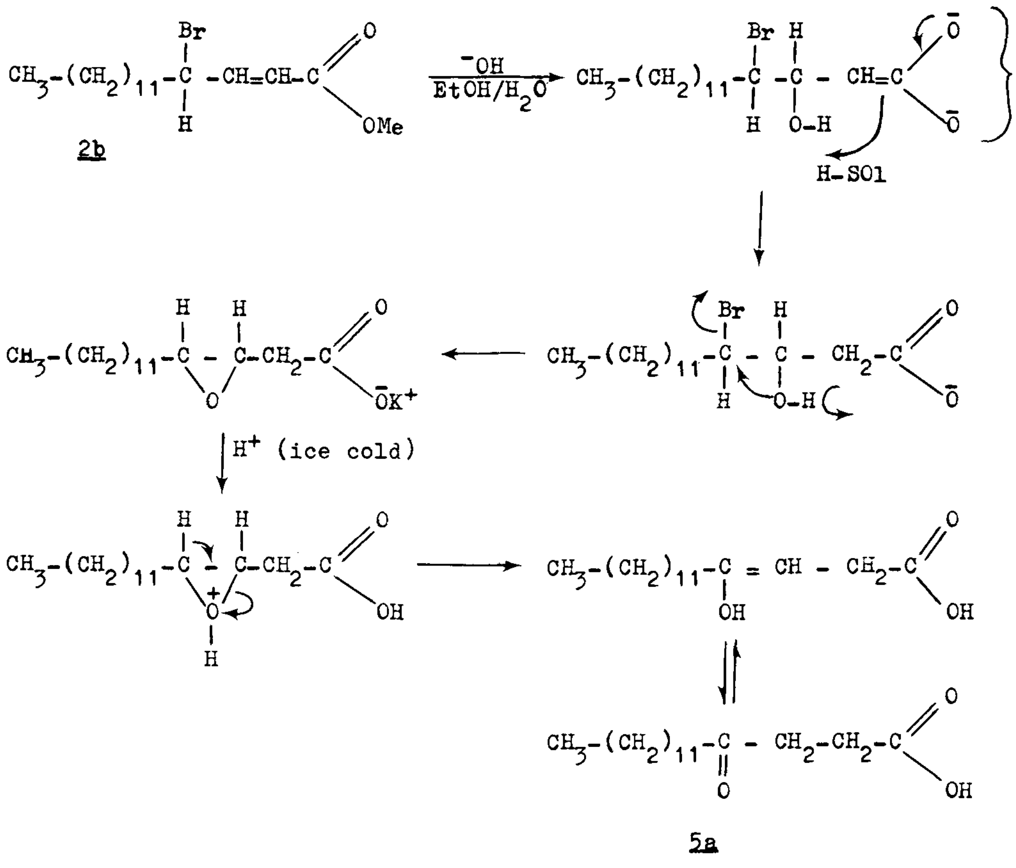


FIG. 2. Mass spectrum of methyl 4-oxo-hexadecanoate.



SCHEME II.

decanoate. This formulation was further supported by mass spectrometry.

The mass spectrum of *5b* (Fig. 2) gave the molecular ion peak at m/e 284 ($C_{17}H_{32}O_3$) followed by other salient ion peaks at m/e 253 ($M\text{-}CH_3O$), 252 ($M\text{-}CH_3OH$), 197, 143, 130, 115, 111 ($143\text{-}CH_3OH$), 99 ($130\text{-}CH_3O$), and other low mass ion peaks.

The fragment ion m/e 130 ($\mathrm{H_2C{=}\overset{.+OH}{C}\text{-}CH_2\text{-}CH_2\text{-}COOCH_3}$) (McLafferty rearrangement involving C-4 keto function) constitutes the base peak of the spectrum, and an ion peak at m/e 143 ($\mathrm{CH_2\text{-}CH_2\text{-}\overset{\overset{O+}{\|}}{C}\text{-}CH_2CH_2\text{-}COOCH_3}$) obviously results from the molecular ion by β-cleavage between C-6, C-7 (non-McLafferty). Two other significant peaks characteristic of a keto compound were observable at m/e 197 (α-cleavage between C-3, C-4) and m/e 115 (α-cleavage between C-4, C-5).

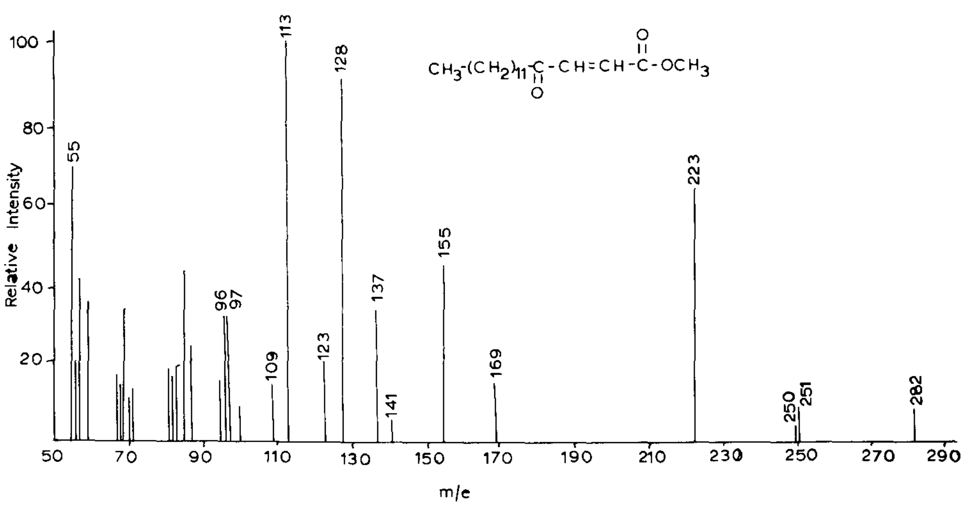


FIG. 3. Mass spectrum of methyl 4-oxo-*trans*-2-hexadecenoate.

Thus, the mass spectral data supported the structure of methyl 4-oxo-hexadecanoate, *5b*, assigned on the basis of combustion data, IR, and NMR studies. The rearrangement of *2b* to *5a* can be rationalized in terms of the mechanistic sequence in Scheme II.

From the above mechanism it appears reasonable to suggest that the conjugated double bond becomes the preferred seat of reaction by hydroxide ($\bar{O}H$) ion. This preferential attack by $\bar{O}H$ ion on β-carbon suppresses the elimination reaction which would have given rise to *6a*. It is pertinent to mention that the bromo compound *2b* did not afford the expected conjugated dienoic acid, *6a*, in isolatable quantity. It is reasonable to believe that *6a* might have been formed in such a small amount that it escaped isolation by conventional methods. The replacement of allylic bromine by nucleophiles in general occur by both $S_N{}^1$ and $S_N{}^2$ processes. In this case, however, the reaction probably occurs by an intramolecular process to give an epoxide intermediate which on acidification rearranges to the ketone *5a*. The nonformation of elimination product by E_2 process is discouraged by the preferred attack of the $\bar{O}H$ on conjugated double bond. On the other hand, E_1 process involving a carbonium ion will not be favored since it will not be resonance stabilized due to the double bond being in conjugation with ester carbonyl group.

Elemental analysis of *7b* corresponded to formula $C_{17}H_{30}O_3$. Its IR spectrum gave peaks at 1730 (C=C-*C*OOCH$_3$), 1700 (C=C-*CO*), 1640 (C=C), and 980 cm^{-1} (*trans* olefin). The assigned structure *7b* finds further support from its NMR spectrum. It gave a doublet centered at δ 6.8 (2H, J=15 Hz) which is ascribable to two vinylic protons. The magnitude of splitting suggested the *trans* configuration of olefinic bond. Other signals were observed at δ 3.8s (3H, COOC*H*$_3$), 2.5m (2H, C*H*$_2$CO), 1.25br,s (chain-C*H*$_2$), and 0.85t (3H, terminal-C*H*$_3$). Its (*7b*) UV spectrum showed absorption maxima at 220 nm.

The mass spectrum of this compound *7b* (Fig. 3) resembles that of *5b* to a certain extent. It has also some distinctive peaks and attempts have been made to rationalize the genesis of important fragment ions. The molecular ion peak at m/e 282 ($C_{17}H_{30}O_3$) was present along with other important peaks at m/e 251 (M-CH_3O), 250 (M-CH_3OH), 223 (M-$COOCH_3$), 169, 155, 141, 137 (155-H_2O), 128, 123 (155-CH_3OH), 113 (M-169, base peak), 109 (141-CH_3OH), 97 (128−CH_3O), 96 (128-CH_3OH), and other low mass ion peaks.

The prominent ion peak at m/e 223 is expected to originate by the loss of mass 59 ($COOCH_3$) from the molecular ion. The ion peaks at m/e 169 (δ-cleavage between C-8, C-9), 155 (ϒ-cleavage between C-7, C-8), and a low intensity ion peak at 141 (β-cleavage between C-5, C-6) were observed in the spectrum, which are characteristic for *7b*. The fragment ion m/e 113 constitutes the base peak of the spectrum and may arise by the loss of a methyl group from the fragment ion m/e 128 (McLafferty, most prominent next to base peak at m/e 113).

Thus, the mass spectral data supported the structure of methyl 4-oxo-*trans*-2-hexadecenoate, *7b*, assigned on the basis of elemental analysis, IR, and NMR studies.

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