Cyclopropanation of Unsaturated Fatty Acid Methyl Esters using Diazomethane and Palladium (II) Acetate

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Cyclopropanation of methyl esters of 10-undecenoic, oleic, elaidic, erucic, *trans*-2-docosenoic and a mixture of hydnocarpic and chaulmoogric acids was effected using diazomethane in the presence of palladium (II) acetate as catalyst. The products were isolated by silver ion thin-layer chromatography and characterized by infrared, proton nuclear magnetic resonance and mass spectrometric techniques. Terminally unsaturated, α, β-unsaturated and cyclopentene fatty acid esters were found to be more reactive than elaidate which in turn was more reactive than oleate. The reaction proceeds stereospecifically under milder conditions in a shorter time than with diiodomethane and zinc-copper couple.

Starting with isolation of lactobacillic (*cis*-11,12-methyleneoctadecanoic) acid from the lipids of the bacterium *Lactobacillus arabinosus* by Hofmann and Lucas (1), the occurrence of various cyclopropane fatty acids was reported in a wide range of bacterial (2), protozoan (3) and plant species (4,5). The seed oil of the *Litchi sinensis* plant was reported to contain about 41% dihydrosterculic (*cis*-9,10-methyleneoctadecanoic) acid (6). Christie and Holman (7) reported the preparation of stereochemically pure cyclopropane fatty acid esters by the Simmons-Smith reaction of different olefinic fatty acid esters with diiodomethane in the presence of zinc-copper couple. Cyclopropanes are reported to be obtained in good yields when conjugated alkenes such as styrenes (8), α, β-unsaturated carbonyl compounds (9,10), strained alkenes (11) and a few terminal olefins (12) are reacted with diazomethane in the presence of palladium (II) acetate under milder conditions. In this paper, we report the use of this reagent for the synthesis of different cyclopropane fatty acid esters, their isolation by silver ion thin-layer chromatography (TLC), characterization by infrared (IR), proton nuclear magnetic resonance (NMR) and mass spectrometric (MS) methods and estimation by gas liquid chromatography (GLC).

MATERIALS AND METHODS

10-Undecenoic acid was purchased from Jayant Oil Mills, Bombay, India. Methyl oleate was purchased from Sigma Chemical Co., St. Louis, Missouri. Elaidic acid, erucic acid and silica gel G were purchased from ACME Synthetic Chemicals, Bombay, India. *Trans*-2-docosenoic acid was prepared by α-bromination of behenic acid followed by dehydrobromination of the resulting α-bromo acid (13). A mixture of methyl hydnocarpate (22.3%) and methyl chaulmoograte (77.7%) was obtained by conventional methods from the methyl esters of *Hydnocarpus wightiana* seed oil (14-16). N-Nitroso-N-methyl urea was prepared according to Vogel (17). Palladium (II) acetate was purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. The fatty acids were converted to their methyl esters by reacting with an ethereal solution of diazomethane containing methanol.

A mixture of monounsaturated fatty acid ester (0.5 mmol) and palladium (II) acetate (10 mg) was dissolved in diethyl ether (15-20 ml) and cooled in an ice-salt bath. An ethereal solution of diazomethane (20-25 ml), generated from N-nitroso-N-methyl urea (2 g), was added drop by drop to the mixture with continuous stirring for 10 min. After removal of ether and excess diazomethane in vacuo, the residue was dissolved in n-hexane and the solution was passed through a silica gel (2 g) column to remove palladium acetate. The product was recovered by removal of solvent in vacuo. In the case of methyl undecenoate and methyl *trans*-2-docosenoate, three mmol of the esters also were used for cyclopropanation with the same amount of the reagent.

The cyclopropane fatty acid esters were separated from the unreacted olefinic esters by preparative TLC on 0.6-mm layers of silica gel G impregnated with silver nitrate (10-12%) using a mixture of n-hexane-benzene (70:30, v/v). IR spectra were recorded in CCl_4 solution using a Perkin-Elmer Model 283 B spectrophotometer. NMR spectra were recorded using a JEOL FX 90Q Fourier Transform NMR spectrometer. Tetramethylsilane was used as an internal standard. Mass spectra were recorded at 20 eV and 70 eV on a V.G. Micromass 7070 H mass spectrometer.

The cyclopropane ester contents in the reaction products were determined by GLC using a Hewlett-Packard 5840 A unit equipped with a flame ionization detector, a glass column (1.8 m x 6 mm) packed with 10% Silar 10 C/Chromosorb W HP (80-100 mesh) and a data processor. The products also were analyzed using a glass column (0.6 m x 6 mm) packed with 5% SE-30/Chromosorb W HP (100-120 mesh). The column, injection port and detector temperatures were maintained at 200, 250 and 300 C, respectively. For methyl undecenoate and its reaction product the temperatures were 150, 250 and 300 C, respectively. The flow rate of nitrogen was 30 ml/min.

RESULTS AND DISCUSSION

Methyl *cis*- and *trans* methyleneoctadecanoates were prepared earlier (18,19) using various positional isomers of octadecenoates and diiodomethane and characterized by GLC, IR and NMR techniques. In the present investigation various unsaturated fatty acid methyl esters (Table 1) were cyclopropanated using diazomethane in the presence of palladium acetate. In each instance the product was separated from the corresponding unconverted ester by silver ion silica

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TABLE 1

Conversions of Unsaturated Fatty Acid Methyl Esters to the Corresponding Cyclopropane Derivatives Using Diazomethane/Palladium Acetate[a]

Unsaturated ester	Rf[b]	Purity (%)[c]	Cyclopropane ester	Rf[b]	Content in the product (%)[c]
Methyl undecenoate[d]	0.18	99.0	Methyl 10,11-methyleneundecanoate	0.56	99.0
Methyl oleate	0.24	99.9	Methyl *cis*-9,10-methyleneoctadecanoate	0.53	39.9
Methyl elaidate	0.27	99.9	Methyl *trans*-9,10-methyleneoctadecanoate	0.53	81.7
Methyl erucate	0.22	99.0	Methyl *cis*-13,14-methylenedocosanoate	0.52	30.5
Methyl *trans*-2-docosenoate	0.21	99.9	Methyl *trans*-2,3-methylenedocosanoate	0.45	99.9
Concentrate of cyclopentene fatty acid methyl esters					
Methyl hydnocarpate plus	0.20	22.3	Methyl 11-bicyclo (3.1.0) hexylundecanoate plus	0.46	20.7
Methyl chaulmoograte	0.20	77.7	Methyl 13-bicyclo (3.1.0) hexyltridecanoate	0.46	79.3

[a]0.5 mmol unsaturated ester, 10 mg $Pd(OAc)_2$; 20 ml diethyl ether solution of CH_2N_2 obtained from 2 g of nitrosomethylurea were used.
[b]Argentation thin layer chromatography using hexane-benzene (70:30, v/v).
[c]By GLC.
[d]Even with 3 mmol, conversion was the same.
[e]With 3 mmol, conversion was 78.5%.

gel TLC for characterization by IR, NMR and mass spectrometric techniques. The content of cyclopropane ester, prior to its isolation, was estimated in total products by GLC; a typical chromatogram of cyclopropanated methyl oleate is shown in Figure 1.

The IR spectra of methyl *cis*-9,10-methyleneoctadecanoate, methyl *cis*-13,14-methylenedocosanoate and methyl *trans*-9,10-methyleneoctadecanoate showed characteristic absorption bands at 1015 cm^{-1} and 3055 cm^{-1} for cyclopropane ring. No difference was thus observed in the position of the bands for *cis*- and *trans*-isomers with the cyclopropane moiety near the middle of the chain, whereas the bands appeared at 1015 cm^{-1} and 3077 cm^{-1} for 10,11-methyleneundecanoate (Fig. 2) and at 1016 cm^{-1} and 3060 cm^{-1} for the cyclopropanated cyclopentene fatty acid methyl esters. Methyl *trans*-2,3-methylenedocosanoate showed only one band at 1115 cm^{-1} for the cyclopropyl group. The ester carbonyl group appeared at 1724 cm^{-1} before and after cyclopropanation of methyl *trans*-2-docosenoate.

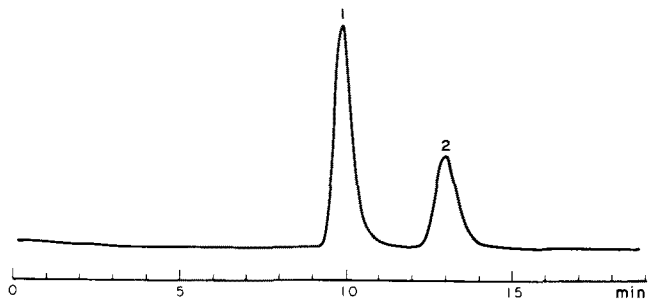


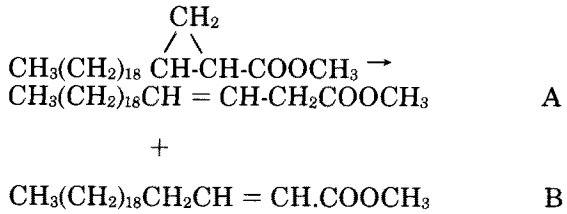
FIG. 1. Gas liquid chromatogram of cyclopropanated compound of methyl oleate using Silar 10 C in glass column and FID. Chromatographic conditions are given in text. Peaks: 1, unconverted methyl oleate; 2, cyclopropanated compound.

The NMR spectrum of the *cis*-9,10-methyleneoctadecanoate (Fig. 3) was similar to that reported by earlier workers (20-23). It showed a multiplet at δ -0.3, equivalent to one proton, and was assigned to the proton (Hb) *cis* to the two alkyl substituents. A broad signal at δ0.6, which previously was assigned (22) to the remaining three protons (Ha, Hc, Hc), was equivalent to only two protons (Hc, Hc) in the present instance. The fourth proton (Ha) has perhaps merged with the end methyl protons signal at δ0.88 which accounted for four protons. Wood and Reiser (23) also found a signal at δ0.8 and attributed it to one of the cyclopropane protons. The pattern of spectrum of methyl *cis*-13,14-methylenedocosanoate was similar to that of methyl *cis*-9,10-methyleneoctadecanoate.

The NMR spectrum of *trans*-9,10-methyleneoctadecanoate showed a single complex four-proton band with fine structure between about δ -0.14 and 0.62, as reported earlier (21). In *trans*-2,3-methylenedocosanoate, all four cyclopropane protons were nonequivalent. Thus, one methine proton (C_2) showed a signal at δ1.8 and the other (C_3) at δ1.52. This could be due to the deshielding effect of the carbomethoxy group on one side and alkyl substituent on the other side of the molecule. Both the protons of the cyclopropyl methylene group merged with the end methyl protons and appeared at about δ 0.7 to 0.88 because of the shielding effects of the alkyl substituent and carbomethoxy group. The NMR spectrum of 10,11-methyleneundecanoate showed two complex bands centered at δ 0.4 and δ 0.88 representing four cyclopropyl methylene protons. The two protons, *cis* to the alkyl substituent, which are expected to be more shielded, appeared at δ 0.4 and the signal for the other two protons appeared at δ 0.88. The methine proton merged with the broad chain methylene protons signal. In the NMR spectrum of cyclopropane derivatives of cyclopentene fatty acid esters the band at δ5.35 due to the cyclopentene double bond (protons) disappeared and the new

signals at δ0.2 and δ1.0 were assigned to cyclopropane moiety of the bicyclic compound.

The mass spectral fragmentation patterns of methyl 10,11-methyleneundecanoate, methyl *cis*-9,10-methyleneoctadecanoate, methyl *trans*-9,10-methyleneoctadecanoate and methyl *cis*-13,14-methylenedocosanoate were similar to their corresponding parent unsaturated esters except that the molecular ions were higher in mass by 14 units than those of the parent esters. The similarities between the spectra of the monocyclopropane fatty acid esters and those of the monoenoic acid esters from which they were derived were explained by Christie and Holman (7). The mass spectrum of methyl *trans*-2,3-methylenedocosanoate showed a distinct molecular ion at m/z 366 and the other usual ions observed for monounsaturated esters. The spectrum also showed a peak at m/z 113 which is in fact a characteristic peak of α, β-unsaturated fatty acid esters. The cleavage of cyclopropane ring of *trans*-2,3-methylenedocosanoate might have resulted in the formation of two monounsaturated fatty acid esters (A and B) with one carbon more than in the parent unsaturated ester, as given below.



$$CH_3(CH_2)_{18}CH\text{-}CH\text{-}COOCH_3 \rightarrow CH_3(CH_2)_{18}CH = CH\text{-}CH_2COOCH_3 \quad A$$

$$+$$

$$CH_3(CH_2)_{18}CH_2CH = CH.COOCH_3 \quad B$$

The monounsaturated ester (B) might be responsible for the formation of an ion at m/z 113 whose stability was attributed to its cyclic structure (24).

The cyclopropane derivatives of cyclopentene fatty acid esters (Fig. 4) gave molecular ions at m/z 280 corresponding to the cyclopropane derivative of methyl hydnocarpate and m/z 308 corresponding to the cyclopropane derivative of methyl chaulmoograte. The ions corresponding to M-74 and M-116, which were present in the mass spectra of monocyclopropane fatty acid esters, were not observed in the present case. The formation of prominent ions at m/z 81, 95 and 96 could be explained as follows. The cleavage of bridged bond of cyclopropane derivatives of cyclopentene fatty acid esters (I) might have taken place resulting in the expansion of the ring, giving rise to structure II as shown in Scheme 1. This structure could undergo an α-cleavage losing a radical ($CH_2CH_2CH_2R$) and producing a cyclohexene cation which immediately undergoes ring contraction, giving rise to methyl cyclopentene cation (m/z 81). This is a prominent peak next to the base peak in the spectrum. The fragment ion at m/z 95 might have resulted from the β-cleavage of structure II, which loses a radical (CH_2CH_2R), giving rise to a fragment ion at m/z 95. Structure II also undergoes an internal McLafferty type rearrangement losing an olefin (CH_2=CH-R) and giving rise to a fragment ion at m/z 96 which was the base peak in the spectrum. The suggested fragmentation proves the expected formation of methyl 11-bicyclo (3.1.0) hexylundecanoate and methyl 13-bicyclo (3.1.0) hexyltridecanoate.

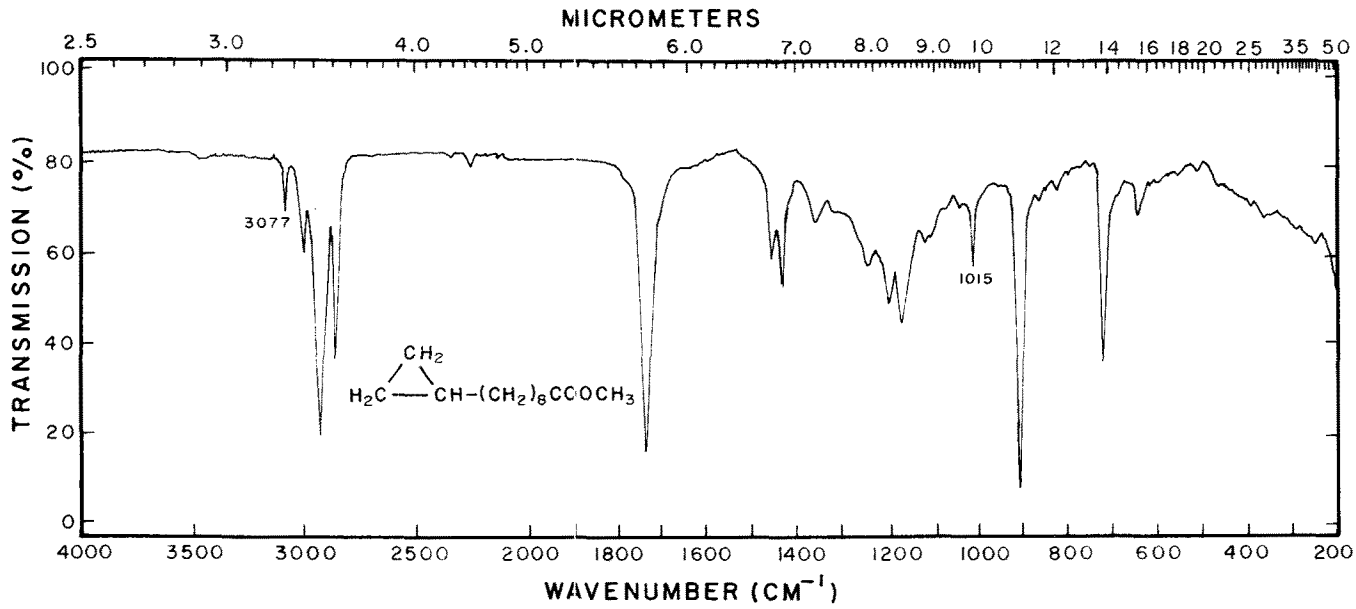
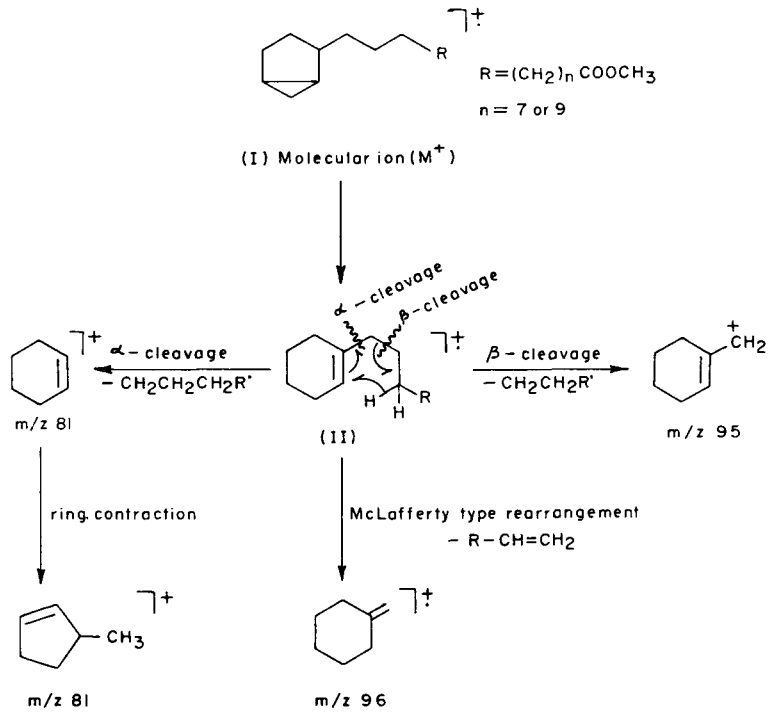


FIG. 2. IR Spectrum of cyclopropanated methyl undecenoate (methyl 10,11-methyleneundecanoate).



Scheme 1

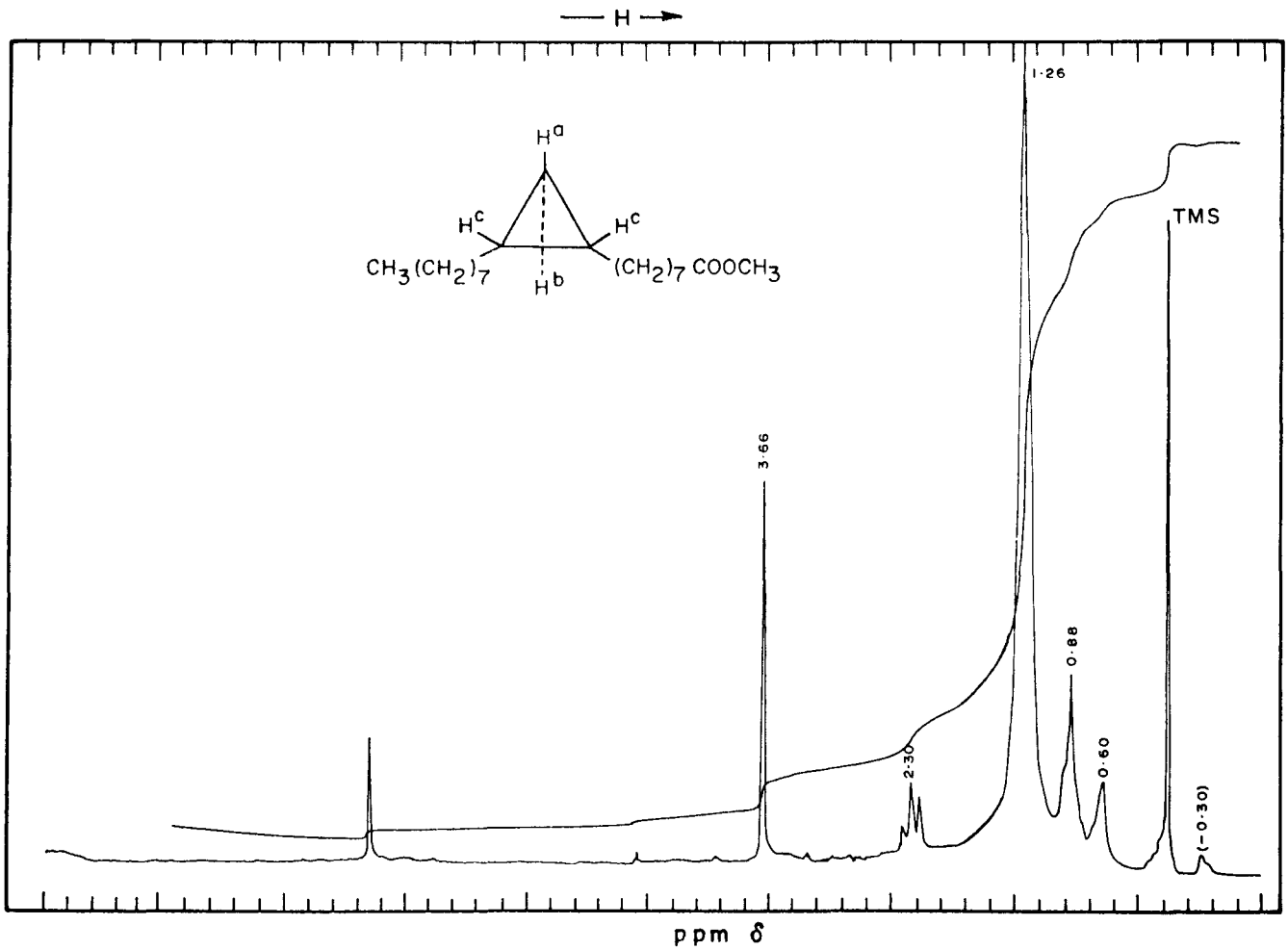


FIG. 3. ^{1}H-NMR Spectrum of methyl *cis*-9,10-methyleneoctadecanoate.

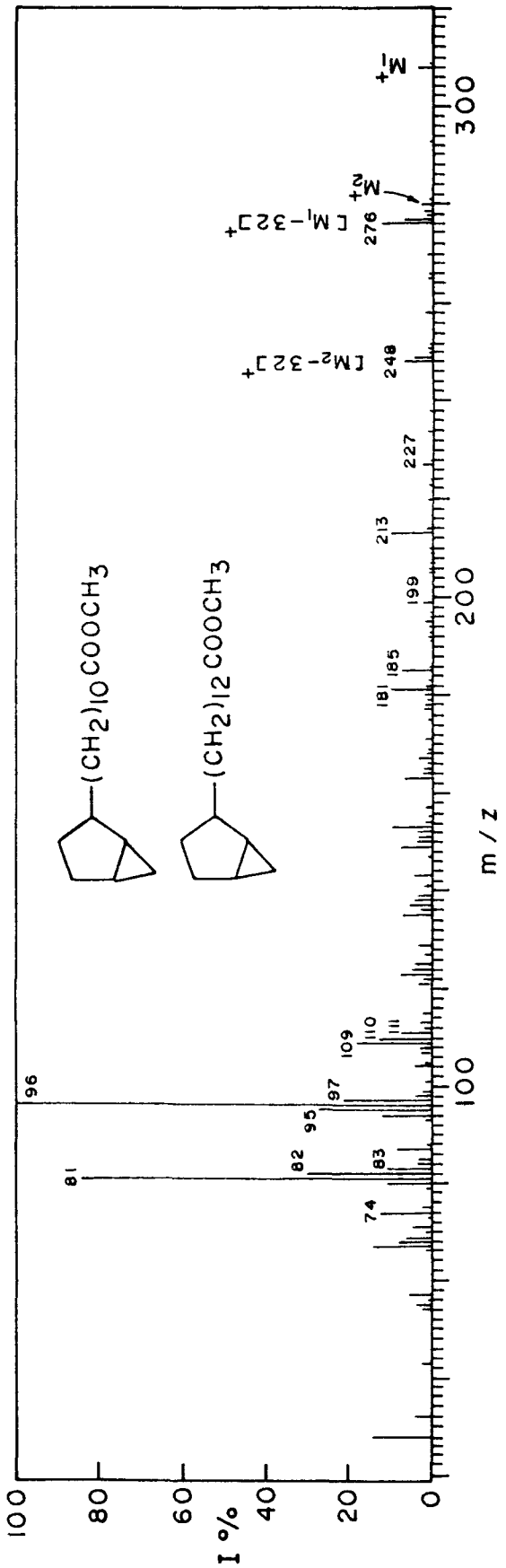


FIG. 4. Mass spectrum of 11-bicyclo (3.1.0) hexylundecanoate and 13-bicyclo (3.1.0) hexyltridecanoate.

The structures and percentage purities of the starting fatty acid esters, as well as the cyclopropanated products prepared by reacting the unsaturated ester (0.5 mmol) with diazomethane in the presence of palladium acetate (10 mg) as the catalyst, are given in Table 1. Terminal double bonds were found to be more reactive than the internal double bonds, as shown by the cyclopropanation of methyl undecenoate and of methyl oleate. Even three mmol of methyl undecenoate could be cyclopropanated completely with the same amount of the reagent as used for 0.5 mmol of methyl oleate. *Trans*-monoenoate reacted faster than *cis*-monoenoate as shown by the comparative results obtained on methyl elaidate and methyl oleate using the same quantities of the respective esters and the reagent. α, β-Unsaturated fatty acid esters were also found to be more reactive than the internal olefins as shown by the complete conversion of *trans*-2-docosenoate to *trans*-2,3-methylenedocosanoate with the same amount of reagent as used for methyl oleate for which the conversion was only 39.9%. When three mmol of *trans*-2-docosenoate were reacted with the same amount of reagent as used for methyl oleate, a conversion of ca. 78.5% was observed.

As with diiodomethane and zinc-copper couple, diazomethane and palladium acetate also yielded stereochemically pure cyclopropanated products. The *cis*-1,2-disubstituted monoenoate gave the corresponding *cis*-cyclopropane derivative without contamination from the *trans*-isomer and vice versa, as confirmed by the presence of signals at δ 0.8, 0.6 and -0.3 for *cis*-form and the absence of a complex signal from δ -0.12 to 0.6 for *trans*-isomer in the NMR spectrum. The data also show that the cyclopentene fatty acid esters (chaulmoograte and hydnocarpate) reacted faster than even methyl elaidate as shown by the extent of conversion when the same quantities of the reagent and the respective esters were used. The reagent thus provides a good procedure for preparing long-chain substituted bicyclo (3.1.0) hexane systems under mild conditions.

The synthesis of stereochemically pure cyclopropane derivatives from the corresponding unsaturated fatty acid methyl esters is generally carried out by the Simmons-Smith reaction (25) using diiodomethane and zinc-copper couple; the same results are achieved as shown here by using diazomethane in the presence of palladium acetate under milder conditions and for a shorter time.

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