Iodoazide Addition to Olefinic Esters and Their Reaction with Methanolic KOH

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ABSTRACT

Addition of iodine azide to methyl 10-undecenoate (I), methyl oleate/elaidate (III,IV) and methyl *trans*-2-hexadecenoate (VII) yielded methyl 10-azido-11-iodoundecanoate (II, ~ 100%), methyl *erythro/threo*-9(10)-azido-10(9)-iodooctadecanoate (V, VI) and methyl *erythro*-3-azido-2-iodohexadecanoate (VIII), respectively. The reaction of iodoazide adduct (II) with methanolic KOH yielded 10-azidoundec-10-enoic acid (IX) and 10-oxoundecanoic acid (X), while V and VI gave a mixture of 9(10)-oxooctadecanoic acid (XI). Adduct VIII, under the identical condition after esterification, gave 3 products, methyl 4-methoxy-*trans*-2-hexadecenoate (XII), 2-oxopentadecane (XIII) and methyl 3-methoxyhexadecanoate (XIV). The unusual behavior of VIII can be tentatively attributed to the role of adjacent carbonyl on the expected elimination of HI by methanolic alkali.

INTRODUCTION

The addition of pseudohalogens to unsaturated acids and the formation of respective adducts are very important as a variety of compounds can be synthesized via this route (1-10). Foglia et al. (11) investigated the addition of IN_3 to a few internal olefins. They have mentioned briefly the reaction with oleate. Thus, with a view to a more systematic study of the addition of IN_3 to long-chain acids, we considered the investigation of this reaction on terminal, internal *cis/trans* and α,β-unsaturated acids interesting.

EXPERIMENTAL PROCEDURES

Uncorrected melting points were reported. Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer in CCl_4 or as liquid films. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A60 spectrometer in deuterated chloroform. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS). The abbreviations s, d, m, q, br and t denote singlet, doublet, multiplet, quartet, broad and triplet. Mass spectrum was obtained with AEI MS-9 mass spectrometer. Thin layer chromatographic (TLC) plates were coated with Silica gel G, and a mixture of petroleum ether/ether/acetic acid (80:20:1, v/v/v) was used as developing solvent. The spots were visualized by charring after spraying with a 20% aqueous solution of perchloric acid. BDH-grade silica gel (60-120 mesh) was used for column chromatography.

MATERIALS AND METHODS

trans-2-Hexadecenoic acid (m.p. 53-54C) was prepared from palmitic acid by the method of Palameta and Prostenik (12), as adopted in our earlier study (13). Methyl undecenoate (I), oleate (III), elaidate (IV), and *trans*-2-hexadecenoate (VII) were prepared by refluxing the respective acids with H^+/MeOH.

Reaction of Iodine Azide (IN_3) with Olefinic Fatty Acid Esters (14)

Methyl esters I, III, IV and VII were treated with iodine azide as follows. To a stirred slurry of sodium azide (1.5 g, 0.023 mol) in 10 mL acetonitrile in an ice bath was slowly added iodine monochloride (1.83 g, 0.011 mol) over a period of 30 min. The reaction mixture was stirred for an additional 10 min and then 0.01 mol of the above-mentioned substrates were added. These were allowed to warm to room temperature and again stirred for an additional 8 hr. The reaction of α,β-ester (VII) took a long period, i.e., 4 days, for completion. In each case, a red brown slurry was obtained and was poured into 250 mL of water and the mixture was extracted with ether (250 mL) in 3 portions. These portions were combined and washed with 150 mL of 5% sodium thiosulphate, leaving a colorless ethereal solution. The solution was washed with 600 mL of water in 3 portions and dried over sodium sulphate.

Methyl 10-azido-11-iodoundecanoate (II)

This compound was formed by the reaction of methyl 10-undecenoate (I) with IN_3 according to the above procedure (yield ~100%). The trace of starting material was separated by column chromatography on silica gel and eluted with petroleum ether containing increasing amounts of ether. Elution with petroleum ether/ether (98:2, v/v) gave starting material (I). Further elution with petroleum ether/ether (94:6, v/v) yielded the compound II as a viscous liquid.

Analysis: calculations for $C_{12}H_{22}O_2N_3I$: C—39.23, H—6.0, N—11.44; found: C—39.31, H—6.11, N—11.38%. (Spectral values are recorded in the discussion part of the paper.)

Methyl *erythro/threo*-9(10)-azido-10(9)-iodooctadecanoate (V, VI)

Methyl oleate (III) and elaidate (IV) on reaction with IN_3 gave column chromatographic purified ca. 100% yield of V and VI respectively.

Analysis (V): calculations for $C_{19}H_{36}O_2N_3I$: C—49.03, H—7.74, N—9.03; found: C—48.97, H—7.81, N—9.2%; (VI) found: C—49.19, H—7.78, N—9.21%.

Methyl *erythro*-3-azido-2-iodohexadecanoate (VIII)

Compound (VIII, ~60%) was obtained by the reaction of VII with IN_3. Column chromatography separation with petroleum ether/ether (95:5, v/v) yielded the compound VIII as a viscous liquid.

Analysis: calculations for $C_{17}H_{32}O_2N_3I$: C—46.68, H—7.32, N—9.61; found: C—46.7, H—7.3, N—9.45%.

Reactions of Iodoazides with Methanolic KOH

One g of iodoazide of I, III, IV and VII were stirred with 2 g of KOH in 10 mL of methanol separately for 4-6 hr, at room temperature (~28 C). Then the reaction mixture was acidified with 20% HCl and finally worked up with ether. The ethereal layer was washed well with water several times. Esterification of the components was carried out using absolute methanol and sulphuric acid. Elemental analysis, IR and NMR were carried out on the esterified sample and sometimes before esterification.

Methyl 10-azido-11-iodoundecanoate (II, 0.0027 mol), when treated with methanolic KOH (20%, 10 mL), yielded 2 products, IX and X, as evidenced by TLC. Compounds were isolated by column chromatography.

10-Azidoundec-10-enoic Acid (IX)

Compound IX was obtained as a viscous oil by subjecting

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the reaction product to silica gel column separation using petroleum ether/ether (99:1, v/v).

Analysis (IX): calculations for $C_{11}H_{19}O_2N_3$: C–58.66, H–8.4, N–18.66; found: C–58.7, H–8.5, N–18.7%.

10-Oxoundecanoic Acid (X)

The second component (X) was eluted with petroleum ether/ether (96:4, v/v) and crystallized from acetone, m.p. 56-57 C (lit. m.p. 59 C) (15).

Analysis (X): calculations for $C_{11}H_{20}O_3$: C–66.0, H–10.0; found: C–66.11, H–9.98%.

9(10)-Oxooctadecanoic Acid (XI)

The iodoazide adducts V and VI (0.0021 mol each) were treated with methanolic KOH (20%, 10 mL) and the product was worked up as described above. The solid compound (XI) isolated by column chromatography was crystallized from acetone and had a m.p. 71-72 C.

Analysis (XI): calculations for $C_{18}H_{34}O_3$: C–72.48, H–11.40; found: C–72.40, H–11.3%.

Reaction of VIII with Methanolic KOH

The iodoazide adduct VIII (0.0023 mol), when treated for 6 hr with methanolic KOH (20%, 10 mL), and subsequently esterified by refluxing (2 hr) with absolute methanol/H^+ yielded a product that showed 3 distinct spots on TLC. A column of Silica gel G (10 g), prepared in petroleum ether, was charged with total crude mixture (0.67 g) and the column was eluted with a mixture of petroleum ether/ether (98:2, v/v). The TLC-monitored elutes were combined to give methyl 4-methoxy-*trans*-2-hexadecenoate (XII) as a colorless liquid (0.34 g, ca. 50.7%).

Analysis: calculations for $C_{18}H_{34}O_3$: C–72.45, H–11.48; found: C–72.31, H–11.41%.

Elution with a mixture of petroleum ether/ether (93:7, v/v) followed by crystallization from petroleum ether gave 2-oxopentadecane (XIII), m.p. 41 C (0.146 g, ca. 21.7%).

Analysis: calculations for $C_{15}H_{30}O$: C–79.20, H–13.27; found; C–79.35, H–13.35%.

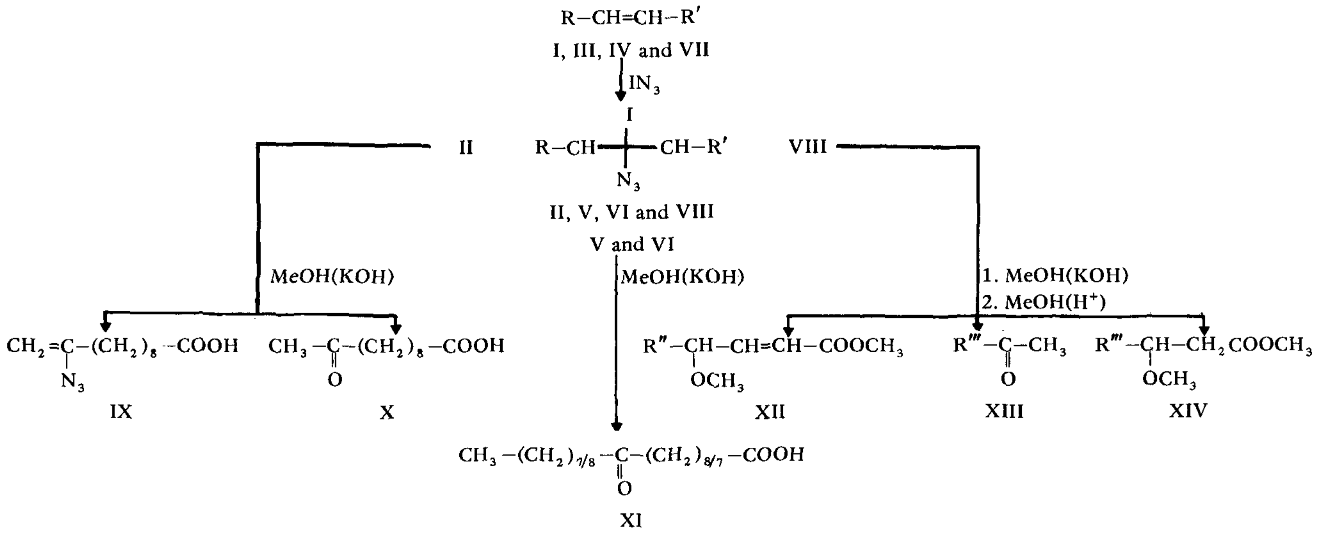
Subsequent elution with a mixture of petroleum ether/ether (87:13, v/v) gave methyl 3-methoxyhexadecanoate (XIV) (0.10 g, ca. 15.8%).

RESULTS AND DISCUSSION

Methyl 10-undecenoate (I) was treated with IN_3 according to the procedure of Fowler et al. (14). The reaction product showed a spot on TLC just below the spot of the starting material. The iodoazide product II was separated from I by subjecting the reaction product to a silica gel column. Compound II gave a positive Beilstein test and was analyzed for $C_{12}H_{22}O_2N_3I$. IR spectrum had bands at 2100 (N_3), 1735 ($\underline{C}OOCH_3$), 1190 and 1170 (C–O) cm^{-1}. The NMR of II gave signals at δ 3.93 t (2H, $-C\underline{H}_2-I$), 3.75 m (1H, $C\underline{H}-N_3$), 3.6 s (3H, $COOC\underline{H}_3$), 2.3 m (2H, $C\underline{H}_2-COOCH_3$) and 1.35 br,s (chain $C\underline{H}_2$). The formation of Markovnikov product methyl 10-azido-11-iodoundecanoate (II) showed regioselectivity of the reaction. Its mass spectrum gave the molecular ion peak at m/z 367. The genesis of structure-revealing fragment ions support structure II (Scheme II, relative intensities are given in parenthesis).

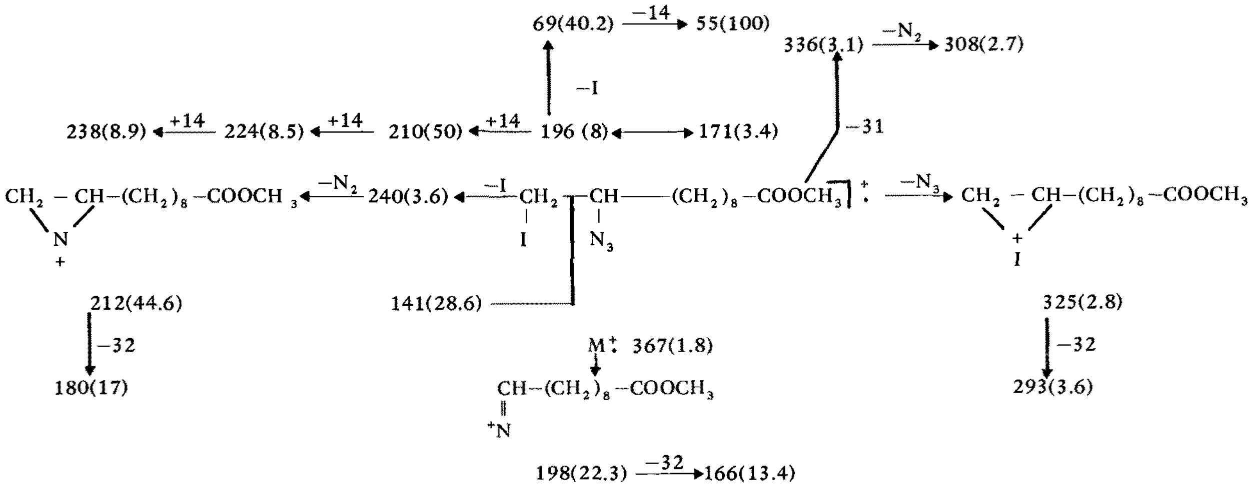
Similar reactions with methyl oleate and elaidate (III and IV) yielded the products methyl *threo*-9(10)-azido-10(9)-iodooctadecanoate (V) and methyl *erythro*-9(10)-azido-10(9)-iodooctadecanoate (VI) (Scheme I). Both gave a positive Beilstein test and corresponded to the formula $C_{19}H_{36}O_2N_3I$. The IR and NMR spectra of the diastereoisomers obtained from *cis*- and *trans*-9-octadecenoates are very similar. The IR spectrum of *threo* adduct showed bands at 2100 (N_3), 1740 ($\underline{C}OOCH_3$), 1240, 1190, 1160, 1110 and 1010 (C–O) cm^{-1} whereas the *erythro* adduct showed a band at 1360 cm^{-1} instead of 1110 cm^{-1}. The NMR of these compounds (V and VI) further supported the structure and gave signals at δ 4.0 m (1H, $C\underline{H}-I$), 3.7 s (3H, $COOC\underline{H}_3$), 3.6 m (1H, $C\underline{H}-N_3$, in part merged with ester proton), 2.3 m (2H, $C\underline{H}_2-COOCH_3$), 1.35 br,s (chain $C\underline{H}_2$), and 0.9 t (3H, $C\underline{H}_3-$). The methine proton is slightly greater in *erythro* compared with the *threo* isomer.

A similar reaction of methyl *trans*-2-hexadecenoate (VII) with IN_3 afforded methyl 3-azido-2-iodohexadecanoate (VIII), which moves just above the starting compound (VII) on TLC. Product VIII was isolated by column chromatography as described earlier. It responded positively to the Beilstein test. Microanalysis of this product gave the composition as $C_{17}H_{32}O_2N_3I$, with characteristic IR bands at 2060 (N_3), 1730 ($\underline{C}OOCH_3$), 1180, 1160, 1115 and

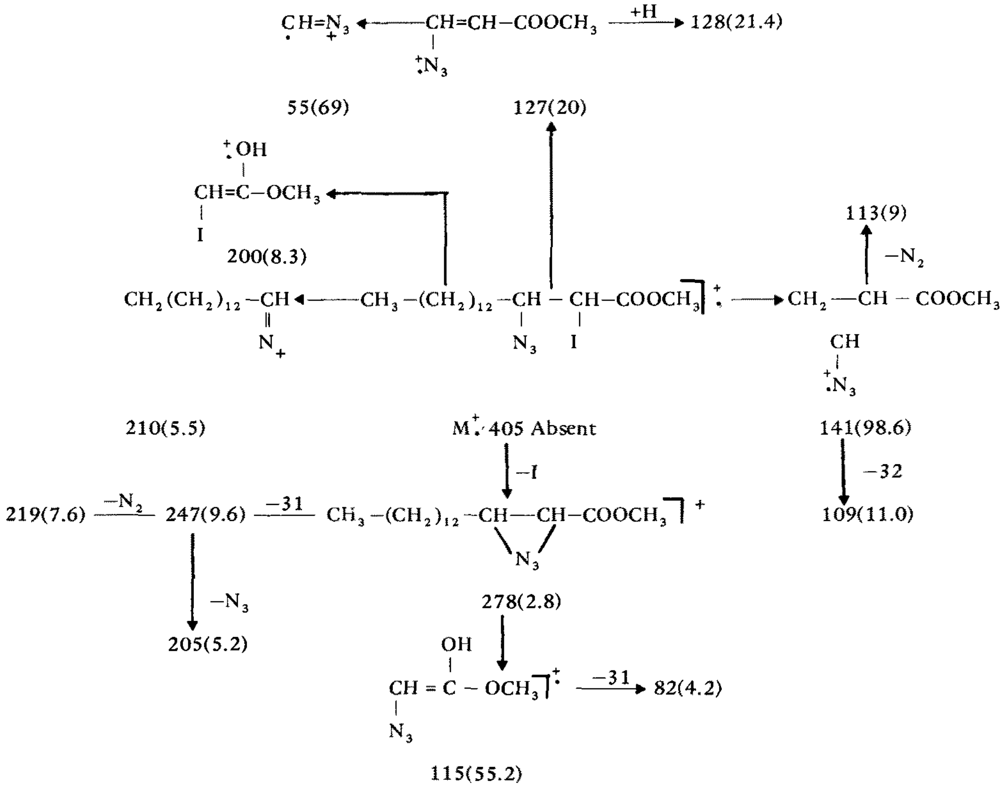


where, I and II: R = H, $R' = (CH_2)_8-COOCH_3$; III, IV, V and VI: $R = CH_3-(CH_2)_7$, $R' = (CH_2)_7-COOCH_3$;
VII and VIII: $R = CH_3(CH_2)_{12}$, $R' = COOCH_3$; XII: $R'' = CH_3(CH_2)_{11}-$; XIII and XIV: $R''' = CH_3(CH_2)_{12}$.

SCHEME 1



SCHEME 2



SCHEME 3

1005 cm^{-1} (C–O). The NMR spectrum gave conclusive support in favor of VIII. It gave signals at δ 4.23 m (1H, $-\underset{\underset{\text{I}}{|}}{\underline{\text{C}}\underline{\text{H}}}-\text{COOCH}_3$), 4.05 m (1H, $\text{C}\underline{\text{H}}\text{N}_3$), 3.7 s (3H, $\text{COOC}\underline{\text{H}}_3$), 1.3 br,s (chain $\text{C}\underline{\text{H}}_2$) and 0.9 t (3H, terminal $\text{C}\underline{\text{H}}_3$). The mass spectrum of methyl 3-azido-2-iodohexadecanoate (VIII) gave no molecular ion peak at m/z 405 but the highest ion peak was observed at m/z 278 (M–I) and other characteristic fragmentation ions are shown in Scheme III.

When the iodoazide (II) was treated with methanolic KOH, mainly a mixture of 2 products, IX (liquid, major) and X (solid, minor) (15) were obtained. Both products gave negative Beilstein tests. The compound IX gave unsaturation test and corresponded to the formula $\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}_3$ by its elemental analysis. IR spectrum gave bands at 2100 (N_3), 1640 (C=C), 1700 cm^{-1} ($\text{C}\underline{\text{O}}\text{OH}$). The NMR spectrum of IX showed signals at δ 5.5 and 4.6 m (1H each, $\text{C}\underline{\text{H}}_2=\underset{\underset{\text{N}_3}{|}}{\text{C}}-$), 2.35 m (2H, $\text{C}\underline{\text{H}}_2-\text{COOH}$), 2.0 m ($\text{CH}_2=\underset{|}{\text{C}}-\text{C}\underline{\text{H}}_2$), 1.35 br,s (chain $\text{C}\underline{\text{H}}_2$) and δ 10.1 s (1H, $\text{COO}\underline{\text{H}}$).

The solid product (X) was characterized as 10-oxoundecanoic acid (15), m.p. 56-57 C and m.m.p. 56-57 C. Its microanalysis supported the formula $\text{C}_{11}\text{H}_{20}\text{O}_3$. In the IR spectrum, bands at 3300-3150 ($\text{COO}\underline{\text{H}}$), 1720 (CO) and 1710 ($\text{C}\underline{\text{O}}\text{OH}$) cm^{-1} were observed. The NMR spectrum gave bands at δ 2.36 m (4H, $^9\text{C}\underline{\text{H}}_2$ and $\text{C}\underline{\text{H}}_2-\text{COOH}$) and 2.05 s (3H, $\text{C}\underline{\text{H}}_3-\text{CO}-$), besides the usual signals for fatty acid.

An idea of the course of the reaction of II (0.0027 mol) with the base was obtained by carrying out the reaction at a lower concentration of methanolic KOH (5%, 10 mL). In this condition only vinyl azide (IX) was formed in 80% yield and no indication occurred of the formation of keto derivative. From this we inferred that in the presence of excess methanolic KOH, the major product, vinyl azide, is finally converted to 10-oxoundecanoic acid (X) via enolization.

When V and VI were treated with methanolic KOH, an isomeric mixture of 9(10)-oxooctadecanoic acids (XI) was isolated (elemental analysis of the compound corresponded to formula $C_{18}H_{34}O_3$). The crystalline product melted at 71-72 C (16). IR spectrum showed bands at 1715 (C=O) and 1700 cm^{-1} ($\underline{CO}OH$). NMR spectrum gave a diagnostic signal at δ 2.3 m (6H, $C\underline{H}_2-\underset{\underset{O}{\|}}{C}-C\underline{H}_2$ and $C\underline{H}_2-COOH$) in addition to the other usual signals of a fatty acid.

Compound VIII was also treated with methanolic KOH and then esterified. Unlike other systems, 3 unusual products were formed. These compounds have been separated with the help of column chromatography and characterized as methyl 4-methoxy-*trans*-2-hexadecenoate (XII), 2-oxopentadecane (XIII) and methyl 3-methoxyhexadecanoate (XIV).

Compound XII did not respond to the Beilstein test, indicating the absence of halogen. Its analysis corresponded to $C_{18}H_{34}O_3$. The IR spectrum was also devoid of an N_3 band and gave bands at 1730 ($CH=CH-\underline{CO}_2CH_3$), 1650 ($\alpha,\beta$-unsaturation), 980 (*trans*-olefin), 1160 ($C-OCH_3$), 1195, 1120 and 1040 cm^{-1} (C–O). The NMR spectrum was found to be more informative in elucidating the structure. It gave signals at δ 6.9 d,d (1H, $-C\underline{H}=CH-COOCH_3$, J = 15 and 5 Hz), 6.0 d (1H, $-CH=C\underline{H}-COOCH_3$, J = 15 Hz), 4.1 m (1H, $C\underline{H}-OCH_3$), 3.7 s (3H, $COOC\underline{H}_3$), 3.6 s (3H, $OC\underline{H}_3$), 1.3 br,s (chain $C\underline{H}_2$) and 0.9 t (3H, terminal $C\underline{H}_3$). The presence of a double bond conjugated with ester carbonyl is supported by the presence of signals at δ 6.9 and 6.0 as mentioned above. The magnitude of splitting suggested the *trans* configuration of olefinic bond. From these data, the structure was formulated as methyl 4-methoxy-*trans*-2-hexadecenoate (XII).

Compound XIII (m.p. 41 C) gave a positive DNP test. Its IR spectrum showed an intense band at 1720 (C=O), 1160 cm^{-1} (C–O) and corresponded to the formula $C_{15}H_{30}O$. The NMR of this compound (XIII) gave conclusive evidence in favor of this structure. It did not give any signal at δ 3.7 ($COOC\underline{H}_3$). Rather, it gave characteristic signals at δ 2.3 m (2H, $-C\underline{H}_2-\overset{\overset{O}{\|}}{C}-$), 2.05 s (3H, $C\underline{H}_3-CO-$), 1.3 br,s (chain $C\underline{H}_2$) and 0.9 t (3H, terminal CH_3). This compound (XIII) was first suspected to be an oxo acid. The compound (XIII) defied all attempts at esterification, ruling out the presence of carboxylic group. Hence, we concluded that VIII has undergone partial decarboxylation, resulting in the formation of XIII.

The elemental analysis of the last compound (XIV) corresponded to formula $C_{18}H_{36}O_3$. IR bands were found at 1725 ($\underline{CO}OCH_3$), 1160 (OCH_3), 1090 and 1010 cm^{-1} (C–O). Its NMR spectrum gave signals at δ 3.7 m (1H, $C\underline{H}-OCH_3$, in part merged with ester proton), 3.62 s (3H, $-COOC\underline{H}_3$), 3.3 s (3H, $-OC\underline{H}_3$), 2.38 d,d (2H, $-C\underline{H}_2-COOCH_3$), 1.75 br,s (chain $C\underline{H}_2$) and 0.89 t (3H, terminal $C\underline{H}_3$).

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