

Studies on Nitroschlorination of Olefinic Fatty Acids: I.

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ABSTRACT

Nitroschlorination of methyl oleate yielded methyl 9(10)-chloro-10(9)-nitrosooctadecanoate, methyl 9(10)-chloro-10(9)-oximinooctadecanoate and an abnormal product 9(10)-chloro-10(9)-nitriminooctadecanoate. A similar reaction with 10-undecenoate yielded a dimer of methyl 10-chloro-11-nitrosoundecanoate, methyl 10-chloro-11-oximinoundecanoate and methyl 10-chloro-11-nitriminoundecanoate. On the other hand, methyl *trans*-2-docosenoate reacted reluctantly up to 10%, yielding methyl 2-oximino-3-chlorodocosanoate. All these products have been characterized with the help of compositional and spectral data.

INTRODUCTION

Nitrosylchloride (NOCl) addition represents one of the simplest ways of elaborating a carbon-nitrogen bond directly from an unsaturated compound. Addition of NOCl to long-chain olefinic derivatives has formed the basis of a number of patents for the manufacture of surface-active agents. Reviews (1, 2) on NOCl describe normal and anomalous reaction products in the nitroschlorination of alkenes. After the first report (3) of the addition of NOCl to oleic and elaidic acids, Miller et al. (4) repeated the investigation but no attempts were made to isolate and characterize the individual products of the reaction. In view of the incomplete published data it was considered desirable to carry out a systematic study of nitroschlorination using a variety of olefinic acids as substrate. This paper reports the results of *in situ* nitroschlorination carried out with three types of olefinic acids: terminal, midchain and α,β -unsaturated fatty acids.

EXPERIMENTAL PROCEDURES

Melting points were observed on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer (liquid film or 1% solutions in carbon tetrachloride). Nuclear magnetic resonance (NMR) spectra were recorded in CDCl₃ using a Varian A60 NMR spectrometer. Chemical shifts were measured in ppm downfield from internal tetramethylsilane ($\delta = 0$). The samples were run as 10% solution in CDCl₃/CCl₄. The abbreviations s, d, t, q, m, um, mc, br, and w denote singlet, doublet, triplet, quartet, multiplet, unresolved multiplet, multiplet centered at, broad and weak, respectively. Only diagnostic and structure specific signals are discussed in Results and Discussion. 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) was used as developing solvent. The spots were visualized by charring after spraying with a 20% aqueous solution of perchloric acid. Petroleum ether refers to a fraction of bp 40–60 C.

Preparation of Nitrosyl Chloride

Nitrosyl chloride was generated *in situ* by the action of hydrochloric acid on isoamyl nitrite as described by Beckham et al. (1).

Nitroschlorination of Methyl Oleate

Methyl oleate (I) was prepared from pure oleic acid. A mixture of 3 g (0.01 mol) of methyl oleate and 1.5 g (0.012 mol) of isoamyl nitrite in 50 mL of methylene chloride was cooled to ca. 0 C in an ice-salt bath and 1.7 mL of conc HCl was added dropwise with stirring in 30 min. Stirring was

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continued at ice bath temperature for 1.5 hr. A deep blue colored solution was obtained. The reaction mixture was washed with water, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The generated isoamyl alcohol was removed by partitioning between 70% methanol and petroleum ether (1:1). The petroleum ether fraction was dried over anhydrous Na₂SO₄ and the product obtained after evaporation of the solvent was chromatographed over a column of silica gel (50 g). Homogeneity of eluted product was checked by TLC. Elution with petroleum ether/ether (98:2, v/v) gave fraction 1. This fraction was obtained in major amount (~75%) as a blue liquid. The combustion and spectral data of this fraction are as follows.

Anal. calcd. for C₁₉H₃₆NO₃Cl: C, 63.04; H, 10.02; N, 3.84. Found: C, 63.12; H, 10.05; N, 3.85. IR (neat): 1730

$\begin{array}{c} \text{O} \\ || \\ \text{(ester-C)} \end{array}$, 1570 (N=O), 1110 (C-N), 710 (C-Cl) cm⁻¹. NMR (CCl₄): δ 3.88 (1H, -CHCl-), 3.66 (s, 3H, -C-OCH₃), 3.35 [1H, -CH(NO)] 2.24 (2H, methylene protons α to ester group), 1.62 (2H, methylene protons α to -CHCl-), 1.35 (br, s, shielded chain methylene protons), and 0.88 (distorted t, 3H, terminal -CH₃).

Subsequent elution with petroleum ether/ether (95:5, v/v) gave fraction 2 in minor amount (20%, R_f 0.3). Anal. calcd. for C₁₉H₃₆NO₃Cl: C, 63.04; H, 10.02; N, 3.84. Found: C, 63.10; H, 10.01; N, 3.86. IR (neat): 3450, 1730, 1690, 720 cm⁻¹. NMR (CDCl₃): δ 7.35, 3.9, 3.65, 2.24, 1.35 and 0.88.

Reaction of Methyl Oleate with Excess NOCl

A mixture of 3 g (0.01 mol) of methyl oleate and 2.5 g (0.02 mol) of isoamyl nitrite in 75 mL of methylene chloride was cooled to ca. 0 C in an ice-salt bath and 2.1 mL of conc HCl was added dropwise with stirring in 45 min. Stirring was continued at ice bath temperature for 2.5 hr. Compound (IV) was produced in addition to compounds (II) and (III). The reaction product was worked up as described earlier. The compound (IV), having an R_f value (0.5) higher than oxime (III), was characterized as methyl 9(10)-chloro-10(9)-nitriminooctadecanoate. The combustion and spectral data of compound (IV) are as follows.

Anal. calcd. for C₁₉H₃₅N₂O₄Cl: C, 58.37; H, 9.02; N, 7.19. Found: C, 58.39; H, 8.98; N, 7.18. IR (neat): 1730, 1640, 1550, 1360 and 710 cm⁻¹. NMR (CCl₄): δ 4.14, 3.66, 2.62 [t, 2H, -CH₂-C-(=NNO₂)-], 2.34, 1.33, 0.88.

Nitroschlorination of V

Nitroschlorination of methyl 10-undecenoate (V, 2.5 g) was carried out with isoamyl nitrite (2.0 g) as described in case of methyl oleate (I). The reaction product showed four components on TLC and were chromatographed over a column of silica gel (40 g). Only three components were isolated and characterized. Elution with petroleum ether gave a blue-colored liquid which was not analyzed further on account of being unstable. Subsequent elution with petroleum ether/ether (90:5; v/v) gave methyl 10-chloro-11-nitriminoundecanoate (IX, 16%) as a green oil.

Anal. calcd. for C₁₂H₂₁N₂O₄Cl: C, 49.23; H, 7.23; N, 9.56. Found: C, 49.21; H, 7.22; N, 9.58. IR (neat): 1730, 1630, 1550 and 720 cm⁻¹. NMR (CCl₄): δ 6.16 (1H, -CH=NNO₂), 4.6, 3.66, 2.24, 1.32.

Further elution with a mixture of petroleum ether/ether

(90:10; v/v) gave methyl 10-chloro-11-oximinoundecanoate (**VIII**, 20%, mp 42 C). Anal. calcd. for $C_{12}H_{22}O_3NCl$: C, 54.64; H, 8.40; N, 5.31. Found: C, 54.62; H, 8.48; N, 5.40. IR (Nujol): 3300, 1730, 1680 and 720 cm^{-1} . NMR ($CDCl_3$); δ 7.4, 6.4, 4.34, 3.66, 2.24, 1.35.

Subsequent elution with a mixture of petroleum ether/ether (60:40; v/v) gave a dimer of methyl 10-chloro-11-nitrosoundecanoate melting at 95 C (**VII**, 34%). Anal. calcd. for $(C_{12}H_{22}O_3NCl)_2$: C, 54.64; H, 8.40; N, 5.31. Found: C, 54.60; H, 8.35; N, 5.38. IR (Nujol): 2910, 2840, 1725, 1450, 1370, 1270, 1205, 1180, 1160, 710 cm^{-1} .

NMR ($CDCl_3$): δ 4.58 (6H, $-\text{CHCl}-$ and $-\text{CH}_2-\text{N}^+=\text{O}$) and 1.33.

Deoxygenation of VIII by Levulinic Acid and HCl (5)

The oxime (200 mg) was mixed with 30 parts of a solution of 9 vol of levulinic acid and 1 vol of 1 N HCl. This mixture was placed in a Erlenmeyer flask and stirred at room temperature for 3 hr. As the oxime was not immediately soluble, it gradually dissolved in 3 hr. The solution was then diluted with water, extracted with methylene chloride, and extracts washed free of levulinic acid with bicarbonate solution. The methylene chloride was removed and the carbonyl compound (**X**) recovered by chromatography. IR (neat): 2910, 2840, 1730, 1450, 1370 and 710 cm^{-1} .

Preparation of α,β -Unsaturated Fatty Acid

trans-2-Docosenoic acid was prepared by α -bromination of docosanoic acid using bromine and red phosphorus followed by dehydrohalogenation (6), and this was characterized as described earlier (7).

Nitroschlorination of XI

To the solution of methyl *trans*-2-docosenoate (2.0 g) in 100 mL methylene chloride was added 2.0 g of isoamyl nitrite. The mixture was cooled to ca. 0 C in an ice-salt bath. Conc HCl (2.5 mL) was added dropwise with constant stirring in 30 min. The reaction flask was kept in a refrigerator at 0–5 C for about a month. The reaction mixture was worked up in the manner described for methyl oleate (**I**). The reaction product showed the presence of three components on analytical TLC. The major component corresponded to starting material. Column separation of the products revealed that only 10% of substrate (**XI**) had reacted, yielding 4% and 6% of **XII** and **XIII**, respectively. Starting material (**XI**) was eluted with petroleum ether.

Elution with petroleum ether/ether (90:5; v/v) gave **XII**. Anal. calcd. for $C_{23}H_{43}O_4N_2Cl$: C, 61.79; H, 9.69; N,

6.26. Found: C, 61.74; H, 9.68; N, 6.28. IR (neat): 1730, 1640, 1550, 1360 and 710 cm^{-1} . NMR(CCl_4): δ 4.1, 3.64, 1.35 and 0.9.

Subsequent elution with petroleum ether/ether (90:10; v/v) gave **XIII**. Anal. calcd. for $C_{23}H_{44}O_3NCl$: C, 66.07; H, 10.60; N, 3.34. Found: C, 66.12; H, 10.61; N, 3.32. IR (neat): 3300, 1730, 1640 and 710 cm^{-1} . NMR($CDCl_3$): δ 7.24, 3.9, 3.66, 1.25 and 0.89.

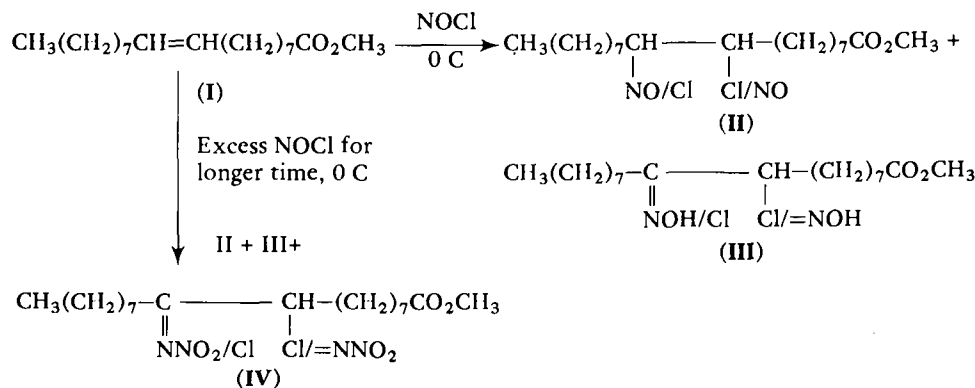
RESULTS AND DISCUSSION

Methyl oleate (**I**) on treatment with approximately stoichiometric quantity of nitrosyl chloride in situ at 0 C gave essentially a quantitative yield of **II** as an azure oil, in a mixture with a little of its isomerised oximino form (**III**), (Scheme 1). A column separation of the product yielded a nitrosyl chloride adduct which is probably a mixture of positional isomers methyl 9(10)-chloro-10(9)-nitrosooctadecanoate (**II**) as evidenced by two closely associated spots (R_f 0.8 and 0.85) on TLC. A minor fraction 2, of lower R_f (0.24), was characterized as the oximino form (**III**) of product (**II**). This fraction was also believed to be an isomeric mixture of oximes methyl 9(10)-chloro-10(9)-oximinooctadecanoate (**III**).

Fraction 1 (compound **II** and negligible quantity of **III**) gave a positive Beilstein test and analyzed for $C_{19}H_{39}NO_3Cl$. The IR spectrum showed, besides the usual bands, absorptions at 1570 ($N=O$), 1110 ($C-N$) and 710 cm^{-1} ($C-Cl$), indicative of the nitrosochloride functions. NMR spectrum displayed an unresolved multiplet at δ 4.88 for methine proton adjacent to the chlorine atom and another unresolved multiplet centered at δ 3.35 assigned to nitroso adjacent methine proton. A signal at δ 1.62 was also observed due to methylene proton α to the $-\text{CHCl}-$ ($-\text{CHCl}-\text{CH}_2-$).

Microanalysis of fraction 2 (compound **III**) supported the formula $C_{19}H_{36}NO_3Cl$ (positive Beilstein test). IR spectrum of **III** displayed bands at 3450 (OH), and 1640 cm^{-1} ($C=N$), indicative of the oximino group. NMR spectrum showed an apparent multiplet centered at δ 7.35 for one D_2O exchangeable proton attributable to the hydroxyl proton of oximino group ($=N-OH$). Another signal at δ 3.9 is attributed to the methine proton adjacent to the Cl atom ($-\text{CHCl}-$).

Presence of hydrogen on the carbon-carrying nitrosyl group permits rearrangement to the oximes (1). For most of the examples cited in the literature, this rearrangement is spontaneous or is prompted under the mildest conditions. The product chlorooxime is usually a solid, more stable than the nitroso isomer. But in this case the isomerization seems to be very slow. About 0.5–1.0% of oxime was already present in the freshly prepared compound (**II**) as



SCHEME 1

evidenced by TLC, IR, and NMR. Oxime content increased at room temp. to a maximum of ca. 2% after ca. 2 weeks.

Many nitroschloro compounds dimerize to white solids (1). We have found no evidence for appreciable dimerization of **II**. The persistent blue color at 0–5 C and the presence of the strong IR nitrosyl band as well as nonformation of any solid adduct, all indicate little, if any, dimer formation. Precedents exists for the suggestion that dimer formation is inhibited due to steric hindrance.

By treating with an excess of NOCl for a longer time, methyl oleate gave a product (**IV**, 10%) in addition to **II** and **III**. The product (**IV**), having an R_f value greater than the R_f of oxime (**III**) was characterized as methyl 9(10)-chloro-10(9)-nitriminoctadecanoate. The formation of nitrimine was not reported by Miller et al. (4). The nitrimine (**IV**) is formed by the oxidizing action of NOCl upon oxime (**III**). The oxidizing action of NOCl to convert an oxime into nitromine was first reported by Shiue et al. (8, 9) and later confirmed by other workers (10).

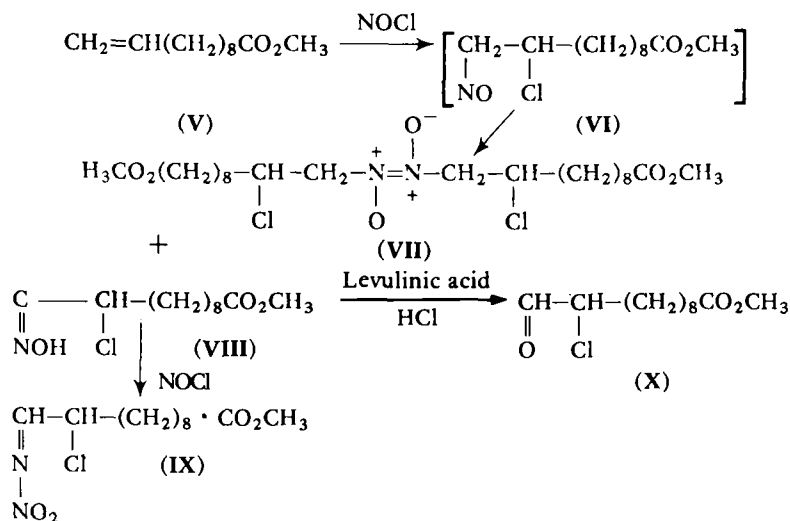
Characterization of IV

Strong IR bands at 1550 and 1360 (NO_2) cm^{-1} and a medium band at 1640 ($\text{C}=\text{N}$) cm^{-1} characteristic of nitrimines (11) were observed. NMR spectroscopy was useful in confirming the structure of product (**IV**). In addition to expected signals for the remainder of the molecule (δ 3.66, 2.24, 1.33 and 0.88), diagnostically useful signals were observed at δ 4.14 (mc) due to the methine proton adjacent to Cl atom ($-\text{CHCl}-$) and at δ 2.62 (t) for methylene group α to the nitrimino group [$-\text{CH}_2-\text{C}(=\text{NNO}_2)-$].

Nitroschlorination of Methyl 10-Undecenoate (V)

In order to probe the regioselectivity of NOCl addition on an unsymmetrically substituted olefinic substrate, methyl ester of 10-undecenoic acid (**V**) was selected as a model compound for the nitroschlorination reaction.

Reaction of methyl 10-undecenoate (**V**) with NOCl resulted in the formation of four distinct products (**VI**–**IX**) as evidenced by analytical TLC (Scheme 2). These components were separated by silica gel column chromatography. Formation of a chloronitroso product (**VI**) was indicated by the appearance of a bluish green color in the reaction mixture. IR spectrum of the product also revealed the formation of nitrosyl chloride adduct. Work-up of the reaction mixture yielded no appreciable amount of the adduct in the pure form as it easily rearranged to an oxime.



SCHEME 2

Characterization of VII

The product (**VII**) separated as white solid (mp 95 C), gave a positive Beilstein test and analyzed for $(\text{C}_{12}\text{H}_{22}\text{O}_3\text{NCl})_2$. The IR spectrum showed absorptions at 1270 cm^{-1} , indicative of dimer formation. The absence of nitrosyl band in the region 1520–1570 cm^{-1} further supported the dimer formation. The NMR spectrum also corroborated the structure of **VII** as a dimer of methyl 10-chloro-11-nitrosoundecanoate. The NMR spectrum exhibited the significant signal at δ 4.58 for six protons due to the methine protons adjacent to chlorine atoms and methylene groups adjacent to nitrogen ($-\text{CH}_2-\text{N}^+=$).

Other usual fatty ester signals were observed at δ 3.66 (S,

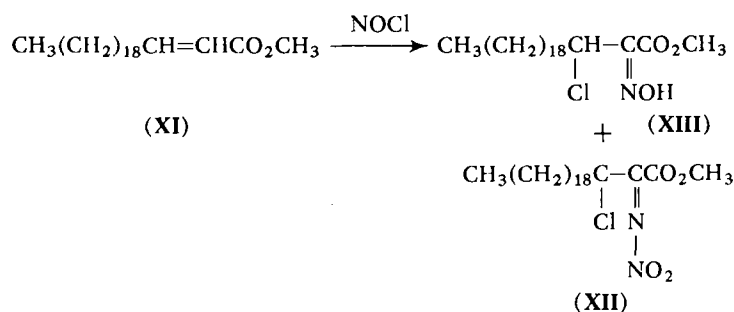
6H, ester CH_3), 2.23 (protons α to the ester C group) and 1.33 (br, s, shielded chain $-\text{CH}_2-$). The dimer (**VII**) appears to have a *trans* structure as suggested by Gowenlock and Luttko (12) in their IR spectral studies on dimers of nitroso compounds.

Characterization of VIII

The compound was separated as a white solid (mp 42 C, R_f 0.2). It gave a positive Beilstein test. The IR spectrum gave absorptions at 3300 (OH) and 1680 ($\text{C}=\text{N}$) cm^{-1} attributed to the oximino group and at 720 cm^{-1} to C–Cl linkage. Its NMR in addition to usual signals exhibited an apparent singlet at δ 7.4 which can be assigned to the proton of oximino group ($=\text{NOH}$). This proton was exchangeable with D_2O . The proton at C_{11} appeared at δ 6.4 ($-\text{CH}=\text{NOH}$). Methine proton adjacent to chlorine atom displayed a signal at δ 4.34. Thus the spectral data agreed with the structure as methyl 10-chloro-11-oximinoundecanoate (**VIII**).

Further support to the structure was obtained from characterization of the corresponding carbonyl compound (**X**) obtained by the deoximation of the product (**VIII**). In this case the compound formed was shown to have an aldehydic group. The presence of aldehydic group was confirmed with the help of chemical tests and spectroscopy. It gave yellow color on heating with NaOH and reduces Fehling's solution. It was also found positive to DNP test on TLC. IR spectrum showed the disappearance of bands at 3300 and 1680 cm^{-1} (shown by oxime) and new bands appeared at 1710 ($\text{C}=\text{O}$) and 2800 (aldehyde C–H str) cm^{-1} attributed to the aldehydic functions.

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SCHEME 3

Characterization of IX

This compound migrated ahead of oxime (VIII) and gave a positive Beilstein test. IR spectrum showed bands at 1630 (C=N) and 1550 (NO₂) cm⁻¹. NMR showed significant signals at δ 6.16 for 1H at C-11(—CH=NNO₂) and a multiplet centered at δ 4.6 for methine proton adjacent to chlorine atom (—CHCl). The product was assigned the structure as methyl 10-chloro-11-nitriminoundecanoate (IX).

The formation of only one isomer (VI) in the nitrosochlorination of 10-undecenoate indicated that the reaction is regiospecific and thus may be believed to be in accordance with Markownikoff's rule.

Nitrosochlorination of Methyl *trans*-2-Docosenoate (XI)

Methyl *trans*-2-docosenoate treated with NOCl in the same way as described in earlier cases except the duration was extended to about a month. Only ca. 10% of the compound (XI) reacted giving two products (XII, XIII) (Scheme 3).

Characterization of XIII

The compound (XIII) gave satisfactory elemental analysis for C₂₂H₄₄O₃NCl (positive Beilstein test). It gave informative IR bands at 3300 and 1640 cm⁻¹, indicative of the oximino group. NMR spectroscopy was useful in confirming the structure of compound (XIII) as methyl 2-oximino-3-chlorodocosanoate. A signal was obtained for a single proton at δ 7.24 (disappeared on addition of D₂O) attributed to the oximino group proton (=NOH). A triplet was observed at δ 3.9 for methine proton adjacent to chlorine atom. The chemical shift and multiplicity of —CHCl— signal confirms the attachment of chlorine atom to C-3 instead of C-2.

Characterization of XII

The compound (XII) analyzed for C₂₃H₄₃O₄N₂Cl and gave a positive Beilstein test. The IR spectrum gave bands at 1640 (C=N), 1550 and 1360 (NO₂) cm⁻¹, characteristic of nitrimino group. The NMR data were also consistent with the structure methyl 2-nitrimino-3-chlorodocosanoate

for the compound (XII). It exhibited a triplet at δ 4.1 for methine proton adjacent to chlorine atom (—CHCl—) as was observed in case of XIII.

The formation of compounds (XII) and (XIII) can well be explained through the nitrosochlorination of compound (XI) as the primary reaction. The isomerization of nitroso compound will give an oxime (XIII) which on subsequent oxidation by NOCl will provide a nitrimino (XII).

In the case of α,β-unsaturated acid (XI), only one isomer resulted during nitrosochlorination. The presence of

adjacent electron withdrawing group (—C(=O)—OCH₃) is involved in its formation.

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