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SYNTHESIS OF METHYL 9-NONYLOXYNONANOATE – THE REDUCTION PRODUCT OF AN UNUSUAL UNSATURATED ETHER FORMED BY ENZYMIC OXIDATION OF LINOLEIC ACID

R.F. CURTIS and R.G. FENWICK
Agricultural Research Council Food Research Institute, Colney Lane, Norwich, NOR 70F, England

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An unambiguous synthesis of methyl 9-nonyloxynonanoate confirms the structure postulated for the reduction product of an unusual fatty acid from Solanum tuberosum and hence the structure of the latter acid as 9-(nona-1′,3′-dienyloxy) non-8-enoic acid.

1. Introduction

Galliard and Phillips recently reported [1] the isolation of a novel unsaturated fatty acid from homogenates of tuber tissue of Solanum tuberosum. Using principally physicochemical data and biochemical considerations they proposed that this compound was 9-(nona-1′,3′-dienyloxy) non-8-enoic acid (II). Hydrogenation of the compound over Lindlar catalyst gave a derivative, which was given the structure, 9-nonyloxynonanoic acid (III), principally on spectral data. The production of a dialkenyl ether derivative from a polyunsaturated fatty acid involving the disruption of the carbon chain and insertion of an oxygen function is so unusual that it appeared desirable to provide additional evidence for the carbon skeleton of the new product or a direct derivative, such as methyl 9-nonyloxynonanoate (I), by an unambiguous synthesis.

A direct approach by a Williamson synthesis [2] between methyl 9-hydroxynonanoate (IV) and 1-bromononane in benzene solution failed to yield any coupled product because intra- and intermolecular reactions of the hydroxyester intervened, but the complementary reaction between methyl 9-bromononanoate and 1-nonanol was eventually successful.

The bromo ester required for this approach has been synthesised by Chuit and Hauser [3] by treatment of methyl 9-hydroxynonanoate (IV), obtained by a Bouveau-Blanc reduction of diethylazelate (V), with hydrobromic acid in acetic acid. We were unable to repeat these experiments; reduction of the diester yielded

only 1,9-dihydroxynonane and bromination of 9-hydroxynonanoic acid produced 9-acetoxynonanoic acid.

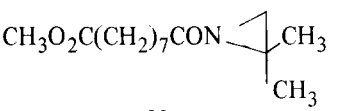
An alternative route to the hydroxy ester lay in selective reduction of the half ester (VI) of azelaic acid. Preferential reduction of an ester function in the presence of a carboxyl group has been described using an excess of sodium borohydride in refluxing methanol [4] and lithium borohydride [5] in alcohol [6], and diglyme [7], the reduction of the potassium salt of a half ester with lithium borohydride in refluxing tetrahydrofuran [8] has also been reported. In our hands all of these methods gave only trace amounts of the desired compound, and with lithium aluminum hydride both functional groups were reduced.

A more selective approach was necessary, and suggested the use of the 5,5-dimethyloxazolinyl residue, which has recently been reported [9] to be a convenient protecting group for carboxylic acids, especially during reduction with lithium aluminum hydride. Treatment of monomethyl azelate (VI) with 2,2-dimethylaziridine [10] and dicyclohexylcarbodiimide in dichloromethane gave a (4 : 1) mixture of the acylaziridine (VII) and the oxazoline (VIII).

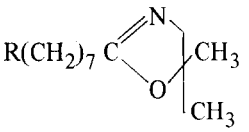
$CH_3(CH_2)_7CH_2OCH_2(CH_2)_7CO_2R$ **I**, R=CH_3; **III**, R=H

$CH_3(CH_2)_4CH{=}CH{-}CH{=}CH{-}O{-}CH{=}CH(CH_2)_6CO_2H$ **II**,

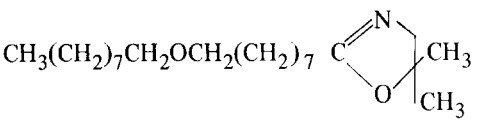
$RCH_2(CH_2)_5CH_2CO_2R^1$ **IV**, R=$HOCH_2-$, $R^1 = CH_3-$; **V**, R=$CH_3CH_2O_2C-$, $R^1 = CH_3CH_2-$; **VI**, R=CH_3O_2C-, R^1 = H



VII,



VIII, R=CH_3O_2C-; **IX**, R=$HOCH_2-$; **X**, R=$BrCH_2-$



XI,

The former was thermally unstable and distillation caused partial rearrangement to the oxazoline. Complete conversion to the oxazoline (VIII) was achieved with ether in dilute sulphuric acid. Reduction of the oxazoline ester with lithium aluminum hydride gave the alcohol (IX) in 69% yield. The protecting group was remarkably unresponsive to removal by hydrolysis with dilute acid and so it was retained during the subsequent Williamson coupling.

Bromination with phosphorus tribromide in toluene/pyridine solution at −10° C gave the corresponding bromide (X). Reaction of this bromide with one equivalent of sodium salt of nonan-1-ol in excess nonan-1-ol as solvent, gave the desired ether derivative (XI) showing an intense band at 1120 cm^{-1} for the C–O–C link but which also contained evidence of a carboxyl function (1715 cm^{-1}) and an ester function (1740 cm^{-1}; nonyl ester) indicating that partial hydrolysis of the oxazoline function had apparently occurred during the coupling.

Prolonged refluxing of the crude product in aqueous potassium hydroxide and esterification by acidic methanol at room temperature gave the methyl ester (I) which was identical with the methyl ester of the acid (III) supplied by Dr. Galliard. The synthesis of this reduction product (I) gives unambiguous support for the unsaturated ether structure (II) for the original product; the mechanism by which the oxygen function is inserted is still a matter for speculation.

2. Experimental

2.1. Physical measurements

Infra red spectra of thin liquid film on NaCl plates or KBr discs were obtained using a Unicam SP 200G spectrophotometer. Nmr spectra were recorded on samples as 1–2% solutions in deuterochloroform, with addition of the tris (dipivalomethanato) europium shift reagent [11] where necessary, using a Varian XL-100 spectrometer. Mass spectra were obtained on an AEI MS902 spectrometer operating at 70 eV and 190–210° C. Samples were introduced via the direct insertion probe or from the effluent of a Pye 104 gas liquid chromatograph via a silicone rubber membrane separator. High resolution data were recorded on magnetic tape and processed using the computer programme of Johnson et al. [12].

2.2. Chromatography

Methyl 9-nonyloxynonanoate was chromatographed on polar (PEGA) and non-polar (SE30) columns as reported by Galliard and Phillips [1]. Preparative liquid chromatography was carried out on a Pye Argon Chromatograph, using a 4 ft × 4 mm column packed with 5% OV 17 on J.J. "CQ" 85–100 BSS mesh (J.J., Kings Lynn, England) at 188° C and an argon flow rate of 45 ml/min. Samples were collected in micro-capillaries, sealed and kept at −5° C.

Methods for standard t.l.c. procedures have been described previously [13].

2.3. Synthesis

2.3.1. 1-(8'-methoxycarbonyloctanoyl)-2,2-dimethylaziridine (VII)

2,2-dimethylaziridine (3.9 g, 0.055 m) was added to a fine suspension formed by mixing a solution of dicyclohexylcarbodiimide (10.3 g, 0.05 m, in 50 ml dichloro-

methane) and monomethyl azelate (bp 120–121° C at 0.03 mm, 10.1 g, 0.05 m) at 5° C, and the resulting mixture was allowed to stand at room temperature for 12 hr, with occasional swirling. Removal of the precipitated urea by filtration and concentration of the filtrate gave a yellow oil which was treated with 200 ml of hexane and chilled; after filtration from a trace of solid material, distillation of the concentrated hexane soluble portion afforded two fractions. The first, bp 118–119° C at 0.05 mm 8.6 g, (68%) was characterised as the acylaziridine (VIII) on the basis of spectral data.

I.R. (film) 1735 cm^{-1} (ester C=O). 1690 cm^{-1} (–CON⁐).
Mass spectrum M^+ 255 ($C_{14}H_{25}NO_3$, 3%), base peak 113 ($C_6H_{11}NO$).
NMR ($CDCl_3$). 6.40 τ (3 p,s) CH_3OCO; 6.61 τ (2 p,m) $N=CH_2$; 7.71, 7.89 τ (4 p,m) CH_2CON, $OCOCH_2$–; 8.1–8.9 τ (10 p,m) $5CH_2$; 8.77 τ (6 p,s) C $(CH_3)_2$.
Anal. $C_{14}H_{25}NO_3$ 255; Calc.: C 65.9; H 9.8; N 5.5.
Found: C 65.9; H 9.8; N 5.4.

The second component, isolated as a viscous oil, bp 144–147° C at 0.05 mm, 2.1 g (17%) solidified on cooling. Repeated crystallisation from light petroleum – diethyl ether (1 : 3) gave the oxazoline (VIII) as colourless needles, mp 46–7° C.

I.R. (KBr disc) 1740 cm^{-1}, 1665 cm^{-1} (oxazoline C=N).
Mass spectrum M^+ 255 ($C_{14}H_{25}NO_3$, 3%), base peak 113 ($C_6H_{11}NO$).
Anal. $C_{14}H_{25}NO_3$ 255; Calc.: C 65.9; H 9.8; N 5.5.
Found: C 65.7; H 9.6; N 5.7.

Redistillation of a pure sample of VII (125° C at 0.07 m) resulted in a 38% yield of the oxazoline VIII, identical with the material previously described.

2.3.2. 2-(7'-carboxymethylheptyl)-5,5-dimethyloxazoline (VIII)

A solution of the aziridine (VII, 8.0 g) in diethyl ether (80 ml, containing 2 drops of concentrated sulphuric acid) was stirred at room temperature for 12 hr. After washing with dilute sodium bicarbonate solution the ethereal solution was concentrated to yield a viscous oil. Vacuum distillation afforded a colourless product, bp 151–153° C at 0.07 mm, 6.2 g (77%) which slowly solidified on cooling. Recrystallisation from light petroleum: diethyl ether (1 : 3) gave the oxazoline as colourless needles, mp 46° C.

2.3.3. 2-(7'-hydroxyheptyl)-5,5-dimethyloxazoline (IX)

The oxazoline ester (VIII, 5.0 g) was dissolved in 40 ml dry ether and stirred with $LiAlH_4$ (1 g) for 2 hr at room temperature. The resulting complex was decomposed with methyl acetate : water (1 : 1) and the organic phase, after washing with water, was dried and concentrated. Distillation of the crude product gave the alcohol as a colourless liquid, bp 125–128° C at 0.04 mm, 3.06 g (69%).

Prolonged chilling caused the liquid to crystallise, and after repeated crystallisations from diethyl ether a colourless product, mp 64–65° C was obtained.

I.R. (KBr disc) 3300 cm^{-1} (–OH), 1660 cm^{-1}.
Mass Spectrum M^+ 227 ($C_{13}H_{25}NO_2$, 4%) base peak 71 ($C_4H_7O + C_4H_9N$).
Anal. $C_{13}H_{25}NO_2$ 227; Calc.: C 68.7; H 11.0; N 6.2.
Found: C 68.5; H 10.7; N 6.3.

2.3.4. 2-(7'-bromoheptyl)-5,5-dimethyloxazoline (X)

A solution of phosphorus tribromide (0.8 g in 4 ml toluene) was added dropwise to a solution of the alcohol (IX, 2.27 g, 0.01 m) in toluene (4 ml, containing 250 μl pyridine) at –10° C. After completion of the addition, the mixture was stirred at 0° C for 1 hr and then at 25° C for 15 hr before being refluxed for 2 hr. The cooled toluene solution was decanted from the yellow semi-solid residue, which was washed (2 × 5 ml) with toluene, and the combined organic fractions were concentrated on the rotary evaporator. The resulting bromide (1.93 g, 67%) was obtained as a viscous yellow gum, and upon t.l.c. in three different solvent systems, it gave a single spot; however the compound decomposed on distillation (175–178° C at 0.14 mm) and all attempts at crystallisation failed.

I.R. (film) 1650 cm^{-1}.
Mass spectrum M^+ 289, 91 ($C_{13}H_{24}NOBr$, 1%) base peak 71 ($C_5H_{11} + C_4H_9N$).

2.3.5. Methyl 9-nonyloxynonanoate (I)

The bromo-oxazoline (X, 1.45 g, 5 mM) was added to a stirred solution of sodium (150 mg) in nonan-1-ol (8 ml), and after 2 hr at room temperature the solution was heated to reflux and maintained there for 13 hr. On cooling and filtering the solution free of precipitated salt, the excess nonan-1-ol in the filtrate was distilled (bp 65–66° C at 0.6 mm), to leave the crude oxazoline XI, as a red oil, I.R. (film) 1740 cm^{-1}, 1715 cm^{-1}, 1660 cm^{-1} and 1120 cm^{-1} (C–O–C).

Heating this residue with 25 ml 8% aqueous potassium hydroxide for 3 hr, followed by acidification of the aqueous solution gave a small amount of acidic material. This was immediately esterified by stirring for 2 hr at room temperature with acidic methanol, to produce the crude methyl ester (I) as a pale yellow oil (315 mg, 27%).

Preparative g.l.c. using a 5% OV 17 column afforded pure methyl 9-nonyloxynonanoate as a colourless oil, identical in all respects to a sample of the reduced ester supplied by Dr. Galliard.

I.R. (film) 1740 cm^{-1}, 1120 cm^{-1}.
Mass spectrum M^+ 314 ($C_{19}H_{38}O_3$, $< 1\%$), base peak 55 (C_4H_7).

Low resolution computer print out and high resolution mass measurements were identical with that recorded previously [1]. Ten major peaks were 155 (85), 139 (64), 138 (68), 87 (69), 74 (81), 71 (63), 69 (71), 57 (59), 55 (100), 43 (81).

Anal. $C_{19}H_{38}O_3$ 314; Calc.: C 72.61; H 12.11.
Found: C 72.85; H 12.69.

G.l.c. Analysis of the purified ester on OV17, PEGA and SE30 columns exhibited only a single component. Fatty acid equivalent chain lengths were calculated to be 19.0 (OV17), 19.7 (PEGA, authentic material 19.8), 18.8 (SE30, authentic material 18.6). A mixture of synthetic and authentic esters was recorded as a single component on all three columns.

T.l.c. On silica gel G developed in 60/80 petroleum : diethyl ether : acetic acid (70 : 30 : 1) both synthetic and authentic esters had R_f 0.61.

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