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FATTY ACIDS, PART 14 *. SYNTHESIS OF FURANOID ESTERS FROM NATURALLY OCCURRING UNSATURATED FATTY ESTERS

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Methyl 9,10,12,13-diepoxystearate yields a mixture of isomeric C_{18}-furanoid esters on treatment with propyl iodide–sodium iodide–dimethyl sulphoxide (PrI–NaI–DMSO). Pure methyl 9,12-epoxyoctadeca-9,11-dienoate can be obtained from (a) methyl 12-oxo-octadec-*cis*-9-enoate by mercuration–demercuration reaction; (b) methyl 9,10-epoxy-12-oxostearate, in the presence of PrI–NaI–DMSO, BF_3 or *p*-TsOH; and (c) methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate when treated with BF_3 or *p*-TsOH. The synthesis of a methyl substituted C_{18}-furanoid ester (methyl 9,12-epoxy-10-methyl-octadeca-9,11-dienoate) is also described.

I. Introduction

Morris et al. [2] isolated a furanoid ester, methyl 9,12-epoxyoctadeca-9,11-dienoate, from *Exocarpus cupressiformis* seed oil. The structure of this compound was later confirmed by synthesis from 2-furoic acid [3], but was more conveniently prepared from methyl ricinoleate [4] or linoleate [5]. Recently a new series of 8 furanoid fatty acids was discovered by Glass et al. [6] as constituents of lipids from the northern pike (*Esox lucius*).

In an earlier publication [7] we described the preparation of a C_{18} furanoid ester isomer from a synthetic methyl octadecadiynoate. In this paper we report the unusual behaviour of methyl 9,10,12,13-diepoxystearate with a mixture of dimethyl sulphoxide, propyl iodide and sodium iodide furnishing two positional furanoid ester isomers instead of the expected methyl dioxostearates [8]. This key reaction led to the subsequent development of several methods for the preparation of methyl 9,12-epoxyoctadeca-9,11-dienoate from derivatives of methyl ricinoleate. A successful method for the synthesis of methyl 9,12-epoxy-10-methyl-octadeca-9,11-dienoate was also developed.

* Part 13, see ref. [1].

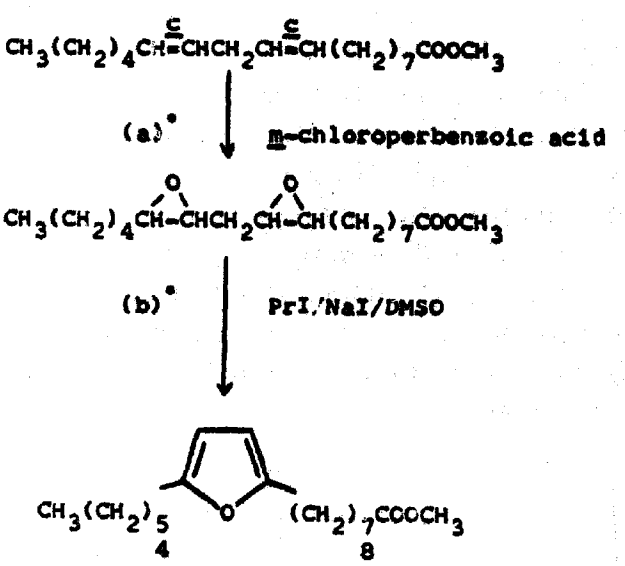
II. Results and discussion

In an effort to prepare the methyl 9,12- and 10,13-dioxostearate isomers from methyl 9,10,12,13-diepoxystearate (derived from the epoxidation of methyl linoleate) for carbocyclisation [7] purposes, we attempted the method described for the conversion of 4,5-epoxyoctane to 4-octanone [8]. However, treatment of methyl 9,10,12,13-diepoxystearate with propyl iodide (PrI), sodium iodide (NaI) in dimethyl sulphoxide (DMSO) at 100°C gave a mixture of methyl 9,12-epoxyoctadeca-9,11-dienoate and 10,13-epoxyoctadeca-10,12-dienoate (43%) instead (scheme 1). No methyl dioxostearate was obtained from this reaction.

From the mechanism proposed by Bethell et al. [8] for the conversion of an epoxide to the corresponding carbonyl derivatives by PrI–NaI–DMSO, we were led to think that methyl 9,10,12,13-diepoxystearate formed a mixture of 1,4-diketones as intermediates, which cyclodehydrated in the presence of DMSO [9] to furnish the furanoid esters. However, when methyl 9,12-dioxostearate (prepared from methyl ricinoleate) was treated under identical reaction conditions (PrI–NaI–DMSO, 100°C), no furanoid ester was obtained but the starting material. From this negative result it is probable that methyl 9,10,12,13-diepoxystearate formed epoxy-oxostearate intermediates instead, which in the presence of PrI–DMSO [$(CH_3)_2\overset{\oplus}{S}OPr$ as activating agent] cyclised to a mixture of C_{18}-furanoid esters (scheme 2).

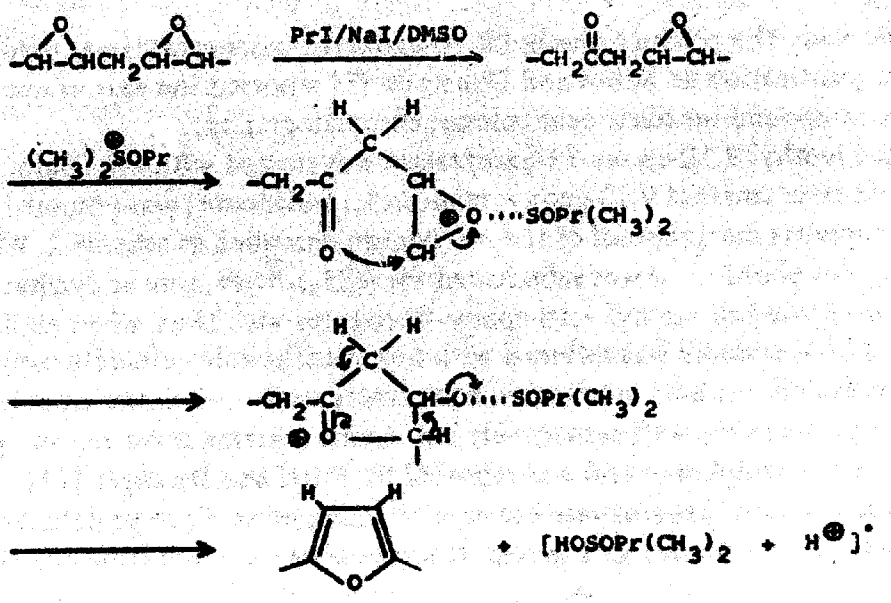
This probable reaction pathway led us to look into the chemistry of methyl 9,10-epoxy-12-oxostearate, obtainable from methyl ricinoleate (scheme 3).

Methyl 9,10-epoxy-12-oxostearate was prepared by the oxidation of methyl ricinoleate according to the method described by Brown et al. [10], followed by epoxidation of the resulting methyl 12-oxo-octadec-*cis*-9-enoate with *m*-chloroper-



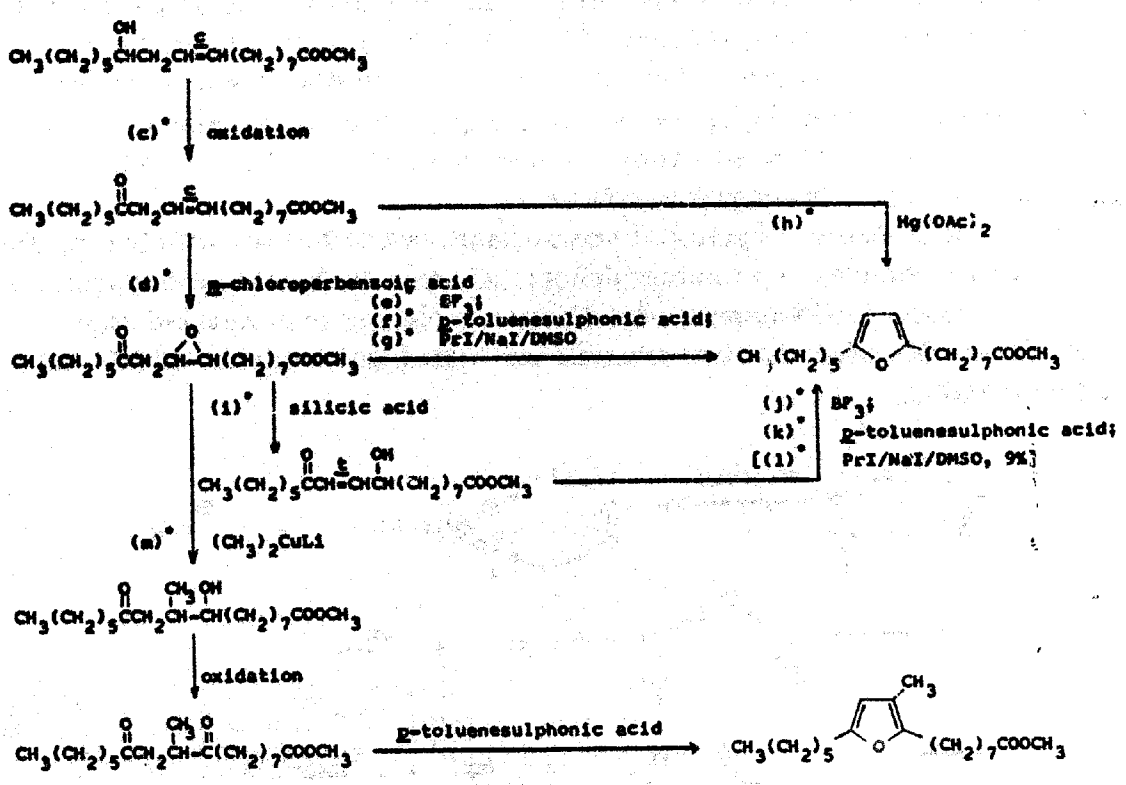
Scheme 1.

* See experimental section.



Scheme 2.

* End products undetermined.



Scheme 3.

* Experimental section refers.

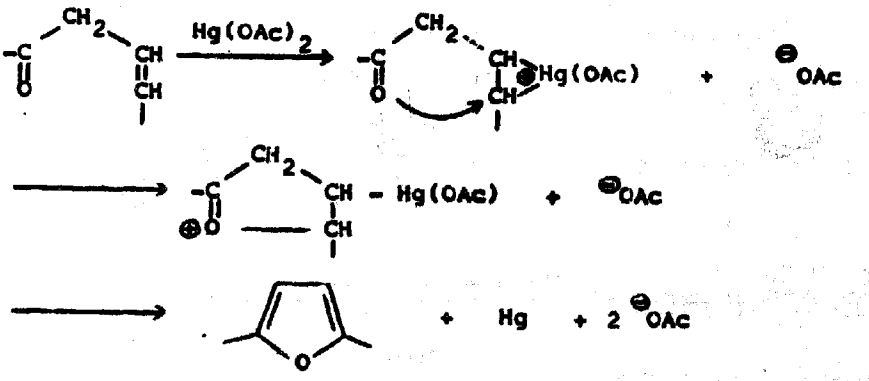
benzoic acid. The product (methyl 9,10-epoxy-12-oxostearate) was used without further purification as Abbot and Gunstone [5] reported the ease of decomposition of this compound on silicic acid column chromatography.

When methyl 9,10-epoxy-12-oxostearate was treated with PrI–DMSO, a single furanoid ester (methyl 9,12-epoxyoctadeca-9,11-dienoate) was obtained (48%). This result supports our proposal of the mechanism described in scheme 2. When BF_3 or *p*-toluenesulphonic acid was substituted for $(CH_3)_2\overset{\oplus}{S}OPr$, similar cyclisation reactions were anticipated of methyl 9,10-epoxy-12-oxostearate. Thus, when methyl 9,10-epoxy-12-oxostearate was refluxed with boron trifluoride–etherate complex or *p*-toluenesulphonic acid in benzene, both reactions furnished the same furanoid ester in good yields (39%, 43% respectively). A similar reaction involving an epoxy-ketone with *p*-toluenesulphonic acid was reported by Fritel and Baranger [11].

These reactions demonstrate the ease of attack of an electron-deficient oxonium system by a β-positioned keto group. It can thus be expected from any similar electron-deficient system [$-CH\overset{\oplus}{=}\overset{X}{C}H-$, where X is an electro-positive species[for furan formation to take place, provided the keto group is located at the β-position. Consequently, when methyl 12-oxo-octadec-*cis*-9-enoate was converted to the corresponding mercurium complex with mercuric acetate in acetic acid [12], isolation of the reaction product yielded methyl 9,12-epoxyoctadeca-9,11-dienoate in good yield (51%) (scheme 4).

In our above experiments we have used exclusively non-chromatographed samples of methyl 9,10-epoxy-12-oxostearate [5] to avoid the presence of any methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate in our experiments. In exploring further the probable mechanism during the cyclodehydration reaction of epoxy-keto compounds to furans, we prepared a sample of methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate for further investigation (scheme 3).

Treatment of methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate with borontrifluoride etherate complex or *p*-toluenesulphonic acid gave methyl 9,12-epoxyoctadeca-9,11-dienoate (53%, 63% respectively). However, only a trace of furanoid ester could be detected when the same substrate was heated with a mixture of PrI–NaI–DMSO at 100°C.



Scheme 4.

These results support further our proposal (scheme 2) that methyl 9,10-epoxy-12-oxostearate produces the C_{18}-furanoid ester directly on treatment with PrI–NaI–DMSO; while in the presence of a Lewis acid, the possibility for methyl 9,10-epoxy-12-oxostearate to form methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate prior to the formation of the furanoid ester cannot be absolutely ruled out.

Isolation of methyl substituted furanoid esters from the lipid of the northern pike were previously reported [6]. In extending our work to include a methyl substituted furanoid ester isomer (scheme 3), methyl 9,10-epoxy-12-oxostearate was treated with lithium dimethyl cuprate [$(CH_3)_2CuLi$] at 0°C for 2 hr to give methyl 9-hydroxy-10-methyl-12-oxostearate (38%) [13–15]. The presence of methyl 10-hydroxy-9-methyl-12-oxostearate in this reaction was ruled out as no such compound was isolated in subsequent reactions. The regiospecific methylation by $(CH_3)_2CuLi$ was likely controlled by the neighbouring carbonyl function.

Oxidation of methyl 9-hydroxy-10-methyl-12-oxostearate gave the corresponding dioxo derivative (92%), which on reflux with *p*-toluenesulphonic acid in benzene furnished methyl 9,12-epoxy-10-methyl-octadeca-9,11-dienoate (76%, ECL * = 18.63 on OV-101).

The GLC analysis (on OV-101 stationary phase) and the mass spectrum of the product showed an impurity (~5%), which is probably a dimethyl substituted furanoid ester (ECL = 19.26 on OV-101, $M^+ = 336$). It is noteworthy to record that no GLC separation could be achieved on Silar 10C stationary phase between an unsubstituted and a methyl or dimethyl substituted furanoid ester of the same (C_{18}) chain length.

III. Experimental

General procedures

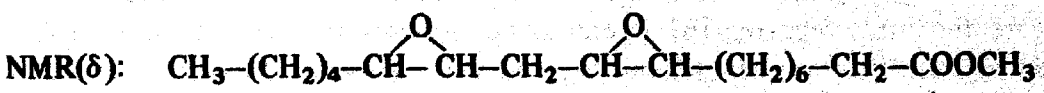
Column, thin-layer and gas-liquid chromatography were carried out by the standard procedures. Phosphomolybdic acid or 2′,7′-dichlorofluoroscein were used as spray reagents. Details of spectroscopic procedures are described in Part 5 [16]. Mass spectral data are given in the order: *m/e*, source of fragment, intensity relative to base peak = 100.

(a) Preparation of methyl 9,10,12,13-diepoxystearate

A mixture of crude methyl linoleate (5 g, 70% pure, 0.012 mol), *m*-chloroperbenzoic acid (4.5 g) and methylene chloride (100 ml) was stirred overnight at room temperature. Saturated sodium sulphite solution (20 ml) was added to the reaction mixture to destroy any excess peracid. The methylene chloride solution was succes-

* ECL = equivalent chain length.

sively washed with aqueous sodium bicarbonate (10%, 30 ml) and saturated sodium chloride solution (50 ml). Purification of the product by column chromatography (silicic acid 100 g, using petroleum ether–diethyl ether, 3 : 0–1, v/v) gave methyl 9,10,12,13-diepoxystearate (2.22 g, 56%).

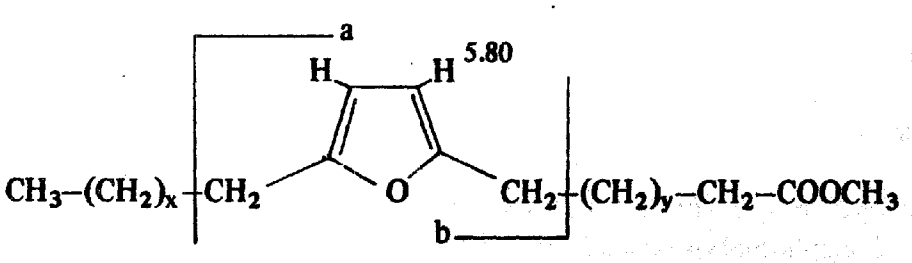


NMR(δ): $CH_3-(CH_2)_4-CH-CH-CH_2-CH-CH-(CH_2)_6-CH_2-COOCH_3$

0.9 1.4–1.65 2.9–3.1 1.4–1.65 2.9–3.1 1.4–1.65 2.25 3.66

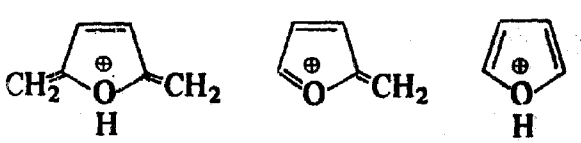
(b) Reaction of methyl 9,10,12,13-diepoxystearate with PrI–NaI–DMSO

Methyl 9,10,12,13-diepoxystearate (519 mg, 1.59 mmol), *n*-propyl iodide (3.9 g, 22.9 mmol) and sodium iodide (540 mg, 3.60 mmol) were heated in dimethyl sulphoxide (50 ml) at 100°C under nitrogen for 5 hr. Free iodine liberated during the reaction was removed by shaking the reaction mixture with sodium thiosulphate solution (10%, 20 ml). Water (100 ml) was added and the product extracted with diethyl ether. Preparative TLC of the crude product furnished a mixture of methyl 9,12-epoxyoctadeca-9,11-dienoate and 10,13-epoxyoctadeca-10,12-dienoate (212 mg, 43%). The infrared spectrum shows aromatic C–H and C=C stretchings at 3100 and 1635, 1550 cm^{-1} respectively.



NMR(δ): 0.89 1.32 2.52 2.52 1.32 2.30 3.63

MS(70eV):



c d e

308 (M, 24) 277 (M–31, 7) 95 (c, 77)
81 (d, 54) 69 (e, 61) 53 (?, 100)

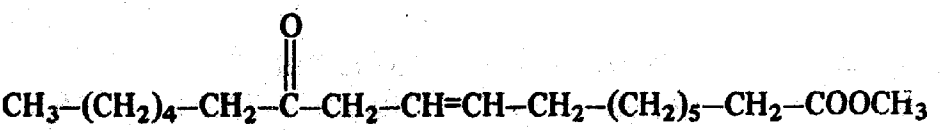
for $x = 4, y = 5$	$x = 3, y = 6$
237 (a, 12)	251 * (a, 10)
205 (a–32, 5)	219 * (a–32, 4)
251 * (a+14, 10)	265 (a+14, 4)
219 * (a+14–32, 4)	233 (a+14–32, 2)
165 * (b, 60)	165 * (b+14, 60)
179 (b + 14, 11)	151 (b, 64)

* Peak due to more than one fragment.

(c) Preparation of methyl 12-oxo-octadec-cis-9-enoate

Chromic acid (prepared from 20 g sodium dichromate, 28 g sulphuric acid and 65 ml of water) was added dropwise to a well-stirred solution of methyl ricinoleate (40 g, 90% pure, 0.115 mol) in diethyl ether (750 ml) over a period of 30 min at room temperature. The reaction mixture was stirred for a further 1.5 hr. The ethereal solution was then isolated and washed with saturated aqueous sodium chloride solution. Purification of a 5 g batch of the product (40 g) by silicic acid (50 g) column chromatography, petroleum ether-diethyl ether, 4 : 0–1, v/v, as eluent, gave pure methyl 12-oxo-octadec-*cis*-9-enoate (4 g, 90%).

NMR(δ):

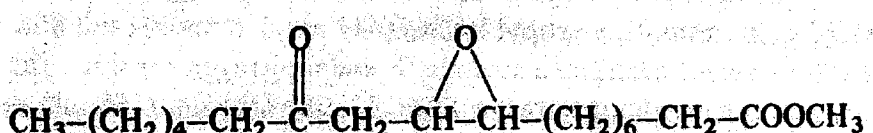


0.88 1.30 2.3 3.11 2.52 2.3 1.30 2.3 3.64

E. Preparation of methyl 9,10-epoxy-12-oxostearate

Methyl 12-oxo-octadec-*cis*-9-enoate (4.54 g, 0.015 mol) was stirred with *m*-chloroperbenzoic acid (4.3 g) in methylene chloride (100 ml) for 12 hr at room temperature. The reaction mixture was washed with aqueous sodium sulphite, water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave crude methyl 9,10-epoxy-12-oxostearate (3.6 g, 73%). No attempt was made to purify this compound further due to its ease of conversion into the methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate.

NMR(δ):

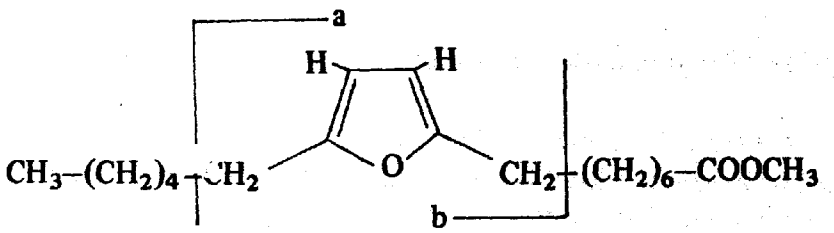


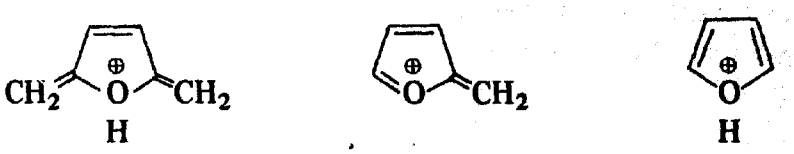
0.85 1.32 2.23 2.5 2.85–3.15 1.32 2.23 3.60

F. Reaction of methyl 9,10-epoxy-12-oxo-stearate with boron trifluoride–etherate

A mixture of methyl 9,10-epoxy-12-oxostearate (650 mg, 1.99 mmol), dioxane (20 ml) and boron trifluoride–etherate complex (1.13 g/ml, 1 g) was stirred overnight at room temperature. The reaction mixture was diluted with water (10 ml), extracted with diethyl ether and silicic acid column chromatography gave pure methyl 9,12-epoxyoctadeca-9,11-dienoate (240 mg, 39%).

MS(20 eV):





c d e

308 (M, 77), 277 (M–31, 11), 237 (a, 26),
205 (a–32, 7), 251 (a+14, 8), 219 (a+14–32, 3), 165 (b, 100),
179 (b+14, 19), 95 (c, 51), 81 (d, 16), 69 (e, 10).

G. Reaction of methyl 9,10-epoxy-12-oxostearate with p-toluenesulphonic acid

Methyl 9,10-epoxy-12-oxostearate (307 mg, 0.94 mmol) was refluxed in benzene (50 ml) in the presence of *p*-toluenesulphonic acid (35 mg) for 2 days using a Dean–Stark trap. The benzene solution was washed with aqueous sodium bicarbonate (10%, 20 ml). Purification by column chromatography on silicic acid (20 g) gave pure methyl 9,12-epoxyoctadeca-9,11-dienoate (125 mg, 43%).

H. Reaction of methyl 9,10-epoxy-12-oxostearate with PrI–NaI–DMSO

A mixture of methyl 9,10-epoxy-12-oxostearate (384 mg, 1.18 mmol), sodium iodide (1.37 g, 9.1 mmol), *n*-propyl iodide (441 mg, 2.6 mmol) and dimethyl sulphoxide (50 ml) was heated on a steambath under nitrogen for 6 hr. The reaction mixture was diluted with saturated sodium chloride solution (150 ml) and extracted with diethyl ether.

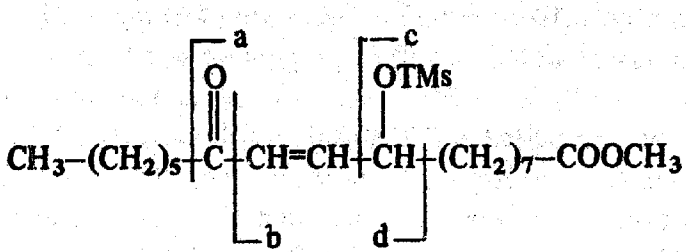
Preparative TLC on silicic acid (petroleum ether–diethyl ether, 7 : 3, v/v) furnished pure methyl 9,12-epoxyoctadeca-9,11-dienoate (175 mg, 48%).

I. Reaction of methyl 12-oxo-octadec-cis-9-enoate with mercuric acetate

A mixture of methyl 12-oxo-octadec-*cis*-9-enoate (2.5 g, 8.06 mmol), mercuric acetate (3.8 g, 11.94 mmol) and acetic acid (50 ml) was refluxed for 1 hr. Droplets of mercury were deposited during the initial period of the reaction. The reaction product was diluted with water and extracted with diethyl ether. Column chromatographic separation on silicic acid (20 g) gave pure methyl 9,12-epoxyoctadeca-9,11-dienoate (1.27 g, 51%).

J. Preparation of methyl 9-hydroxy-12-oxo-octadec-trans-10-enoate

Methyl 9,10-epoxy-12-oxostearate (0.9 g, 2.76 mmol) was percolated through a silicic acid (30 g) column using petroleum ether–diethyl ether, 7 : 3, v/v, 300 ml, as eluent. Methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate (0.62 g, 69%) was obtained on evaporation of the solvent under reduced pressure. Infrared analysis showed absorptions at 3500 cm^{-1} (O–H stretching), 1630, 1680, 1698 cm^{-1} (conjugated enone system) and at 980 cm^{-1} (*trans*- = C–H). The mass spectrum of its trimethylsilyl derivative was as follows.



399 (M+1, 17),	383 (M–15, 17),	367 (M–31, 8),
308 (M–HOTMS, 10),	313 (a, 10),	285 (b, 43),
270 (b–15, 30),	259 (c, 20),	241 (d, 100),
73 ($SiMe_3$, 50).		

K. Reaction of methyl 9-hydroxy-12-oxo-octadec-trans-10-enoate with boron trifluoride etherate complex

A mixture of methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate (104 mg, 0.32 mmol), dioxane (20 ml) and boron trifluoride etherate (1.13 g/ml, 0.5 ml) was stirred for 12 hr. Water (50 ml) was added and the ethereal extract (100 mg) was separated on preparative TLC to give methyl 9,12-epoxyoctadeca-9,11-dienoate (56 mg, 53%) and unreacted substrate (26 mg).

L. Reaction of methyl 9-hydroxy-12-oxo-octadec-trans-10-enoate with p-toluenesulphonic acid

Methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate (41 mg, 0.12 mmol) was refluxed in benzene (25 ml) in the presence of *p*-toluenesulphonic acid (50 mg) for 2

days. Isolation by preparative TLC of the crude product gave methyl 9,12-epoxy-octadeca-9,11-dienoate (24 mg, 63%).

M. Reaction of methyl 9-hydroxy-12-oxo-octadec-trans-10-enoate with PrI–NaI–DMSO

A mixture of methyl 9-hydroxy-12-oxo-octadec-*trans*-10-enoate (97 mg, 0.29 mmol), *n*-propyl iodide (257 mg, 1.48 mmol), sodium iodide (369 mg, 2.46 mmol) and dimethyl sulphoxide (25 ml) was heated at 100°C under nitrogen. The reaction mixture was washed with dilute sodium thiosulphate (10%, 50 ml) to remove the liberated iodine. Preparative TLC separation of the ethereal extract (79 mg) gave methyl 9,12-epoxyoctadeca-9,11-dienoate (7 mg, 9%) and unreacted substrate (48 mg, 59%).

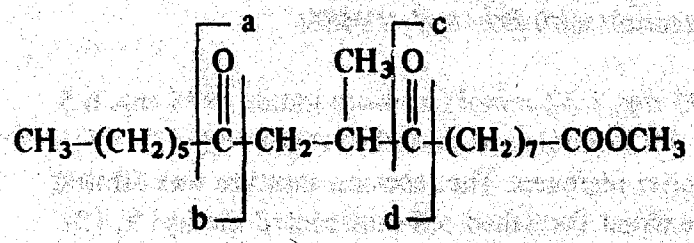
N. Synthesis of methyl 9,12-epoxy-10-methyl-octadec-9,11-dienoate

Methyl lithium in diethyl ether (2 M, 25 ml) was added dropwise to a well-stirred ethereal suspension of copper (I) iodide (446 mg, 2.34 mmol) at 0°C under nitrogen, until the yellow colouration was discharged to give a clear solution. The solution was stirred for a further 30 min and methyl 9,10-epoxy-12-oxostearate (428 mg, 1.31 mmol) in dried diethyl ether (20 ml) was added. A yellow precipitate was formed and the reaction product allowed to stir for a further 2 hr at 0°C. Saturated aqueous ammonium chloride solution (20 ml) was added at 0°C and then followed by dilute ammonium hydroxide (10 ml) when two distinct layers were observed. The ethereal extract was concentrated and the product chromatographed on a silicic acid column (30 g) to give methyl 9-hydroxy-10-methyl-12-oxostearate (170 mg, 38%).

Infrared analysis showed absorption at 3450 cm^{-1} (O–H stretching), 1740 and 1720 cm^{-1} (C=O stretching for ester and oxo group respectively). The NMR spectrum indicated a broad signal at 3.50 δ for –*CH*OH.

Methyl 9-hydroxy-10-methyl-12-oxostearate (150 mg, 0.46 mmol) was dissolved in diethyl ether (75 ml) and chromic acid (2.0 ml, prepared from 20 g $Na_2Cr_2O_7$, 28 g H_2SO_4, 65 ml H_2O) was added over a period of 5 min at room temperature and the mixture allowed to stir for 30 min. The ethereal solution was successively washed with water (50 ml), sodium bicarbonate solution (10%, 20 ml) and dried over sodium sulphate. Column chromatographic separation of the isolated product gave methyl 9,12-dioxo-10-methyl stearate (137 mg, 92%).

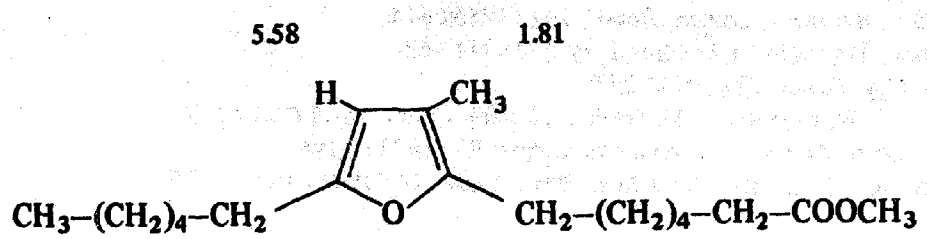
The NMR spectrum showed a doublet at 1.05 δ (J = 7 Hz, $-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CO-$) and a triplet at 2.86 δ (J = 7 Hz, $-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CO$), while the mass spectrum gave the following peaks:



341 (M+1, 66),	323 (M–17, 43),	309 (M–31, 47),
270 (a+15, 10),	255 (a, 4),	227 (M–b, 22),
223 (a–32, 39),	198 (d + 15, 100),	195 (M–b–32, 24),
185 (c, 96),	183 (d, 49),	155 (M–c, 57),
153 (c–32, 20),	128 (b+15, 35),	113 (b, 57).

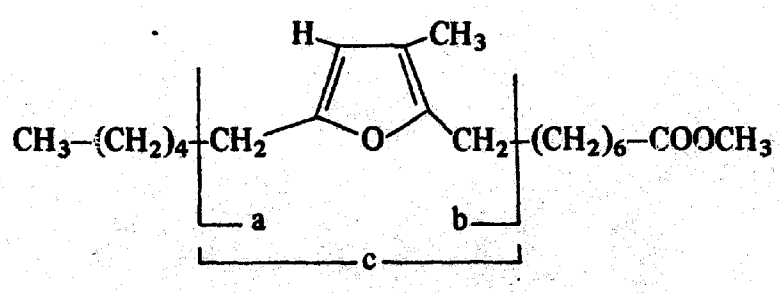
Methyl 9,12-dioxo-10-methyl stearate (109 mg, 0.32 mmol) was refluxed for 12 hr in benzene in the presence of *p*-toluenesulphonic acid (30 mg) with a Dean–Stark trap. The benzene solution was washed with sodium bicarbonate (10%, 20 ml) and saturated aqueous sodium chloride solution. Preparative TLC of the product gave methyl 9,12-epoxy-10-methyl-octadec-9,11-dienoate (78 mg, 76%).

The infrared spectrum showed aromatic absorptions at 3100, 1635 and 1550 cm^{-1}. The NMR (δ) spectrum was as follows:



0.89 1.32 2.2–2.4 2.2–2.4 1.32 2.2 3.58

MS(20eV):



322 (M, 6),	291 (M–31, 1),
251 (a, 4),	179 (b, 100),
109 (c, 12),	336 (M+15, 0.5).

O. Refluxing methyl 9,12-dioxostearate with PrI–NaI–DMSO

Methyl 9,12-dioxostearate (495 mg, 1.52 mmol), sodium iodide (975 mg, 6.5 mmol), *n*-propyl iodide (837 mg, 4.92 mmol) and dimethyl sulphoxide (50 ml) were heated on a steambath for 5 hr under nitrogen. The reaction mixture was diluted with water and the diethyl ether extract furnished only unreacted methyl 9, 12-dioxostearate (450 mg) as shown from its chromatographic and spectroscopic properties.

References

[1] M.S.F. Lie Ken Jie, J. Chromatog. 131 (1977) 239
[2] L.J. Morris, M.O. Marshall and W. Kelly, Tet. Lett. (1966) 4249
[3] J.A. Elix and M.V. Sargent, J. Chem. Soc. (C) (1968) 595
[4] G.G. Abbot, F.D. Gunstone and S.D. Hoyes, Chem. Phys. Lipids 4 (1970) 351
[5] G.G. Abbot and F.D. Gunstone, Chem. Phys. Lipids 7 (1971) 290
[6] R.L. Glass, T.P. Krick, D.M. Sand, C.H. Rahn and H. Schlenk, Lipids 10 (1975) 695
[7] M.S.F. Lie Ken Jie and C.H. Lam, Chem. Phys. Lipids, 19 (1977) 275
[8] D. Bethell, G.W. Kenner and P.J. Powers, Chem. Commun., (1968) 227
[9] L.F. Fieser and M. Fieser, Reagents for Organic Synthesis, Wiley, New York, (1967) 302
[10] H.C. Brown, C.P. Garg and K.T. Liu, J. Org. Chem., 36 (1971) 387
[11] H. Fritel and P. Baranger, Compt. Rend., 241 (1955) 674
[12] F.D. Gunstone, Topics in Lipid Chemistry 2 (1971) 142
[13] G.H. Posner, Org. React. 22 (1974) 253
[14] C.R. Johnson, R.W. Herr and D.M. Wieland, J. Org. Chem. 38 (1973) 4263
[15] J. Staroscik and B. Rickborn, J. Am. Chem. Soc. 93 (1971) 3046
[16] C.H. Lam and M.S.F. Lie Ken Jie, Chem. Phys. Lipids 16 (1976) 181