Monoepoxidation of Methyl Linoleate: (±)-Methyl Vernolate and (±)-Methyl Coronarate

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Abstract

The two monoepoxides resulting from the epoxidation of methyl linoleate with monoperphthalic acid have been separated from each other by column chromatography. Degradation reactions on each of these established that the separation occurred without concomitant rearrangement of the double bond or the epoxide ring. Thus, (±)-methyl vernolate (I) and (±)-methyl coronarate (II) were obtained in a pure state.

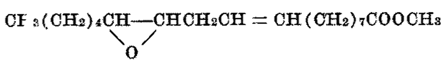
Introduction

ALTHOUGH THE EPOXIDATION of linoleic acid or its methyl ester has been carried out repeatedly in the past, it was not until recently that a study of positional selectivity in the monoepoxidation of methyl linoleate was reported. Maerker et al. (1) showed that this epoxidation with one mole of peracetic acid per mole of ester resulted in the formation of equal amounts of the two possible epoxyesters. The two products of epoxidation were not separated by these authors. That the formation of the two possible isomers had indeed occurred was shown by a study of the degradation products of the mixture.

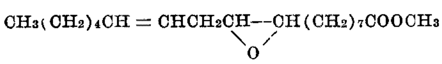
In the course of our research (2) we became interested in the preparative separation of the two monoepoxyesters obtained by epoxidation of methyl linoleate with monoperphthalic acid. This separation was effected by chromatography of the mixture on a silica gel column without concomitant rearrangement of either the double bond or the epoxide ring of the two monoepoxides.

By this method we obtained methyl *cis*-12,13-epoxyoctadec-*cis*-9-enoate (I; (±)-methyl vernolate) and methyl *cis*-9,10-epoxyoctadec-*cis*-12-enoate (II). The corresponding acid of the latter is the racemate of coronaric acid which occurs as a glyceride in the oil of *Chrysanthemum coronarium* (3).

The preparation of (±)-methyl coronarate (II) and of (±)-coronaric acid reported here constitutes the first example where these have been obtained pure by synthetic means. The characteristics and properties of these compounds are described below.



I



II

Experimental Procedures

Methyl Linoleate

The material used for epoxidation was natural methyl linoleate (Fluka, A. G.). GLC showed a major peak with impurities amounting to less than 5%.

Pelargonic, Caproic, Azelaic and Dodecanedioic Acids

These acids (Fluka, A. G.) were esterified with diazomethane and the esters were used as references in GLC and mass spectra comparisons.

GLC Analyses

GLC analyses were performed with a Perkin-Elmer F 20 gas chromatograph, equipped with a 2-m glass column of SE 30 (2.5%) on chromosorb W, at temperatures of 220 C (flash heater 270 C) with a nitrogen flow rate of 25 ml/min.

IR

Infrared spectra were recorded with a Perkin-Elmer 137 instrument.

NMR

NMR spectra were recorded on a Perkin-Elmer 60 Mc spectrometer for $CDCl_3$ solutions with tetramethylsilane as internal reference.

GLC-MS

Combined gas chromatography and mass spectra measurements were recorded on an LKB 9,000. The conditions of gas chromatography used were as reported above.

TLC

Thin-layer chromatography was conducted on silica gel plates (0.2 mm; Merck G) with petroleum ether:ether (3/1) as eluent. The plates were developed by spraying with conc. sulfuric acid and then heating at 100 C.

Column Chromatography

Columns were prepared with silica gel-celite mixture (1:1 v/v) with an adsorbent:substance ratio of 40/1 or 50/1. The columns were packed in ligroin and kept under a nitrogen atmosphere during the chromatography.

Epoxidation of Methyl Linoleate

A solution of methyl linoleate (10 g; 0.032 mole) in ether (300 ml) was treated with an ethereal solution of monoperphthalic acid (4) (102 ml; 60 mg/ml; 0.032 mol) and left for seven days at 0 C under a nitrogen atmosphere. The solution was poured into water (200 ml) and the ether solution was separated, washed with 5% aq $NaHCO_3$ (200 ml), water (200 ml), dried over sodium sulphate and evaporated to give an oil (9.8 g).

GLC analysis indicated it to be a mixture of methyl linoleate (40%) and an epoxide fraction (55%). TLC showed the presence of three major compounds, one of which corresponded to methyl linoleate, the other two appeared with similar R_f and with equal intensity, and corresponded to the two monoepoxides. Trace quantities of more polar compounds were also present.

Isolation of Monoepoxides

The reaction mixture (9.8 g) was adsorbed on a silica gel-celite (390 g) column and eluted with ligroin, ligroin 2% ether, and then with increasing

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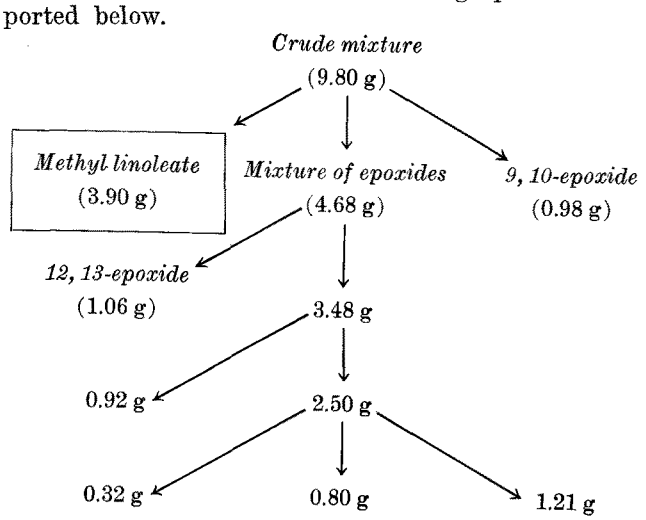
quantities of ether until the ligroin 5% ether ratio was reached. Fractions of 400 ml were collected.

Fractions	Composition	Amount
1–10	methyl linoleate	3.90 g
12–25	mixture of epoxides	4.68 g
26–29	methyl 9,10-epoxyoctadec-12-enoate	0.98 g

The mixture of epoxides from this chromatography and for each successive one was rechromatographed until a total of four chromatographies had been performed. In each of these last three chromatographies the eluent was ligroin for the first 10 fractions, then ligroin 2% ether for the next 5 fractions and then the column was eluted with ether in order to recover the more polar 9,10-epoxide. The scheme for the four chromatographies is reported below.



In this way a total of 2.30 g of 12,13-epoxide and 2.19 g of the 9,10-epoxide was obtained.

Determination of Epoxide Ring Position

The epoxyester II (100 mg) on treatment with refluxing acetic acid (3 ml) gave a product which resulted more polar than the starting ester and consisted of a mixture of the two possible monohydroxy acetates. This mixture showed bands in its IR spectrum at 3400 cm^{-1} (hydroxyl), 1740 and 1240 cm^{-1} (esters and acetates), while in its NMR spectrum signals for the two protons of the epoxide ring present at 7.1 τ in the NMR spectrum of II had been replaced by signals at 6.4 τ (>C*H*–OH) and at 5.2 τ (>C*H*–OAc).

The mixture of monohydroxy acetates in ethanol was hydrogenated over palladium-charcoal (10%). The hydrogenated product (70 mg) was dissolved in ethanol (3 ml) and heated under reflux with 5% aq KOH (0.5 ml) for 2 hr. The solution was poured into water, acidified and extracted with ether (3 × 10 ml). Evaporation of the solvent gave a product (65 mg) which crystallized from chloroform-hexane as microcrystals of (±)-threo-9,10-dihydroxystearic acid, m.p. 95 C (5). The latter was treated with diazomethane and the resulting ester in methanol (23 ml) was oxidized with 0.1 M sodium periodate (5 ml) for 15 hr at room temperature yielding a product (82 mg) which was then stirred with $AgNO_3$ (0.5 g) in 10% aq NaOH (5 ml) for 4 hr. The product (80 mg) recovered was treated with diazomethane. The esterified product thus obtained was shown to consist of a mixture of methyl pelargonate (III) and methyl azelate (IV) present in approximately equal quantities. A comparison between these products and authentic samples in GLC-MS showed them to be identical.

An analogous reaction sequence on the monoepoxide I yielded methyl caproate (V) and methyl dodecanedioate (VI).

(±)-Coronaric Acid

The monoepoxyester II (130 mg) in ethanol (10 ml) was heated under reflux with 1 N aq KOH (2 ml) for 1 hr under a nitrogen atmosphere. The product (100 mg) isolated in the usual way, crystallized from petroleum ether at −20 C as microcrystals of (±)-coronaric acid, m.p. 24 C.

Treatment of this acid with diazomethane reformed the epoxyester II.

Determination of Double Bond Position

(±)-Coronaric acid (90 mg) was dissolved in 0.1 N aq KOH (20 ml) and water (120 ml). To this solution, 0.05 M sodium periodate (60 ml) and 0.1 M potassium permanganate (0.8 ml) were added. The mixture was diluted with water to 400 ml and left at room temperature for 15 hr. Acidification with 5 N HCl liberated iodine and the solution was decolorized with gaseous SO_2. NaOH (5 N) was added until the solution was alkaline (phenolphthalein) and then the solution was concentrated to 50 ml, acidified, extracted with ether and the solvent was evaporated to give a mixture of acids (60 mg) which was esterified with diazomethane. GLC-MS showed the presence of two compounds which were identified with methyl azelate (IV) and methyl caproate (V).

(±)-Vernolic Acid

The 12,13-epoxyester I was hydrolyzed with aq KOH to give the 12,13-epoxyoctadec-9-enoic acid, m.p. 35–36 C (6). The acid was treated with periodate permanganate, as described above, and the products on esterification were identified as methyl azelate (IV) and methyl caproate (V).

Treatment of the acid with diazomethane reformed the epoxyester I.

Methyl 12,13-diacetoxyoctadec-9-enoate (VII)

The mixture of monoacetates (100 mg), obtained by treatment of I with acetic acid, was heated under reflux with acetic anhydride (2 ml) for 2 hr and then water (2 ml) was added and the solution heated at 100 C for 2 hr. The cooled solution was extracted with chloroform. Recovery of the product in the normal way gave a mixture (55 mg) of starting material and diacetate VII with the latter predominating as indicated by TLC. Chromatography of the mixture on a column of Woelm alumina (2.5 g; Act. III) gave, on elution with petroleum ether:benzene (1/1), fractions of the diacetate VII (35 mg). The IR spectrum lacked absorption for hydroxyl groups and showed bands at 1,740 and 1,240 cm^{-1} (esters and acetates). The NMR spectrum showed two proton signals at 5.2 τ (multiplet) attributed to the >C*H*-OAc groups.

$CH_3(CH_2)_4CH_2CH_2CH_2COOCH_3$
III

$CH_3OOC(CH_2)_7COOCH_3$
IV

$CH_3(CH_2)_4COOCH_3$
V

$CH_3OOCCH_2CH_2CH_2(CH_2)_7COOCH_3$
VI

$CH_3(CH_2)_4CH(OAc)—CH(OAc)CH_2CH=CH(CH_2)_7COOCH_3$
VII

Discussion

Examination of the reaction mixture obtained by treatment of methyl linoleate with one mole of monoperphthalic acid showed that it consisted of starting material, the two monoepoxides and a minor quantity of a more polar material. Furthermore, although the two monoepoxides were not distinguishable from each other in GLC, they could be differentiated on TLC (7). Thus, by careful chromatography of the mixture on a silica gel column we were able to separate amounts of each of the two monoepoxides in a pure state.

The more polar monoepoxide was identified as methyl *cis*-9,10-epoxyoctadec-*cis*-12-enoate (II) and was obtained in 18% yield (calculated with respect to the total monoepoxide fraction). Repeated chromatography of the mixture of monoepoxides increased the yield to 39%.

The mass spectrum of II indicated a molecular weight of 310, corresponding to the formula $C_{19}H_{34}O_3$. The infrared spectrum (CS_2 or film) showed absorption bands between 830–850 cm^{-1} and 770 cm^{-1} (*cis*-epoxide) (8), at 1,650 cm^{-1} (C = C stretching) and at 720 cm^{-1} (*cis*-double bond). The possibility that the double bond had isomerized to the *trans* form was excluded by the lack of absorption at 960 cm^{-1} (9).

The NMR spectrum of II showed a triplet at 9.1 τ (3 H; CH_3–CH_2–), a broad peak centered at 8.7 τ (18 H; $-(CH_2)_n-$), multiplets between 7.6–8.0 τ (6 H; $-CH_2-C=$ and $-CH_2-COOCH_3$) and at 7.1 τ (2 H; H–C(–O–)C–H), a singlet at 6.3 τ (3 H; $-OCH_3$), and a 10 line multiplet centered at 4.5 τ (2 H; H–C = C–H).

The position of the double bond and of epoxide ring in II could not be localized from the physicochemical data but were established by oxidative degradation.

Application of the classical method of degradation described by Gunstone (10) for vernolic acid allowed the determination of the position of the epoxide ring of II. The monoepoxide II on treatment with acetic acid yielded a mixture of the two possible monoacetates. This on hydrogenation with a palladium catalyst followed by alkaline hydrolysis was transformed into (±)-threo-9,10-dihydroxystearic acid, m.p. 95 C (5). The latter on successive treatments with diazomethane, sodium periodate, silver oxide and diazomethane gave a mixture of methyl pelargonate (III), and methyl azelate (IV), identified by comparison in GLC-MS with authentic samples.

To determine the position of the double bond the epoxyacid was oxidized with a dilute aqueous solution of sodium periodate and potassium permanganate (11).

The products from this oxidation, after esterification with diazomethane, were identified as methyl caproate (V) and methyl azelate (IV). The formation of only these two acids indicated that the oxidative degradation with periodate permanganate had not resulted in isomerization of the double bond. This evidence confirmed that the epoxyacid was (±)-coronaric acid.

The less polar monoepoxide, obtained in 40% yield, was identified as methyl *cis*-12,13-epoxyoctadec-*cis*-9-enoate (I). IR and NMR data were identical to those of II. The position of epoxide ring was established by a sequence of reactions parallel to that for the monoepoxyester II and in this case yielded methyl caproate (V) and methyl dodecanedioate (VI).

Alkaline hydrolysis of I yielded an epoxyacid (m.p. 35–36 C) which on degradation with periodate permanganate gave the same acids as those obtained by similar degradation of (±)-coronaric acid described above. All these results are in agreement with those reported by Osbond (6) for (±)-vernolic acid.

In a publication on the NMR of fatty acids it was reported that the acetylated oil of *Vernonia colorata* (12) showed signals for the protons on carbon carrying the acetoxyl group at −2.4 p.p.m. (with reference to the paraffinic methylenes). This assignment resulted from a comparison with the position of the signals for the analogous protons of 9,10-diacetoxystearic acid. Since the reported value for the resonance of these protons did not appear in accordance with their nature, we have recorded the NMR spectrum of methyl 12,13-diacetoxyoctadec-9-enoate (VII). In fact the protons concerned appear at 5.2 τ (−3.8 p.p.m. with reference to the paraffinic methylenes) expected for protons in such an environment.

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