Some Derivatives of 5-Eicosenoic Acid

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Abstract

cis-5-Eicosenoic acid and its methyl ester have been epoxidized. Preparation of an hydroxylactone through lactonization of both the 5,6-epoxy acid and the 5,6-dihydroxy acid has been investigated. 5-Eicosenoic acid has also been converted to γ-lactone through use of perchloric or *p*-toluenesulfonic acid. The preparation of several other related new compounds is described.

Introduction

cis-5-EICOSENOIC ACID is the major component of oil from seed of *Limnanthes douglasii* (1–3), a possible new oilseed crop. Because of the proximity of its ethylenic bond to the carboxyl group, this fatty acid should be a good subject for reactions such as lactonization which involve both of these groups. Such lactones should prove to be versatile intermediates for further synthesis. The conversion of oleic acid and other unsaturated fatty acids to γ-lactones through use of heat and acid catalysts has been reported (4–6). It appeared likely that δ-lactones could be prepared through an epoxide intermediate. The present work describes the preparation of lactones and other related derivatives from 5-eicosenoic acid.

Experimental

Analytical Methods

Melting points are corrected unless noted otherwise. Boiling points are uncorrected. Infrared spectra were obtained on either a Perkin-Elmer 137B or 237B spectrophotometer. In all cases where wavelengths are reported the latter instrument was used. Unless noted otherwise, spectra were obtained as 1% solutions of the samples in either carbon tetrachloride or carbon disulfide. TLC analyses were carried out on 250μ thick plates of Absorbosil 1 using petroleum ether:diethyl ether:acetic acid, 60:40:2 by volume, as developing solvent. Samples were spotted on the plates as 5–20% solutions in either chloroform, diethyl ether, or acetone.

The neutral equivalent of the epoxy acid was determined by the following procedure: Samples of the epoxide (ca. 0.14 g, accurately weighed) were dissolved in 70-ml portions of ethanol and cooled in an ice-water bath during titration with 0.025 *n* aqueous sodium hydroxide, using *m*-cresol purple as indicator. If titration was carried out at room temperature or higher, indefinite end-points were encountered, and less than the theoretical amount of alkali was absorbed. Values were corrected by a factor obtained by titrating pure stearic acid in the same manner. Oxirane oxygen determinations were made by a micro procedure using hydrogen bromide titration. Wijs iodine value determinations were made by Thionville Laboratories, New Orleans, La. Other analyses were made by Galbraith Laboratories, Inc., Knoxville, Tenn., who determined oxygen by a modified Unterzaucher method and molecular weights through use of a vapor pressure osmometer.

cis-5-Eicosenoic Acid. Methyl 5-eicosenoate was obtained by fractional distillation of the mixed methyl esters prepared from the seed oil of *Limnanthes douglasii.* It distilled at 180–182/1.0 mm, had N_D^{25}, 1.4520, and was approximately 99% pure by GLC analysis. Unless noted otherwise, the *cis*-5-eicosenoic acid used in this work was obtained by saponification of this ester, and melted at 26.0–27.5C.

Anal. Calc for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33; O, 10.31; neut. equiv., 310.5; iodine value, 81.7. Found: C, 77.34; H, 12.43; O, 10.46; neut. equiv., 306; iodine value 80.5.

4-Eicosanolactone. Method A: A mixture of 3.10 g (0.01 mole) of 5-eicosenoic acid and 1.0 ml of 70% perchloric acid in a glass stoppered Erlenmeyer flask was immersed in an oil bath maintained at 85C and stirred for 16 hr. The reaction mixture was then taken up in 100 ml of petroleum ether and washed 3 times with 50-ml portions of distilled water containing sodium chloride. After the petroleum ether had been removed at room temperature under nitrogen, 3.05 g of solid remained which contained ca. 75% γ-lactone by infrared analysis. 4-Octadecanolactone was used as standard for the infrared determination. A 3.00-g sample of the crude lactone was recrystallized twice from carbon tetrachloride to yield 1.40 g of white solid (mp, 59.2–60.3C) having a γ-lactone content of 99% by infrared analysis. Neither the melting point nor the apparent lactone content was increased by further crystallization from carbon tetrachloride or absolute ethanol.

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33; O, 10.31; sap equiv, 310.5: Found: C, 77.48; H, 12.25; O, 10.14; sap equiv, 321.

The infrared spectrum of the 4-eicosanolactone was qualitatively identical to that of 4-octadecanolactone.

Method B: 5-Eicosenoic acid (3.10 g) and *p*-toluenesulfonic acid monohydrate (1.90 g) in a glass stoppered Erlenmeyer flask were stirred and heated at 130C for 4½ hr. The reaction mixture was cooled to room temperature and then triturated 4 times with 25-ml portions of petroleum ether (bp, 30–60C). The petroleum ether extract was stirred for 1 hr with 1.00 g of Dowex 1 × 4 resin in the anion state. The petroleum ether solution was decanted, the resin was washed 3 times with 10-ml portions of petroleum ether, then petroleum ether was removed from the combined solutions by evaporation under a stream of nitrogen gas. The residue, 1.81 g analyzed 89% lactone by infrared and melted at 56.0–59.0C. Crystallization from carbon tetrachloride gave 1.40 g of white crystals, mp 59.2–59.7C, which analyzed 99% γ-lactone by infrared.

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33; O, 10.31; sap equiv, 310.5. Found: C, 77.26; H, 12.26; O, 10.42; sap equiv, 298.

cis-5,6-Epoxyeicosanoic Acid. A 31.05-g sample (0.10 mole) of 5-eicosenoic acid, dissolved in 70 ml of acetic acid, was stirred and maintained at 15–20C during the dropwise addition, over a period of 5 min, of 14.9 ml of peracetic acid which contained 0.11 mole of active oxygen. Peracetic acid was treated with sodium acetate immediately before use to remove sulfuric acid. The reaction mixture was maintained at 15–20C for an additional 55 min and at 25C for an additional 3 hr and then poured into 700 ml of ice water. The precipitate was separated by filtration and washed with 6 portions, 100 ml each, of ice

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water, after which it was crystallized twice from acetone (10 ml/g of epoxide) at 5C. The purified epoxide, 16.00 g melted at 64.6–65.6C and its infrared spectrum contained the weak band at 12.1 μ characteristic of *cis*-epoxides.

Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.30; O, 14.56; oxirane O, 4.90; neut equiv, 326.5. Found: C, 73.48; H, 11.70; O, 14.74; oxirane O, 4.58; neut equiv, 326.

TLC analysis of the epoxy acid indicated that the sample contained a contaminant which had the same R_f value as the hydroxy lactone. Both because of the agreement of the neutral equivalent with the theoretical value and the complete absence of any indication of hydroxy lactone contaminant in the infrared spectrum of the epoxy acid, it was concluded that the additional spot arose either from a contaminant other than the hydroxy lactone which had the same R_f value, or that hydroxy lactone was being produced from the epoxide during the analysis. The presence of a trail connecting the two spots tended to support the latter conclusion. When a sample of the epoxide was adsorbed on Absorbosil 1 for ½ hr and then recovered and examined by infrared, it was found to contain some lactone. Therefore, it is probable that the extraneous spot observed by TLC is hydroxy lactone which formed during the analysis.

The mother liquor from the first crystallization of the epoxide was crystallized at −5C, yielding 6.90 g of crystals, mp 50–65C. Its infrared spectrum indicated that this material contained a substantial proportion of an ester. A diethyl ether solution of the sample was washed first with 200 ml of 2% sodium carbonate solution and then with water and finally dried over sodium sulfate. The residue remaining after removal of the solvent, 2.18 g, melted at 65.7–78.4C. After 2 recrystallizations from carbon tetrachloride at 5C, the sample (1.59 g) melted at 78.3–79.5C. Bands of particular interest in the infrared spectrum are a sharp band at 2.78 μ and a broader band at 2.88 μ characteristic of the hydroxyl group, and bands of medium or strong intensity at 8.10, 8.58, 9.53 and 10.72 μ. Bands similar to the latter 4 appear at approximately these wavelengths in the spectrum of δ-valerolactone but not in that of ε-caprolactone (7). The melting point of this material was not depressed when it was mixed with the -hydroxy-5-eicosanolactone described below.

Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73; O, 14.70; mol wt, 326.5. Found: C, 73.76; H, 11.71; O, 14.50; mol wt, 328.

6-Hydroxy-5-Eicosanolactone. A number of preliminary experiments were carried out in order to establish suitable conditions for preparation of 6-hydroxy-5-eicosanolactone. In these experiments 0.10-g samples of either 5,6-epoxyeicosanoic acid, mp 61–78C, or 5,6-dihydroxyeicosanoic acid, mp 97.5–99.2C were heated, with or without solvent (1.0 ml), and progress of the lactonization was followed by noting the disappearance in the infrared spectrum of a band at about 5.84 μ attributable to carboxylic acid, and the concurrent development of a band at about 5.75 μ attributable to ester. For the epoxide maximum conversion of acid to ester was obtained in 3 hr either without solvent at 80C or in refluxing xylene, while less than 50% conversion to ester occurred when the sample was refluxed in toluene for 3 hr. When a highly purified sample of epoxide was refluxed in xylene, lactonization required ca. 10 hr, but if 1% of dihydroxyeicosanoic acid was added, lactonization was completed in about 3 hr under the same conditions. The dihydroxy acid alone was converted completely, or nearly completely, to ester within 10 min either at 110C without solvent or in refluxing xylene, and in about 3 hr in refluxing carbon tetrachloride. In all cases, the infrared spectra indicated that products obtained without use of solvent contained much larger amounts of by-products than those prepared in a solvent. On the basis of the above results, refluxing of the dihydroxy acid in xylene appeared to be the most satisfactory method of preparing the hydroxy lactone.

Accordingly, crude *cis*-5,6-epoxyeicosanoic acid was prepared from 31.05 g of eicosenoic acid as described above, saponified and then acidified with 10% aqueous acetic acid. The precipitated dihydroxyeicosanoic acid was separated by filtration, washed with six portions (100 ml each) of distilled water and then partially dried on the filter funnel. The sample, along with 350 ml of xylene, was then transferred to a flask equipped with a stirrer, condenser and Dean-Stark trap, and the solution was refluxed until water no longer collected in the trap (35 min). At this point no band was discernible at 5.85 μ in the infrared spectrum of the compound so it was assumed that little or no acid remained. The precipitate which formed when the reaction mixture, at room temperature, was diluted to 1:1 with petroleum ether was triturated with benzene to remove a small amount of dihydroxy acid and the benzene soluble fraction was crystallized 3 times from carbon tetrachloride to yield 14.35 g of crystals, mp 78.8–79.7C. The infrared spectrum of the compound was identical to that of the hydroxy lactone obtained as a by-product of the epoxidation reaction. No impurities were discerned in the sample by TLC analysis.

Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73; O, 14.70; OH, 5.21; sap equiv, 326.5. Found: C, 73.64; H, 11.70; O, 14.74; OH, 4.97; sap equiv, 329.

Threo-5,6-Dihydroxyeicosanoic Acid. A 1.00-g sample of *cis*-5,6-epoxyeicosanoic acid was refluxed for ½ hr with a solution of 0.61 g of 87% KOH in 10 ml of 90% ethanol. The saponification mixture was diluted with 20 ml of distilled water and acidified in the presence of 50 ml of diethyl ether with 1.4 ml of glacial acetic acid dissolved in 14 ml of distilled water. The free acid was extracted twice more with 50-ml portions of diethyl ether and the ether solution was washed with water and then dried over sodium sulfate. The ether was removed at room temperature leaving 1.03 g of white crystals, mp 98.5–99.2C. A 0.75 g sample of this material was crystallized twice from chloroform to yield 0.66 g of 5,6-dihydroxyeicosanoic acid, mp 99.3–99.9C. Only one spot was observed when the sample was subjected to TLC analysis. The infrared spectrum of the compound, obtained as a Nujol mull, was consistent with the dihydroxy acid structure.

Anal. Calcd for $C_{20}H_{40}O_4$: C, 69.72; H, 11.70; O, 18.58; OH, 9.87; neut equiv, 344.5. Found: C, 69.60; H, 11.65; O, 18.56; OH, 9.63; neut equiv, 346.

Hydrogenation of cis-5,6-Epoxyeicosanoic Acid. A 3.65-g sample of *cis*-5,6-epoxyeicosanoic acid was mixed with 50 ml of ethanol and 0.31 g of 10% Pd/C catalyst and hydrogenated for 45 hr in a shaking type hydrogenation apparatus. A 3.00-g sample of the recovered product (total product, 3.49 g) was refluxed for ½ hr in xylene, after which the reaction mixture was diluted with diethyl ether and separated into an acid fraction (1.40 g) and an ester fraction

(1.43 g) by means of sodium carbonate washing. Repeated crystallization of the neutral fraction from a variety of solvents failed to give pure 5-eicosanolactone. The best product isolated, 0.17 g, melted at 50.5–53.1C. TLC analysis of the product indicated that it contained a small amount of the hydroxy lactone, though no hydroxyl band was discernible in its infrared spectrum. The infrared spectrum had bands at 8.08, 9.51, and 10.72 μ, similar to those found in the spectra of 6-hydroxy-5-eicosanolactone and δ-valerolactone. Its infrared spectrum differed from that of 4-eicosanolactone in several respects including: Its C = O stretching vibration was located at 5.72 μ while that of the γ-lactone was at 5.61 μ. The strongest of the bands in the area associated with the C–O stretching mode appeared at 8.08 μ in the δ- but at 8.50 μ in the γ-lactone. The strong band at 9.51 in the δ-lactones was not found in the γ-lactone. A band of medium intensity occurred at 10.72 μ in the δ-, but at 10.93 μ in the γ-lactone.

Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33; O, 10.31. Found: C, 77.27; H, 12.25; O, 10.43.

A 0.18 g sample of crystals (mp 78.0–79.8C) was also isolated from the neutral fraction. Its melting point was not depressed by mixture with 6-hydroxy-5-eicosanolactone and its infrared spectrum and TLC characteristics were identical to those of that compound.

Repeated crystallization from various solvents of the acid fraction gave 0.24 g of material (mp, 86.2–88.0C) which appeared, on the basis of its infrared spectrum, to be hydroxy acid. TLC analysis of the product indicated that it was hydroxy acid contaminated with a small amount of dihydroxy acid. Since the 5-isomer should have lactonized completely, or nearly completely, it is assumed that the material is principally 6-hydroxyeicosanoic acid.

Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27; O, 14.61. Found: C, 73.18; H, 12.20; O, 14.52.

In addition to the hydroxy acid, 0.18 g of crystals (mp 76–88C) was isolated from the acid fraction. It appeared, on the basis of its infrared spectrum and TLC analysis, to be saturated fatty acid contaminated with small amounts of mono- and dihydroxy acids.

TLC of the whole hydrogenation product gave 6 spots which corresponded in R_f values to monohydroxy acid, dihydroxy acid, lactone, hydroxylactone and unreacted epoxide or keto acid. All or part of the hydroxy lactone indicated by TLC analysis may have arisen through isomerization of unreacted epoxide during the analysis.

Methyl cis-5,6-Epoxyeicosanoate. A 32.4-g sample of methyl *cis*-5-eicosenoate was epoxidized and the crude epoxide recovered in the manner described for 5-eicosenoic acid. The crude epoxide was crystallized at −5C from 340 ml of acetone to yield 26.08 g of crystals (mp 28–62C). The sample was taken up in 260 ml of carbon tetrachloride and crystallized at 5C to remove 2.24 g of material (mp 81.2–83.0C). Solvent was removed from the mother liquor and the residue was dissolved in 200 ml of petroleum ether (bp 30–60C) and, after removal of a small amount of insoluble material, was crystallized at −5C to yield 10.11 g of crystals which melted at 29.2–29.9C. The infrared spectrum had a weak band at 12.1 μ characteristic of *cis*-epoxides. No impurity was discernible in the sample by TLC.

Anal. Calcd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84; O, 14.09; Oxirane O, 4.70. Found: C, 74.22; H, 11.92; O, 13.96; Oxirane O, 4.43.

Methyl Threo-5,6-Dihydroxyeicosanoate. The fraction separated from the epoxy ester by crystallization from carbon tetrachloride, after two additional crystallizations from that solvent, amounted to 2.06 g and melted at 83.0–83.8C. Its infrared spectrum had two sharp bands at 2.74 and 2.79 μ, attributable to O–H stretching of the free and bonded hydrogens, respectively, of the intramolecularly bonded vicinal dihydroxyl group, and a broad band at 2.85 μ attributable to intermolecularly bonded hydroxyl (8).

Anal. Calcd for $C_{21}H_{42}O_4$: C, 70.34; H, 11.81; O, 17.85; OH, 9.49. Found: C, 70.15; H, 11.72; O, 17.78; OH, 9.26.

5-Eicosenamide. A sample of 300 g of methyl 5-eicosenoate (assaying 90% by GLC analysis) was saponified and the resulting acid converted to the amide as follows: The acid and 70 ml of xylene were heated under reflux (using a Dean-Stark trap) for 5 hr while a slow stream of ammonia was bubbled into it, giving a quantitative conversion to crude amide, mp 63–69C. After 3 recrystallizations from hexane, 10 g of this material gave 6.5 g of 5 eicosenamide, mp 79–81C (uncor.).

Anal. Calcd for $C_{20}H_{39}NO$: C, 77.61; H, 12.70; N, 4.53. Found: C, 77.75; H, 12.77; N, 4.58.

N-Hydroxyethyl-5,6-Dihydroxyeicosanamide. A mixture of 5.12 g (0.016 mole) of 6-hydroxyeicosanolactone and 25 ml of ethanolamine was heated under reflux for 2 hr. The light brown reaction mixture solidified on standing overnight. An attempt to partition it between water and diethyl ether revealed that a solid was present which was only slightly soluble in either solvent. After the solid had been separated from the ether:water mixture by filtration, it was washed first with water until the wash-water was neutral and then with 2 portions (50 ml each) of diethyl ether, after which it was air dried. The yield of product was 5.49 g (90%), mp 103–104.5C.

Anal. Calcd for $C_{22}H_{45}NO_4$: C, 68.17; H, 11.70; N, 3.61; OH, 13.16. Found: C, 67.57; H, 11.66; N, 3.70; OH, 13.57.

Discussion

A 75% conversion of *cis*-5-eicosenoic acid to 4-eicosanolactone was obtained through use of perchloric acid catalyst, essentially as reported by Swern and Coleman (6) for the conversion of oleic acid to 4-octadecanolactone. There was no evidence that the location of the double bond in a position closer to the carboxyl than in oleic acid had any influence on the course of the reaction. Many other acid catalysts were investigated in search of a safer reagent than perchloric acid for promoting the reaction. None of these was as effective as perchloric acid, but *p*-toluene sulfonic acid proved to be fairly satisfactory, giving a 65% conversion to the γ-lactone.

Both *cis*-5-eicosenoic acid and its methyl ester were satisfactorily epoxidized by peracetic acid. It was found that the dihydroxy acid derived from the epoxide lactonized much more readily than the epoxide itself and that addition of a catalytic quantity of dihydroxy acid to the epoxide resulted in an increase of its rate of lactonization, probably through hydrolysis of the epoxide to the more readily lactonizable dihydroxy acid by water introduced into the system through lactonization of the dihydroxy acid initailly present. 6-Hydroxy-5-eicosanolactone was best prepared from 5-eicosenoic acid by epoxidation, followed by hydrolysis of the epoxide ring, and refluxing of the resultant dihydroxy acid in xylene using a Dean-Stark trap to remove the water formed in the reaction.

Our assumption that the 5-hydroxyl group is involved in the lactonization of 5,6-dihydroxyeicosanoic acid cannot be stated unequivocally, but, as pointed out in an analogous case, the precedent for assigning the δ- rather than the ε-lactone structure is overwhelming (9). Furthermore, we found that a mixture of 6 and 7 hydroxystearic acids (from the hydrogenation of 6,7-epoxystearic acid) failed to yield any lactone under the conditions used to effect the lactonization described here. The fact that the infrared spectrum of the hydroxy lactone is quite similar to that of δ-valerolactone but very different from that of ε-caprolactone is additional evidence that the δ-lactone was formed.

The preparation of 5-eicosanolactone by hydrogenation of the 5,6-epoxy acid and subjection of the resulting mixture to lactonization conditions was briefly explored. Although separation of neutral and acidic materials after the lactonization gave quantities which suggested approximately equal amounts of 5- and 6-hydroxy acid from the hydrogenation, the large amounts of by-products formed during both the hydrogenation and lactonization reactions make it impossible to draw any definite conclusions about this matter. Only small amounts of nearly pure 5-eicosanolactone and 6-hydroxyeicosanoic acid were isolated from the reaction mixture.

In the course of this work two new amides were prepared. 5-Eicosenamide was prepared from the acid by the procedure of Placek and Dollear (10), involving ammonolysis in refluxing xylene. N-Hydroxyethyl-5,6-dihydroxyeicosanamide was readily obtained on refluxing the hydroxy δ-lactone prepared in this work with ethanolamine.

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