Technical

The Performic Acid Oxidation of Linoleic Acid

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ABSTRACT AND SUMMARY

The performic acid oxidation of linoleic acid has been shown to form 9,12-dihydroxy-*trans*-10,11-methylene-heptadecanoic acid (I) after hydrolysis of the formate ester. A sequence of reactions led to the identification of dimethyl-*trans*-1,2-cyclopropanedicarboxylate by gas liquid chromatography. Spectroscopic evidence is presented for the *trans* geometry in I. Failure of the monoepoxide of linoleic acid to give the formate ester of I suggests the alternative that a homoallylic carbonium ion is formed directly upon attack of the peroxide reagent.

INTRODUCTION

One of the classic reactions in organic chemistry is the peroxidic oxidation of an alkene double bond. In the case of performic acid, usually an intermediate epoxide is formed, which then is opened by an attacking formic acid molecule giving the glycol monoformate ester. This can be hydrolyzed to the glycol. Since nucleophilic attack on the protonated epoxide occurs on the backside, with inversion of configuration at one carbon atom, the two enantiomeric *threo* (RR and SS) glycol isomers are obtained from a *cis* double bond.

Linoleic acid is an interesting substrate for the reaction since it contains two *cis* double bonds which are separated by a methylene carbon. Electrophilic reactions on this system are of concern because of possible interactions between the two adjacent reaction centers. Two pairs of enantiomers of tetrahydroxystearic acids (the RRSS and SSRR pair and the RRRR and SSSS pair) might be expected from peracid treatment of linoleic acid; however the reaction gives poor yields of the tetrahydroxystearic acids (1). MacKay et al. were able to isolate another compound from the product mixture in 20% yield, which they suggested might have a cyclopropane ring. The possible cyclopropane formation from linear substrates under conditions usually associated with epoxide formation is of interest because of recent concern with the cyclization of epoxyolefins especially as metabolic processes, such as in the biosynthesis of lanosterol from epoxysqualene.

RESULTS

An investigation of this $C_{18}H_{34}O_4$ peroxidation product (I) has been carried out which confirms the cyclopropane structure. The infrared spectrum of its methyl ester (II) showed a CH stretching absorption at 3.28 μ indicative of the cyclopropane ring. The near infrared spectrum clearly showed absorptions at 1.642 μ, attributed to the first overtone of the cyclopropyl C–H stretching fundamental, and at 2.213 μ, due to a combination band of the cyclopropyl ring (2,3). Absorptions in the infrared spectrum corresponding to OH stretching were evident (see below). The nuclear magnetic resonance (NMR) spectrum of the methyl ester (II) indicated the presence of two

Oxidation of I with chromic oxide-pyridine gave a diketo-acid (III), $C_{18}H_{30}O_4$, m.p. 88 C. This was esterified with diazomethane to thediketo-ester (IV), m.p. 45 C. This same diketo-ester was prepared from the methyl ester (II) by oxidation with manganese dioxide. Oxidation of a carbinol with manganese dioxide generally requires activation by a double bond or a cyclopropyl group (4).

A Baeyer-Villager oxidation (5) of the diketoacid (III) gave the diester V. Hydrolysis of V with sodium hydroxide gave 8-hydroxyoctanoic acid, *trans*-cyclopropane-1,2-dicarboxylic acid, and pentanol, identified by GLC analysis. Similarly, lithium aluminum hydride reduction of the diester V gave 1,8-octandiol, *trans*-cyclopropane-1,2-dimethanol and pentanol.

Baeyer-Villager oxidation of cyclopropyl methyl ketone gives cyclopropyl acetate, which involves migration of the cyclopropyl group rather than the methyl group. The results with the diketone (III), in which an alkyl group rather than a cyclopropyl group has migrated, indicate that the migratory aptitude of cyclopropyl lies between methyl and alkyl.

Evidence for the *trans* structure in I was obtained from the OH stretching adsorptions in the infrared spectrum of the methyl ester (II). A solution in carbon tetrachloride shows a symmetrical H-bonded absorption at 3376.3 cm^{-1} as well as the free O–H absorption at 3639.3 cm^{-1}. At high dilutions the free OH peak increases in intensity and the H-bonded absorption decreases, indicating the intermolecular nature of the H-bonding. Thus the *trans* configuration of

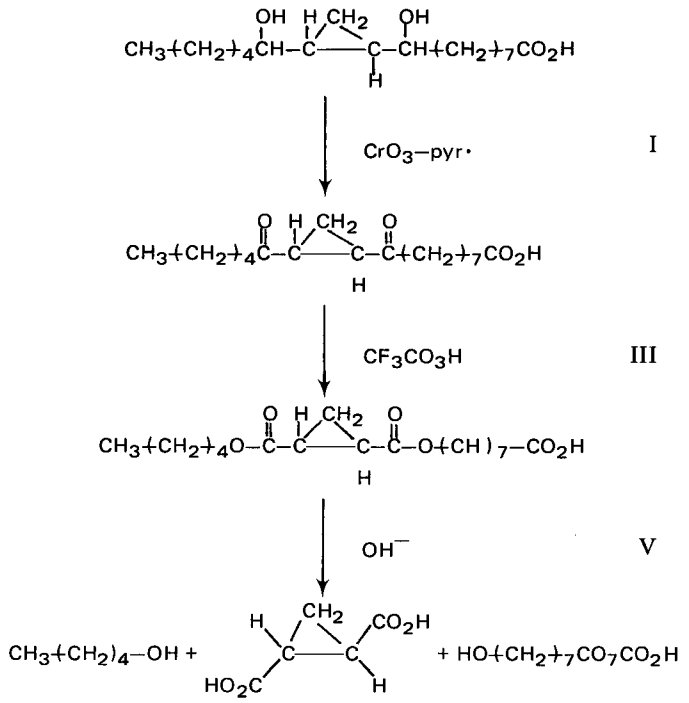

FIG. 1. Degradation of I.

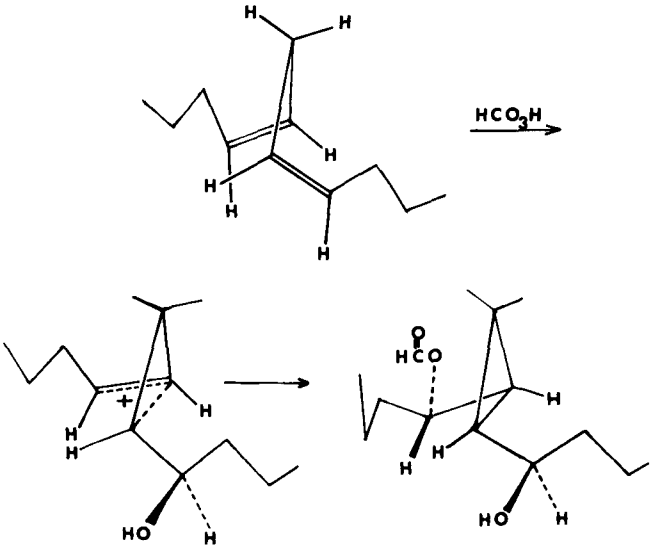

FIG. 2. Proposed addition mechanism.

the carbinol groups in II would not allow much intramolecular H-bonding, and none was reported for 3,3-dimethylcyclopropane-*trans*-1,2-dimethanol (6).

The NMR spectrum for the ester II also supports assignment of the *trans* geometry. A multiplet is exhibited at 0.4 δ with an intensity corresponding to two hydrogens. This δ-value compares with that of the methylene hydrogens of *trans*-cyclopropane-1,2-dimethanol. The other two cyclopropane hydrogens in the spectrum of II are obscured by the end methyl group absorption. Cyclopropanes which are *cis* substituted generally show a complex peak at -0.3 δ for the single hydrogen *trans* to the substituents (7). Thus the *cis* geometry for the ester II can be ruled out, since the AA′ part of an AA′BB′ complex is observed at 0.4 δ.

Two possibilities for the formation of the cyclopropanediol might be suggested. First, the monoepoxide is formed and then the protonated oxirane ring opens with concomitant cyclization. This kind of cyclization occurs in the formation of six-membered rings (8) from epoxyolefins and has particular significance in the formation of lanosterol from squalene monoepoxide (9). The monoepoxide of linoleic was prepared; however, the same conditions used in the performic acid oxidation of linoleic did not yield the cyclopropanediol fatty acid (I).

The second possibility is the direct formation of a stabilized carbonium ion (homoallylic type) which gives the cyclopropane product. An analogous reaction has been shown for the peracid oxidation of norbornylene (10). A mechanism of this type or a similar mechanism with a dioxolan transition state, proposed by Kwart et al. (11), involving interactions or bonding between the two double bonds can account for the product from linoleic acid.

Presumably, the conformation with the *anti* relationship of the double bonds is more stable than a *syn* conformation and thus would form the *trans* product (Fig. 2). The configuration of the OH groups in the products has not been proven, but we might expect them to be as shown in Figure 2 on the basis of back side attacks.

In contrast with the products obtained from reactions in formic acid, the ring opening of the monoepoxides with boron trifluoride etherate has been shown to give *cis* and *trans* ketocyclopropanes and cyclic ethers (12,13).

EXPERIMENTAL PROCEDURES

Performic Acid Oxidation

The procedure of MacKay (1) was followed, using 30% hydrogen peroxide rather than 90%, the temperature of the reaction being maintained at 40 C by adjusting the rate of dropwise addition of the performic acid. After hydrolysis with 3 N sodium hydroxide, impure δ-tetrahydroxystearic acid (sativic acid) was filtered from the ether-aqueous interface. The ether solution was dried with magnesium sulfate and concentrated. Impure γ-tetrahydroxystearic acid crystallized out on refrigeration at 0 C for several hours. The mother liquor was evaporated and the residue dissolved in acetone. After several days of refrigeration at 0 C, white crystals of 9,12-dihydroxy-*trans*-10,11-methylenehexadecanoic acid (I) formed, m.p. 84-85 C. Recrystallization from acetone increased the melting point to 90-91 C. Usually more of the compound could be obtained by further concentration of the acetone mother liquor and cooling. Typical yields were δ-sativic, 6%; γ-sativic, 5%; and I, 20%.

Analysis

Calcd. for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.56; H, 10.64.

Methyl 9,12-dihydroxy-*trans*-10,11-methylenehexadecanoate

Diazomethane in ether distilled from a suspension of 30% aqueous potassium hydroxide, bis-(N-methyl-N-nitroso)-terephthalamide, diethylene glycol monomethyl ether, was added to a solution of the acid I in ether with a few drops of methanol until the solution turned slightly yellow. It was allowed to stand 15 min and then was evaporated under nitrogen. Recrystallization of the white solid from a small volume of acetone gave white crystals, m.p. 45-46 C.

Infrared spectrum (0.0016 M in carbon tetrachloride (1.0 cm cell): ν_{max} 3639.3 cm^{-1} (free OH), 3376.3 cm^{-1} (H-bonded OH). At 0.00016 M the intensity of the 3376.3 cm^{-1} peak decreased to one-tenth the intensity of the 3639.3 cm^{-1} peak.

Near infrared spectrum (5% in carbon tetrachloride–1.0 cm cell): λ_{max} 1.642 μ, 2.213 μ.

NMR spectrum ($CDCl_3$): δ 0.4 multiplet (2H) (cyclopropane-CH_2); 0.9 triplet ($C-CH_3$); 1.3 multiplet $(CH_2)_n$; 2.3 triplet (2H) ($-CH_2-CO_2-$); 2.7 multiplet (2H) ($-CHOH$); 3.6 singlet (3H) ($-OCH_3$); 6.0 broad singlet (2H) ($-OH$).

9,12-Dioxo-*trans*-10,11-methylenehexadecanoic Acid (III)

To a solution of 500 mg of I in 5 ml of pyridine was added the chromic acid-pyridine complex (14) prepared from 1 g of chromic acid and 10 ml of pyridine. After mixing, the stoppered flask was allowed to stand overnight. The mixture was poured into 200 ml of water and acidified with dilute sulfuric acid. The dark suspension was extracted with ether three times. It was necessary to break the emulsion by filtration through Celite. The ether extracts were washed with water, with dilute acid, and with water and saturated sodium chloride. The solution was dried over magnesium sulfate and evaporated, giving a white powder. Recrystallization from acetone gave white crystals of (III), m.p. 88 C, 330 mg (66%).

Analysis

Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.48; H, 9.67.

Methyl 9,10-dioxo-*trans*-10,11-methylenehexadecanoate (IV)

The ketone (III) was methylated with diazomethane as above and recrystallized from ethanol-water, giving white plates, m.p. 45 C.

Near infrared spectrum (5% in carbon tetrachloride): λ_{max} 1.632 μ, 1.682 μ, 2.215 μ.

Oxidation of Methyl Ester (II)

A mixture of 1 g of active manganese dioxide (15) and 100 mg of the methyl ester II in 30 ml of petroleum ether (30-60) were vigorously stirred overnight at room temperature. The mixture was filtered and the manganese dioxide washed with petroleum ether. Evaporation of the petroleum ether gave a white material which was recrystallized from ethanol-water, giving 58 mg of the diketone ester, m.p. 45 C. A mixed m.p. with the methyl ester of the product of chromate oxidation (IV) was not depressed. The infrared spectra were identical.

Baeyer-Villager Oxidation of the Diketoacid (III)

The method of Emmons and Lucas (5) was used to effect the oxidation. The resulting oily diester (V) was obtained in 87% yield. The diester (V) was cleaved in two ways. Half was hydrolyzed with 3N sodium hydroxide. The basic solution was acidified with dilute sulfuric acid and extracted with ether. The ether solution was dried and concentrated and treated with diazomethane. Gas chromatographic analysis with comparisons of retention times with authentic standards showed the presence of dimethyl *trans*-cyclopropane-1,2-dicarboxylate, methyl 8-hydroxyoctanoate, and 1-pentanol. Trace amounts of dimethyl nonanedioate and dimethyl octanedioate were also present.

The other half of the diester was refluxed with lithium aluminum hydride in ether, and a saturated solution of sodium sulfate was added dropwise. The ether solution was filtered and subjected to GLC analysis. *Trans*-cyclopropane-1,2-dimethanol, 1,8-octanediol, and 1-pentanol were observed.

ACKNOWLEDGMENT

Helpful discussions with David Howton, Robert A. Stein, and Vida Slauson were greatly appreciated. The support provided by PHS Training Grant HTS-5306 is gratefully acknowledged.

REFERENCES

1. MacKay, A.F., N. Levitin, and R.N. Jones, J. Am. Chem. Soc. 76:2383 (1954).
2. Washburn, W.H., and J.J. Mahoney, Ibid. 80:504 (1958).
3. Weitkamp, H., and F. Korte, Tetrahedron. 20:2125 (1964).
4. Crombie, L., and J. Crossley, J. Chem. Soc. 4983 (1963).
5. Emmons, W.D., and G.B. Lucas, J. Am. Chem. Soc. 77:2287 (1955).
6. Kuhn, L.P., P. von R. Schleyer, W.F. Baitinger, Jr., and L. Eberson, Ibid. 86:650 (1964).
7. Minnikin, D.E., Chem. and Ind. 2167 (1966).
8. Goldsmith, D.J., J. Am. Chem. Soc. 84:3913 (1962).
9. Corey, E.J., W.E. Russey, and P.R.O. de Montellano, Ibid. 88:4750 (1966); E.E. van Temelen, J.D. Willett, R.B. Clayton, and K.E. Lord, Ibid. 4752.
10. Schaefer, J.P., Ibid. 82:4091 (1960).
11. Kwart, H., P.S. Starcher, and S.W. Tinsley, Chem. Comm. 335 (1967).
12. Cononica, L., M. Ferrari, U.M. Pagnoni, F. Pelizzoni, S. Maroni, and T. Salvatori, Tetrahedron, 25:1 (1969).
13. Conacher, H.B.S., and F.D. Gunstone, Chem. Comm. 984 (1967).
14. Poos, G.I., G.E. Arth, R.E. Beyler and L.H. Sarett, J. Am. Chem. Soc. 75:427 (1953).
15. Attenburrow, J., A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen and T. Walker, J. Chem. Soc. 1094 (1952).

[Received May 10, 1976]