absorb at this wavelength. No explanation is given for the peculiar behavior.

(3) J. Higgins, *Ind. Eng. Chem.*, **59**, 18 (1967).

(4) In all experiments the ionic strength was 1.0 M and the temperature was kept 25 ± 0.1 °C. The spectrophotometric experiments were made with Beckman ACTA III recording spectrophotometer. For the potentiometric measurements, a Radiometer PM 50 pH meter, "Servotrace" potentiometric recorder, and Radelkis iodide and bromide selective electrodes were used. The reference electrode was SCE in all cases. For iodine determination the measurements were made at 460 nm, in the case of bromine at 393 nm; in both cases 1-cm thermostated cells were used. The reaction was started by mixing of solution A (containing reductant and malonic acid) and solution B (containing halogenate).

(5) The concentration of halogen was spectrophotometrically followed and in all cases one maximum was found under the same experimental conditions.

(6) J. Bognár, *Mikrochim. Acta*, **3**, 473 (1968).

(7) A. Skrabal and S. R. Weberitsch, *Monatsh.*, **36**, 211 (1915); W. C. Bray and H. A. Liebhafsky, *J. Am. Chem. Soc.*, **57**, 151 (1935).

(8) The rate of this reaction was determined by following the concentration of bromine spectrophotometrically. The hydrogen ion concentration was kept at constant value of pH 2 using phosphoric acid and sodium dihydrogen phosphate buffer.

(9) R. K. Leopold and A. Haim, *Int. J. Chem. Kin.*, **9**, 83 (1977).

(10) R. J. Field, E. Körös, and R. M. Noyes, *J. Am. Chem. Soc.*, **94**, 8649 (1972).

(11) The integration can be easily carried out if the step size is equal to 10^{-4}. For the calculation a Hewlett-Packard 9810 calculator was used.

(12) The calculated values of the concentrations of both bromine and bromide ion are rather insensitive to the value of k_3 if it is larger than the given limiting one.

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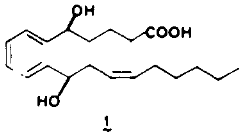
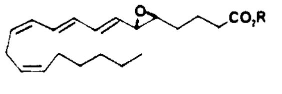
Total Synthesis of (±)-5,6-Oxido-7,9-*trans*,11,14-*cis*-eicosapentaenoic Acid, a Possible Precursor of SRSA

Sir:

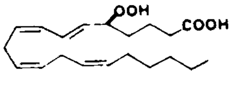
Recent studies by Borgeat and Samuelsson[1] have shown that arachidonic acid is metabolized by rabbit or human peripheral polymorphonuclear leucocytes to a lipoxygenase type product, 5(*S*)-hydroxy-6,8,11,15-eicosatetraenoic acid, and to another substance demonstrated to be 5(*S*),12(*R*)-dihydroxy-6,8,10,14-eicosatetraenoic acid (**1** or double-bond stereoisomer). It was also found that **1** was formed from a labile precursor which could not be isolated but which could be intercepted chemically in various ways. For example, by quenching with methanol a mixture of products results which consists principally of the 12(*R*)- and 12(*S*)-methyl ethers of 5(*S*),12-dihydroxy-6,8,10,14-eicosatetraenoic acid.[2] During an informal discussion of the early results of this project with Professor Samuelsson in March of 1977, one of us proposed that the unstable precursor of **1** could be 5(*S*),6-oxido-7,9,11,14-eicosapentaenoic acid (**2** or Δ-7,9 stereoisomer) which might arise from the lipoxygenase-like intermediate 5(*S*)-hydroperoxy-6-*trans*,8,11,14-*cis*-eicosatetraenoic acid (**3**) by a pathway that has straightforward mechanistic precedent.[3,4] To test the correctness of this surmise, the synthesis of **2** and the Δ-7,9 stereoisomers has been undertaken. The synthesis of **2** has now been accomplished by the route described herein.[5] Very recently, Samuelsson and collaborators have proposed that the structure of the "slow-reacting substance of anaphylaxis" (SRSA)[6-8] involves the linkage of the sulfur of cysteine and C-5 of 5,6-oxido-7,9,11,14-eicosapentaenoic acid as exemplified by **4** (or Δ-7,9 stereoisomer), or a larger molecule having one or more additional amino acid units attached to cysteine.[9] Since there is abundant evidence which implicates SRSA in asthma and other diseases of the respiratory system (especially those involving hypersensitivity), the chemical synthesis of epoxy tetraene **2** and the Δ-7,9 stereoisomers assumes added significance and value for an ultimate proof of detailed structure.



1



2 R : H
14 R : CH_3



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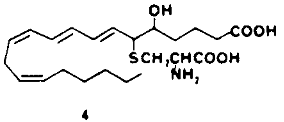

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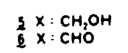
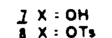
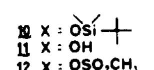


5 X : CH_2OH
6 X : CHO



7 X : OH
8 X : OTs
9 X : $\overset{+}{P}Ph_3$



10 X : OSi—+
11 X : OH
12 X : OSO_2CH_3
13 X : $(CH_3)_2S^+$

The mono-*tert*-butyldimethylsilyl ether (**5**)[10] of *trans*-2,4-hexadiene-1,6-diol[11] was converted into the aldehyde **6** (70% yield) by oxidation with 1.1 equiv or pyridinium dichromate[12] in methylene chloride at 25 °C for 4.5 h.[13] The phosphonium salt **9**, mp 89–90 °C, was prepared by the sequence (1) reaction of amylmagnesium bromide and cuprous bromide–dimethyl sulfide complex in ether with excess acetylene followed by treatment of the adduct with 1-lithio-1-pentyne and hexamethylphosphoric amide (to form the mixed Gilman reagent) at −70 °C and subsequent exposure to excess ethylene oxide at −78 to −20 °C over 1 h to give, after quenching with aqueous ammonium chloride–ammonia buffer and extractive isolation, *cis*-3-nonen-1-ol (**7**);[14] (2) reaction of **7** with *p*-toluenesulfonyl chloride (1.3 equiv) and pyridine (4 equiv) at 0 °C for 9 h to form tosylate **8** (76%); (3) displacement of tosylate by iodide using sodium iodide in acetone at 25 °C for 16 h (90%); and (4) reaction of the iodide with triphenylphosphine in benzene at reflux for 18 h to afford **9** (83%).

The phosphonium iodide **9** was converted into the corresponding ylide by reaction in tetrahydrofuran at −78 °C for 10 min with *n*-butyllithium (1 equiv) and then treated sequentially and without delay with 16 equiv of hexamethylphosphoric amide and the aldehyde **6** (1 equiv). After stirring at −78 °C for 10 min, the reaction mixture was brought gradually to 0 °C, stirred at that temperature for an additional 30 min, and quenched with pH 7 phosphate buffer. Extractive isolation afforded the tetraene ether **10** which was cleaved with tetra-*n*-butylammonium fluoride (1.05 equiv)[10] in tetrahydrofuran at 0 °C for 30 min to give, after chromatographic purification on silica gel, the hydroxy tetraene **11** (90% overall yield from **6** and **9**). The tetraene ether **10** showed ultraviolet λ_{max} (ethanol) at 263, 271.5, and 283 nm (ε 38 400, 49 100, 36 600).

The hydroxy tetraene **11** was converted into the epoxy ester by the following procedure. A solution of **11** in tetrahydrofuran at −25 °C was treated with 1.25 equiv of triethylamine and 1.2 equiv of methanesulfonyl chloride with stirring for 1 h to form the mesylate **12** and this solution was treated with 20 equiv of dimethyl sulfide, first at −20 °C and then at 0 °C for 18 h. The resulting solution of sulfonium salt **13** was then cooled to −78 °C and treated dropwise with a tetrahydrofuran solution of lithium diisopropylamide (~1.5 equiv) until a dark color persisted, at which point an additional 1.2 equiv of lithium diisopropylamide was added followed after 30 s by 2 equiv of methyl 4-formylbutyrate.[15] After stirring at −78 °C for 15 min

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and −78 to 0 °C for 2 h, the reaction mixture was quenched by the addition of water, concentrated in vacuo to remove tetrahydrofuran and extracted with hexane containing a few drops of triethylamine.[16] The crude product was isolated by drying over sodium sulfate and removal of solvent in vacuo and then rapidly chromatographed on basic alumina (activity V) using ether–hexane (2:3) containing a little triethylamine to afford in 35% yield pure epoxy ester **14**, R_f 0.48 (triethylamine-treated silica gel plate with ether–hexane, 1:1): ultraviolet λ_{max} (methanol) 269, 278, 287 nm (ϵ 30 500, 40 000, 34 400). Since the epoxy ester **14** is both air and acid sensitive, it was stored at −78 °C under argon in frozen benzene containing a small amount of triethylamine and 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical[17] as stabilizers.[18] The ^{1}H NMR spectrum of **14** indicates that the synthetic product consists of approximately equal amounts of 5,6-cis and 5,6-trans epoxides. Saponification of **14** with cold aqueous base under argon produced solutions of the salt of **2**, which could be reconverted into **14** with dimethyl sulfate.

The methyl ester **14**, when treated with methanol, undergoes rapid solvolysis to form approximately the same mixture of methyl ethers as are observed to form when the unstable biosynthetic precursor of **1** in neutrophils is quenched with methanol and esterified with diazomethane (comparison by gas chromatography–mass spectrometry).[19] In addition a similar mixture of the methyl esters of **1** and its isomers resulted from nonenzymic, acid-catalyzed hydrolysis of synthetic **14** and the natural unstable intermediate from neutrophils (after treatment with diazomethane).[19]

The ready availability of **2** and its methyl ester **14** by a simple synthesis opens the way for a host of interesting biological experiments. We are currently studying the large-scale synthesis of SRSA and related compounds and, in addition, other synthetic routes to the eicosanoid **14** and its Δ-7,9 stereoisomers.[20] It now appears that proof of the detailed structure of SRSA is most likely to be obtained by a comparison of synthetic and naturally derived compounds.[21]

References and Notes

(1) See: (a) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643; *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2148.
(2) Borgeat, P.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3213.
(3) Agata, I.; Corey, E. J.; Klein, J.; Proskow, S.; Ursprung, J. J. *J. Org. Chem.* **1965**, *30*, 98.
(4) Prior to this time the structure of the unstable intermediate had been tentatively regarded as the 5,12-oxide of 6,10-*trans*,8,14-*cis*-eicosatetraenoic acid, a highly strained but fascinating structure. Studies on the generation of this ring system by Dr. Pierre Lavallee in these laboratories (1977–1978) indicated it to be exceedingly unstable.
(5) This synthesis has been outlined in a lecture presented on May 28, 1979, at the 1979 International Conference on Prostaglandins held at Washington, D.C.
(6) Jakschik, B. A.; Falkenhein, S.; Parker, C. W. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 4577.
(7) Bach, M. K.; Brashler, J. R.; Gorman, R. R. *Prostaglandins* **1977**, *14*, 21.
(8) Orange, R. P.; Murphy, R. C.; Karnovsky, M. L.; Austin, K. F. *J. Immunol.* **1973**, *110*, 760.
(9) Borgeat, P.; Hammarström, S.; Samuelsson, B., lecture presented at the 1979 International Conference on Prostaglandins, May 28, 1979, in Washington, D.C. See *Chem. Eng. News* **1979**, *57*, No. 24, 19.
(10) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. Pyridine was used as base (25 °C) in the preparation of **5** (76% yield).
(11) Bates, E. B.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1854.
(12) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(13) Satisfactory infrared, ultraviolet, ^{1}H NMR, and mass spectra were obtained using purified, chromatographically homogeneous samples of each synthetic intermediate. All reactions involving air-sensitive components were conducted under argon.
(14) See: (a) Alexakis, A.; Normant, J.; Villiéras, J. *Tetrahedron Lett.* **1976**, 3461. (b) McGuirk, P. R.; Marfat, A.; Helquist, P. *Ibid.* **1978**, 2465.
(15) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.
(16) Triethylamine is used as a stabilizer because of the great sensitivity of the epoxide **14** to traces of acid.
(17) This agent is, in our experience, an outstanding antioxidant for readily oxidized polyunsaturated fatty acid derivatives.
(18) The experimental conditions for the conversion of hydroxy tetraene **11** into the sulfonium salt **13** and for the subsequent coupling reaction with methyl 4-formylbutyrate are very critical. Because of the high reactivity of the mesylate **12** and the sulfonium salt **13**, it is preferable that these intermediates not be isolated but used in situ. The formation of the required ylide from sulfonium salt **13** is carried out at low temperatures and short reaction time to avoid conversion into the isomeric methylide which is susceptible to facile [3,2] sigmatropic rearrangement. For the formation of oxiranes from sulfonium ylides see: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Corey, E. J.; Oppolzer, W. *Ibid.* **1964**, *86*, 1899.
(19) This comparison which was performed in the laboratory of Professor Samuelsson will be described in detail in a separate publication.
(20) It is convenient to use the term "eicosanoids" to describe the broad group of C_{20} fatty-acid-derived compounds as recently proposed (lecture cited in ref 5). The eicosanoid family thus includes lipoxygenase-derived hydroperoxides or alcohols (e.g., Samuelsson's HETE), SRSA, thromboxanes, and prostaglandins. Professor Samuelsson has proposed the names leucotriene A, B, and C for epoxytetraene **2** (or Δ-7,9 stereoisomer), **1**, and SRSA, respectively (see ref 9).
(21) This research was assisted financially by the National Science Foundation.

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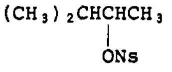
Contribution of Tunneling to Relative Reactivity in an Elimination Reaction[1]

Sir:

We have found that tunneling can make different contributions to the rates of proton removal from different sites in the same molecule.

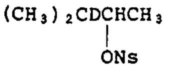
The influence of tunneling on the magnitude and the temperature dependence of kinetic hydrogen isotope effects has been explored by numerous workers,[2-4] but the possible contribution of tunneling to relative reactivities has to our knowledge not been discussed. It is evident, however, that two reactions with different tunnel corrections to their isotope effects must also have different tunnel corrections to the reaction rates for the light isotopic species.

We determined isotope effects as a function of temperature by careful GLC measurement of 1-ene:2-ene ratios for the E2 reaction of **1–3** (ONs = *p*-nitrobenzenesulfonate) with sodium ethoxide in ethanol (10–60 °C) and potassium *tert*-butoxide in *tert*-butyl alcohol (20–70 °C). The isotope effect on formation of 1-ene is then given by $k_H/k_D = (\text{1-ene:2-ene})_1/(\text{1-ene:2-ene})_3$, and similarly for the isotope effect on formation of 2-ene. The rate of elimination into the undeuterated branch is taken to be unaffected by deuterium in the other branch, an assumption that is probably good to within a few percent. The results are corrected for the small amount of solvolysis that occurs in ethanol and for the incomplete deuteration (2.88 atoms D) of **3**. **2** was >99% deuterated.



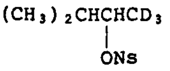
$(CH_3)_2CH\underset{ONs}{CH}CH_3$

1



$(CH_3)_2CD\underset{ONs}{CH}CH_3$

2



$(CH_3)_2CH\underset{ONs}{CH}CD_3$

3

Linear regression fits to the Arrhenius equation give the apparent Arrhenius parameters A_{aH}/A_{aD} and $E_{aD} - E_{aH}$ for the reactions yielding 1-ene and 2-ene. From these parameters, the tunnel corrections Q_{tH} and Q_{tD} can be evaluated by means of equations derived on the assumption that the first term of the Bell equation suffices to describe the tunneling behavior of the system.[5] The computer program used for this purpose is described in more detail elsewhere.[6] It is based on essentially the same principles as the program of Caldin and Mateo.[7]

From the tunnel corrections the *semiclassical* values of