

Studies are in progress not only on further reactions of dilithio salts II and VII but also on the preparation and reactions of 1,1-dilithio and 1,1,1-trilithio (or other trialkali) derivatives of other active hydrogen compounds having a functional group.

Edwin M. Kaiser, Charles R. Hauser
Department of Chemistry, Duke University
Durham, North Carolina
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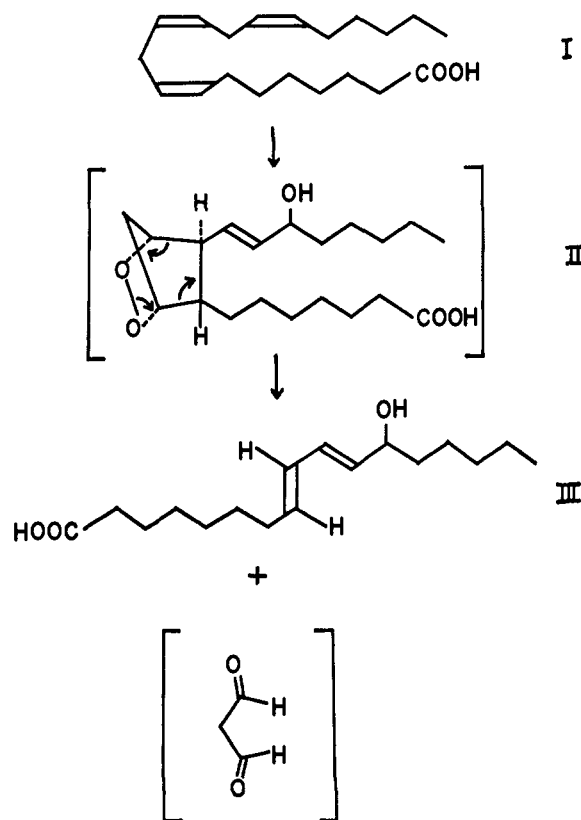
Novel Biological Transformations of 8,11,14-Eicosatrienoic Acid

Sir:

It was previously shown that 8,11,14-eicosatrienoic acid (I) is converted into prostaglandin E_1 by homogenates of the vesicular gland of sheep.^{1,2} We now wish to report on the transformation of I into monohydroxy acids catalyzed by the same tissue. The hydroxy acids formed have been shown to consist of two C_{20} trienoic acids and one dienoic acid. The latter acid was identified as 12-hydroxy-*trans,trans*-8,10-heptadecadienoic acid (III), and it is suggested to be formed by a novel reaction involving elimination of three carbon atoms from the central part of the molecule.

Fifty micromoles of $[2-^{14}C]8,11,14$ -eicosatrienoic acid¹ plus 75 μ moles of tetrahydrofolate were incubated for 60 min with the washed microsomal fraction and 30% of the high-speed supernatant obtained from a homogenate of 30 g of vesicular gland from sheep. Of the incubated radioactivity 10% was recovered as prostaglandin E_1 , 11% as prostaglandin F_{1a} , and 27% as monohydroxy acids by silicic acid chromatography. The monohydroxy acid fraction, which was eluted from the silicic acid column with ethyl acetate-benzene (10:90), was esterified by treatment with diazomethane. Further separation by preparative thin layer chromatography using silica gel G impregnated with silver nitrate and ethyl acetate-2,2,4-trimethylpentane (1:1) as solvent yielded two monohydroxytrienoate esters³ and one monohydroxydienoate ester. The latter compound (isolated in 14% yield, based on incubated $[2-^{14}C]8,11,14$ -eicosatrienoic acid) was acetylated and subjected to oxidative ozonolysis.⁴ The product consisted of two main components which were identified using mass spectrometry in combination with gas-liquid partition chromatography⁵ as 2-acetoxyheptanoic acid and monomethyl suberate. The methyl ester of the isolated compound was also

hydrogenated and oxidized with chromic acid.⁶ The product was identified as methyl 12-ketoheptadecanoate



by gas chromatography and mass spectrometry.^{6,7} The mass spectrum showed ions at m/e 298 (M), 267 (M - 31), 242 (β -cleavage with loss of $CH_2=CHCH_2CH_3$), 227 (α -cleavage with loss of $-(CH_2)_4-CH_3$), and 185 (β -cleavage with loss of $-CH_2CO-(CH_2)_4CH_3$). These experiments therefore show that the isolated compound was 12-hydroxy-8,10-heptadecadienoic acid. That both of the double bonds had the *trans* configuration was established by the infrared spectrum⁸ exhibiting one absorption band at 10.13μ but no absorption at 10.56μ and was further supported by the ultraviolet absorption which showed $\lambda_{max}^{E_1OEt}$ 231 m μ .

In another experiment, $[3-^{14}C, 15-^3H]8,11,14$ -eicosatrienoic acid⁹ was incubated with the same system. The isolated 12-hydroxy-8,10-heptadecadienoic acid contained the tritium label at C-12 since oxidation of the hydrogenated derivative with chromium trioxide-pyridine complex¹⁰ to 12-ketoheptadecanoic acid resulted in practically complete loss of the tritium label. It was also shown by degradation experiments¹¹ that the

(1) S. Bergström, H. Danielsson, D. Klenberg, and B. Samuelsson, *J. Biol. Chem.*, **239**, PC4006 (1964).

(2) D. A. van Dorp, R. K. Beerthuis, D. H. Nugteren, and H. Voncken, *Nature*, **203**, 839 (1964).

(3) This fraction was identified as a mixture of methyl 11-hydroxy-8-*cis*,12-*trans*,14-*cis*-eicosatrienoate (80-90%) and methyl 15-hydroxy-8-*cis*,11-*cis*,13-*trans*-eicosatrienoate (10-20%) by oxidative ozonolysis by mass spectrometric analysis of the derived saturated keto-esters, by their ultraviolet spectra (λ_{max}^{EtOH} 233 m μ), and by thin layer chromatographic comparison with methyl 15-hydroxy-8-*cis*,11-*cis*,13-*trans*-eicosatrienoate. It was also shown that incubation of linoleic acid with the same system gave 9-hydroxy-10-*trans*,12-*cis*-octadecadienoic acid (80-90%) and 13-hydroxy-9-*cis*,11-*trans*-octadecadienoic acid (10-20%). The structure of these acids was established by oxidative ozonolysis, mass spectrometry, and ultraviolet spectroscopy.

(4) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).

(5) R. Ryhage, *Anal. Chem.*, **36**, 759 (1964).

(6) M. Hamberg and B. Samuelsson, *Biochem. Biophys. Res. Commun.* **21**, 531 (1965).

(7) R. Ryhage and E. Stenhagen, *Arkiv Kemi*, **15**, 545 (1959).

(8) J. R. Chipault and J. M. Hawkins, *J. Am. Oil Chemists' Soc.*, **36**, 535 (1959).

(9) The labeled acid was prepared according to a previously reported procedure: D. Klenberg and B. Samuelsson, *Acta Chem. Scand.*, **19**, 534 (1965).

(10) G. E. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(11) The labeled 12-hydroxy-8,10-heptadecadienoic acid formed from $[2-^{14}C]8,11,14$ -eicosatrienoic acid was hydrogenated, acetylated, and degraded by oxidation with permanganate in acetone followed by gas-liquid partition radiochromatography of the product as previously described; see E. Granström, U. Inger and B. Samuelsson, *J. Biol. Chem.*, **240**, 457 (1965). Only the C_{16} and C_{17} acids contained ^{14}C .

^{14}C label at C-2 of the precursor was retained in the same position in the C_{17} acid. These results show that neither the methyl end nor the carboxyl end of 8,11,14-eicosatrienoic acid contributes to the three carbon atoms which are eliminated.^{11a}

It is therefore suggested that the elimination of the three carbon atoms occurs by way of the cyclic peroxide II, which was earlier postulated to be an intermediate in the formation of prostaglandins.¹² This hypothetical intermediate can be visualized to be converted, by expulsion of a three-carbon fragment,¹³ to 12-hydroxy-8,10-heptadecadienoic acid. Since the two side chains attached to the five-membered ring are *trans* to each other, this mode of formation is also

(11a) NOTE ADDED IN PROOF. Recent experiments with $[3-^{14}\text{C}, 10-^3\text{H}]8,11,14$ -eicosatrienoic acid demonstrate that the tritium label is lost during the conversion to III.

in agreement with the established *trans* configuration of the Δ^8 double bond of the product. No labeled heptadecadienoic acid could be isolated, indicating that the hydroxyl group is introduced prior to elimination of the carbon atoms.

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(12) B. Samuelsson, *J. Am. Chem. Soc.*, **87**, 3011 (1965).

(13) The three-carbon fragment shown in Scheme I as malonaldehyde has not been identified. However, substrate-dependent formation of material giving a positive thiobarbituric acid test (see F. Bernheim, M. L. Bernheim, and K. M. Wilbur, *J. Biol. Chem.*, **174**, 257 (1948)) could be demonstrated during the incubation.

Mats Hamberg, Bengt Samuelsson

Department of Chemistry, Karolinska Institutet
Stockholm 60, Sweden

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Book Reviews

The Chemistry of Alkenes. Edited by SAUL PATAI, The Hebrew University, Jerusalem, Israel. Interscience Publishers, John Wiley and Sons, Inc., 605 Third Ave., New York, N. Y. 1964. xi + 1315 pp. 16.5 × 23.5 cm. \$37.00.

This volume is the first of a planned series under the editorship of Professor Patai of The Hebrew University on the chemistry of various functional groups. Its aim is an up-to-date presentation of the chemistry of the carbon-carbon double bond. Emphasis is on a comparative and critical discussion addressed to the advanced student and research chemist; encyclopedic coverage is not intended nor achieved. Theoretical and mechanistic aspects of the subject are stressed. Except for the first chapter which discusses wave mechanical aspects of the alkene bond, treatment of the material is limited to reactions in which this bond is formed or is the site of reaction. The literature is generally covered through 1962; some references to papers published during 1963 will be found. Each chapter presents a single aspect of the chemistry of alkenes. The result is a valuable collection of individual monographs by authors who are authorities in the specialty involved. This review will comment on each monograph.

Chapter 1. Wave Mechanics and the Alkene Bond. Professor C. A. Coulson is the senior author of this interesting chapter which is next to the longest in the book. It was indicated that the general purpose was "to enable the reader without previous knowledge of quantum-chemical procedures to appreciate the significance and also the limitations of wave-mechanical calculations, but not to enable him to perform such calculations himself or to encourage him to investigate subtle problems in valence theory. . . ." The authors state that ". . . a wave-mechanical description of bonding in organic molecules requires far more than just the assimilation of a little quantum-chemical terminology into the language of classical organic chemistry. We would do wrong not to make it clear at the outset that, from the wave mechanical point of view, the σ - π systems with which this book is concerned are by no means as straightforward as is often suggested. Any worthwhile study of the bonding in an alkene or polyene molecule (or, indeed, any polyatomic molecule) demands, quite inescapably, a prior understanding of the quantum chemistry of much simpler molecules. . . ." With regard to the mathematics needed to understand the chapter the authors say, "It is idle to pretend that any but the most trivial features of organic quantum chemistry can be presented in non-mathematical terms. For our purposes, however, the mathematical analysis required is very straightforward and well within the repertoire of the average chemist. Although we have not tried to avoid any essential mathematics, we have assumed nothing more than a knowledge of the differentiation and integration of simple trigonometric and

exponential functions, and we have explained other routine mathematical procedures wherever necessary."

The reviewer believes that the authors have seriously overestimated the degree of mathematical sophistication of the average organic chemist. However, if a reader does possess sufficient facility with mathematics or is willing to spend enough time to acquire it, the chapter should be very useful. The authors' conviction that a prior understanding of the quantum chemistry of much simpler molecules is required before olefins can be examined is demonstrated by the fact that two-thirds of the chapter is devoted to the former and only one-third to alkenes (under sections on the π -electron hypothesis, the Hückel approximation and spectra). It seems somewhat irrational to place this chapter first when it is so different in emphasis from the remaining chapters.

Chapter 2. Elimination Reactions in Solution. This relatively brief chapter presents little of the massive amount of experimental data which has been obtained on elimination reactions, but does give a well-organized understandable discussion of the mechanisms of olefin formation by removal of H and an adjacent leaving group. Pyrolytic elimination reactions are left for Chapter 3 and reactions in which neither group lost is hydrogen are not covered. There is no emphasis on synthesis, and references to elimination of HX, where X is other than the more usual groups, are not included. Literature coverage is roughly through 1962 so that a number of significant papers which have appeared during the last 3 years could not be included.

Chapter 3. Olefin-Forming Elimination in the Gas Phase. This brief chapter is concerned primarily with the evidence that there is a class of homogeneous gas phase elimination reactions which are essentially heterolytic in character and in which the effects of substitution on the rates can be discussed in terms of effects in the heterolytic bond dissociation energies. Analogies between such reactions and eliminations occurring by the unimolecular mechanism in polar solvents are stressed. Discussion of the groups that leave with the β -hydrogen includes halogens, RCO_2 , $\text{CH}_2=\text{CHO}$, OCS_2CH_3 , OH, NH_2 , and ClCO_2 . Although the author states that interest in these reactions lies in two areas, one of which is their synthetic application, and that the synthetic importance derives from those cases where more than one olefin can be formed, he does not in fact deal with this area beyond pointing out the differing proportions of 1- and 2-butene obtained from *sec*-butyl chloride and acetate. Gas phase eliminations which occur by chain or heterogeneous mechanisms are not discussed.

The author is well known for his advocacy of the mechanism propounded again in the chapter under review. A more recent review has appeared in *Advan. Phys. Chem.*, **3**, 91 (1965) [Academic