K. N. Sannes, *Angew. Chem., Int. Ed. Engl.*, **13**, 99 (1974); (b) C. C. Leznoff, *Chem. Soc. Rev.*, **3**, 65 (1974).
(3) (a) G. A. Crosby, N. M. Weinshenker, and H.-S. Uh, *J. Am. Chem. Soc.*, **97**, 2232 (1975); (b) N. M. Weinshenker, G. A. Crosby, and J. Y. Wong, *J. Org. Chem.*, **40**, 1966 (1975).
(4) (a) G. S. Banker, German Patent 1 944 694 (1970); *Chem. Abstr.*, **73**, 18 482a (1970); (b) S. Yolles, J. E. Eldridge, and J. H. R. Woodland, *Polym. News*, 1 (4), 9 (1971); (c) T. Nagai, *Kobunshi*, **21**, 190 (1972); (d) H. G. Batz, G. Franzmann, and H. Ringsdorf, *Makromol. Chem.*, **172**, 27 (1973).
(5) (a) G. J. H. Melrose, *Rev. Pure Appl. Chem.*, **21**, 83 (1971); (b) G. Manecke, *Biotechnol. Bioeng. Symp.*, **3**, 185 (1972); (c) R. Epton, J. V. McLaren, and T. H. Thomas, U.S. Patent 3 761 357 (1973); *Chem. Abstr.*, **80**, 15 671v (1974).
(6) (a) D. O. Cowan, J. Park, C. U. Pittman, Jr., Y. Saski, T. K. Mukherjee, and N. A. Diamond, *J. Am. Chem. Soc.*, **94**, 5110 (1972); (b) C. U. Pittman, Jr., and B. Surynarayanan, *ibid.*, **96**, 7916 (1974).
(7) L. R. Melby, *J. Am. Chem. Soc.*, **97**, 4044 (1975).
(8) (a) F. Cramer, R. Helbing, H. Hettler, K. H. Scheit, and H. Sellger, *Angew. Chem., Int. Ed. Engl.*, **5**, 601 (1966); (b) G. R. Stark, Ed., "Biochemical Aspects of Reactions on Solid Supports", Academic Press, New York, N.Y. 1971.
(9) (a) J. P. Collman, L. S. Hegedus, M. P. Cooke, J. R. Norton, G. Dolcetti, and D. N. Marquardt, *J. Am. Chem. Soc.*, **94**, 1789 (1972); (b) R. H. Grubbs, C. Gibbons, L. C. Kroll, W. D. Bonds, Jr., and C. H. Brubaker, Jr., *ibid.*, **95**, 2375 (1973).
(10) (a) T. Ida, S. Takahashi, and I. Utsumi, *Yakugaku Zasshi*, **89**, 517 (1969); (b) T. Ida, T. Watanabe, S. Takahashi, and I. Utsumi, *Ibid.*, **89**, 524 (1969); (c) I. Utsumi, T. Ida, T. Watanabe, S. Takahashi, and T. Hasimoto, *Kogyo Kagaku Zasshi*, **73**, 1151 (1970).
(11) From acryloyl chloride via the preparation, polymerization, and hydrolysis of *N*-vinyl *tert*-butylcarbamate: (a) R. Hart, *Makromol. Chem.*, **32**, 51 (1959); (b) C. J. Bloys van Treslong and C. F. H. Morra, *Recl. Trav. Chim. Pays-Bas*, **94**, 101 (1975).
(12) From *N*-vinylphthalimide by polymerization and hydrazinolysis: (a) D. D. Reynolds and W. O. Kenyon, *J. Am. Chem. Soc.*, **69**, 911 (1947); (b) A. Katchalsky, J. Mazur, and P. Spitnik, *J. Polym. Sci.*, **23**, 513 (1957).
(13) From poly(acrylic acid) by a Schmidt reaction: (a) H. Rath and E. Hilscher, German Patent 1 153 528 (1963); *Chem. Abstr.*, **59**, 14 131f (1963); (b) T. St. Pierre, G. Vigee, and A. R. Hughes in "Reactions on Polymers", J. A. Moore, Ed., D. Reidel Publishing Co., Boston, Mass., 1973, pp 61–72.
(14) A single reference dealing with the homopolymerization of *N*-vinylacetamide has appeared.[15] There are no reports concerning the conversion of *N*-vinylacetamide into poly(vinylamine).
(15) Farbwerke Hoechst A.-G., Belgian Patent 636 327 (1964); *Chem. Abstr.*, **61**, 16 189d (1965).
(16) (a) W. A. Noyes and D. B. Foreman, *J. Am. Chem. Soc.*, **55**, 3493 (1933); (b) S. L. Vail, G. M. Morgan, and H. B. Moor, *J. Org. Chem.*, **27**, 2067 (1962); (c) N. Yanalhara and M. Saito, *Chem. Pharm. Bull.*, **15**, 128 (1967).
(17) D. Ben-Ishai and R. Giger, *Tetrahedron Lett.*, 4523 (1965).
(18) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry", Reinhold, New York, N.Y., 1961, pp 738–739.
(19) Prepared by coupling diazotized sulfanilamide to sodium 2-naphthol-6-sulfonate.
(20) H. E. Fierz-David, *Helv. Chim. Acta*, **21**, 664 (1938).
(21) F. Muzik, *Collect. Czech. Chem. Commun.*, **30**, 559 (1965).
(22) Satisfactory coupling was carried out at neutrality. Alkaline coupling afforded a crosslinked product.
(23) Details of the methods involved will be the subject of a forthcoming publication: P. L. Dubin, S. L. Koontz, and K. L. Wright, submitted for publication.
(24) Lower yields were obtained when an inert atmosphere was employed during the distillation.
(25) P. Kurtz and H. Disselnkötter, *Justus Liebigs Ann. Chem.*, **764**, 69 (1972).
(26) Precipitation takes place on naphthol protonation because of the high salt content of the medium. The precipitate readily dissolves upon dilution, dialysis, or base addition.

The Formation of Cyclic Peroxides from Unsaturated Hydroperoxides: Models for Prostaglandin Biosynthesis[1,2]

Ned A. Porter,* Max O. Funk, Dennis Gilmore, Ramdas Isaac, and John Nixon

Contribution from the Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706. *Received March 1, 1976*

Abstract: Several unsaturated hydroperoxides were synthesized by reaction of alkenyl mesylates with hydrogen peroxide and potassium hydroxide in methanol/water. These hydroperoxides were treated with di-*tert*-butyl peroxyoxalate in oxygenated benzene. Following reduction of the product mixture with triphenylphosphine, cyclic peroxides were isolated and purified by chromatographic methods. Acetophenone-initiated photodecomposition of unsaturated hydroperoxides also led to cyclic peroxide products. Another route to the same cyclic peroxides generated by peroxy radical cyclization (vide supra) was via bifunctional oxirane hydroperoxides. Unsaturated hydroperoxides were epoxidized by *m*-chloroperbenzoic acid. Treatment of the oxirane hydroperoxides prepared in this way with trichloroacetic acid led in most cases to cyclic peroxides. The mechanism of the free radical cyclization and the oxirane hydroperoxide reaction are discussed with reference to the proposed mechanism for prostaglandin biosynthesis.

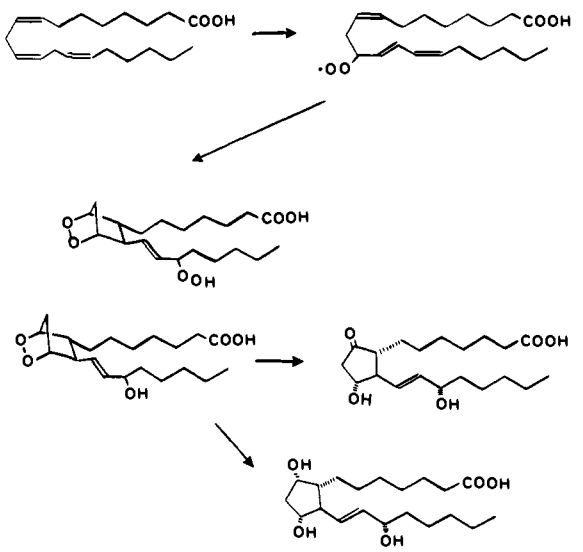
The universal presence of prostaglandins in mammalian tissues coupled with their high potency in a divergent set of biological functions has prompted a comprehensive investigation into the nature of these compounds. While the functions in which prostaglandins have thus far been identified include reproduction, blood pressure regulation, inflammation, plasma electrolyte regulation, and platelet aggregation, the mechanism of their formation and action remains a matter of great research interest.[3-7]

A peroxy radical cyclization mechanism leading to intermediate endoperoxides has been proposed for the biosynthesis[8] (Scheme I). The intermediacy of endoperoxides has, in fact, been concretely established by the isolation of two such compounds, PGG and PGH.[9] Not only have these compounds been identified as intermediates in prostaglandin formation, they have also been shown to exhibit strong and independent physiological effects as well.[10,11]

In light of the potential importance of peroxy radical cyclization as outlined in Scheme I, it is remarkable that little information is available about this class of reaction. Cyclization of peroxy radicals has been proposed in order to account for the autoxidation products formed from a variety of different hydrocarbons. Anet,[12] for example, has proposed a peroxy radical cyclization in the autoxidation of α-farnesene. Similarly, Nugteren[13] and Haverkamp-Begeman[14] have suggested peroxy radical cyclization steps in the autoxidation of lipid. More recently, Pryor[15] has studied the autoxidation of methyl α-linolenate and has reported the isolation and identification of cyclic peroxide products.

Due to the complex and random nature of the autoxidation reaction, a different, more specific, method for the study of unsaturated peroxy radicals would appear to be desirable. We describe herein a method of generation of specific peroxy radicals from unsaturated hydroperoxides. Simple unsaturated

Scheme I



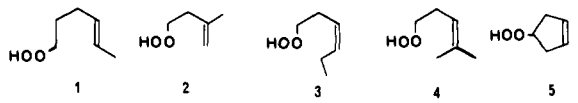
peroxy radicals generated in this way undergo cyclization reactions yielding five- and six-membered ring peroxide compounds.[16]

Results and Discussion

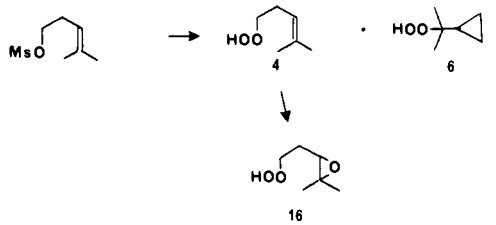
Synthesis of Unsaturated Hydroperoxides. Hydroperoxides have been prepared by a variety of means including the autoxidation of hydrocarbons, the reaction of singlet oxygen with olefins, and the solvolysis of alkyl sulfonates in basic solutions of hydrogen peroxide.[17] The latter method has been applied to the synthesis of primary,[18] secondary,[19] allyl,[20] and long-chain hydroperoxides.[21]

$$\text{R-OH} \xrightarrow[\text{pyridine}]{\text{MsCl}} \text{R-OMs} \xrightarrow[\text{KOH}]{H_2O_2} \text{ROOH}$$

By the use of this method, several unsaturated hydroperoxides were prepared from the corresponding mesylate in 40-60% yield. For example, **1** was prepared in yields of 44% from the mesylate precursor. Hydroperoxides synthesized by this method also include **2-6.** The isolation of **4** was compli-



cated by the fact that appreciable amounts of **6** were formed during the nucleophilic substitution reaction. Thus, **4** could not be easily isolated completely free of **6.**



The mixture of **4** and **6** was used, however, to prepare **16,** the epoxide derivative of **5. 16** could be easily purified by chromatography on silica gel.

Free Radical Cyclization. The unsaturated hydroperoxides prepared as described above may serve as a source of unsaturated peroxy radicals. Peroxy radicals have been generated from hydroperoxides by two general methods: (1) radical abstraction of the hydroperoxy hydrogen[22] and (2) metal ion oxidation.[23-25] The radical abstraction method was chosen for our initial studies due to the anticipated reactivity of the reduced metal, $M^{+(n-1)}$, with the starting hydroperoxides.

Table I. The Relative Reactivity of Hydrogen Atoms Toward Abstraction by *tert*-Butoxy Radicals

Position	Relative reactivity per H	No. equiv positions	Reactivity	%
ROO-H	19 800	1	19 800	98.6
	94.4	2	188.8	0.9
	19.9	3	59.7	0.3
	12.1	2	24.2	0.15
 ADD.	4.4	1	4.4	0.05

$$\text{R-OOH} + \text{R}'\cdot \rightarrow \text{R-OO}\cdot + \text{R}'\text{-H} \quad (1)$$

$$\text{R-OOH} + M^{+n} \rightarrow \text{R-OO}\cdot + M^{+(n-1)} + H^{+} \quad (2)$$

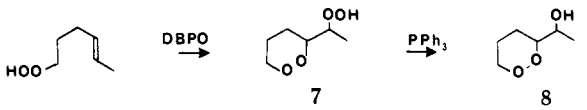
Di-*tert*-butyl peroxyoxalate (DBPO)[26] was chosen as a source of *tert*-butoxy radicals for the induced decomposition of the hydroperoxides **1-4.** Hiatt[27,28] has reported on decompositions of primary and secondary saturated hydroperoxides that are catalyzed by *tert*-butoxy radicals generated from DBPO.

tert-Butoxy radicals could react with unsaturated hydroperoxides in several ways. Estimates of the relative reactivity of various hydrogens of the hydroperoxide toward abstraction by *tert*-butoxy radicals as well as radical addition to the double bond rate data have been reported in the literature.[29,30]

In this way, the relative reactivity of hydrogen atoms in the unsaturated hydroperoxide **1** toward abstraction by *tert*-butoxy radicals could be estimated as in Table I.

The calculations predict that greater than 98% of the *tert*-butoxy radical abstraction would occur from the hydroperoxide hydrogen. The only hydrogen atoms in the molecule that could not be dealt with on a quantitative basis were those of the methylene group α to the hydroperoxide. Hiatt,[28] however, has suggested that abstraction does not take place from the α position to any significant extent in the radical induced decomposition of primary and secondary hydroperoxides.

The *tert*-butoxy radical induced decomposition of the hydroperoxides **1-4** were carried out in oxygenated benzene solution (0.01 M). In a typical reaction, the hydroperoxide was let stand for 48 h with 0.39 equiv of DBPO. The workup of the reaction mixture and purification of the reaction products is presented below for the hydroperoxide **1** and is illustrative of the general procedure used for other hydroperoxides.



The cyclized hydroperoxide **7** was obtained in nearly pure form by simply removing the benzene solvent and applying the technique of preparative high performance liquid chromatography (HPLC) to the separation of the products in the residue. The NMR spectrum of **7** (Figure 1) revealed the presence of two diastereomers (threo and erythro). The methyl region of the spectrum was composed of a pair of closely spaced doublets (δ 1.1) due to the methyl of the two diastereomers β to the -OOH.

The hydroperoxide group of the cyclized product **7** was reduced to the corresponding alcohol **8** by direct treatment of the reaction mixture with triphenylphosphine. Compound **8** was thus obtained in 30% overall yield from **1** in the two-step se-

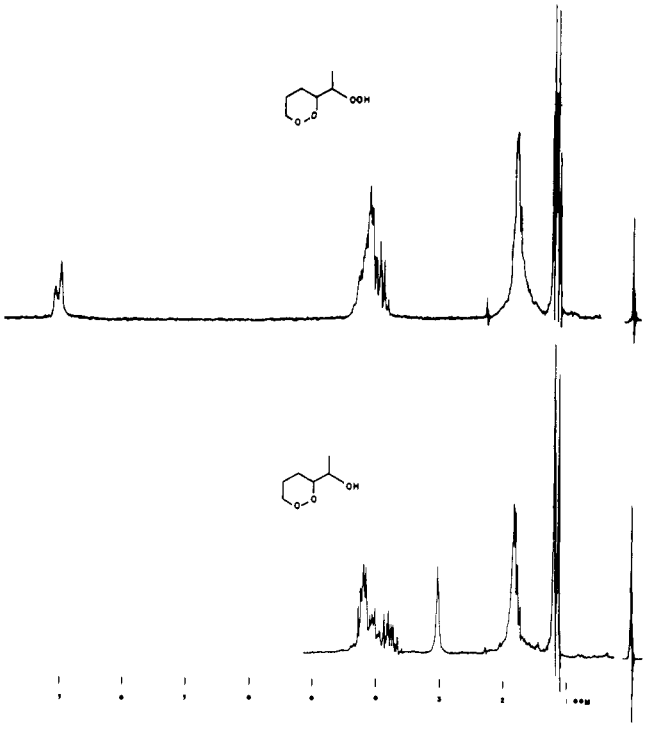
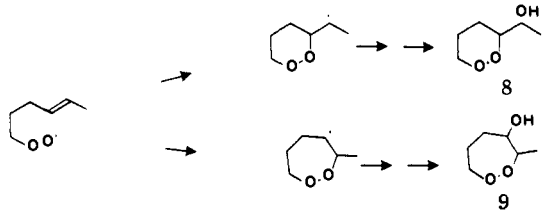


Figure 1. 60 MHz NMR spectrum of the cyclic peroxides **7** and **8** in CCl_4.

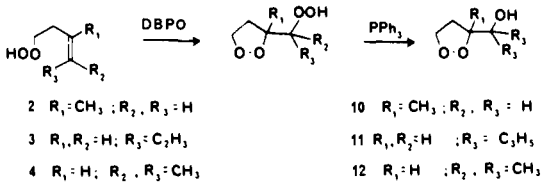
quence. Hiatt[31] has determined the rate of the phosphine reduction for several hydroperoxides in a variety of solvents. The second-order rate constant for *n*-butyl hydroperoxide and triphenylphosphine at 25 °C was approximately 2 M^{-1} s^{-1} for all the solvents employed. The 1,2-dioxane group was not expected to be reduced under the reaction conditions. Holtz et al.[32] have demonstrated that the reaction of 1,2-dioxane with this reagent is relatively slow at room temperature (approximately 150 days to completion).

The comparison of the NMR spectra of **7** and **8** was informative (Figure 1). As in the hydroperoxide, the reduced compound also contained a pair of doublets in the methyl region indicating the presence of threo and erythro isomers. The deshielding effect of the hydroperoxide group was observed in the shift of the proton attached to oxygen (-OOH: 9.0, 9.1 ppm; -OH: 3.02 ppm) and the α-methine protons (-CH(OOH)-, 3.96 ppm; -CH (OH)-, 3.76 ppm) for these two compounds. Double resonance experiments on **8** established that the α-methine proton was also adjacent to the methyl group. This finding eliminated the possibility that the compound was **9**, the seven-membered ring peroxide.



Further corroboration for this conclusion was obtained by oxidation of **8.** Oxidation with *N*-chlorosuccinimide-dimethyl sulfide-triethylamine[33] did yield a peroxy ketone which displayed only a methyl singlet in the α-carbonyl region of the NMR as expected.

By the use of similar cyclization and reduction procedures to those already described, the hydroperoxides **2, 3,** and **4** were converted into the cyclic peroxides, **10, 11,** and **12.** Product structure in each case was supported by C, H analysis and NMR. Double irradiation experiments and spectra obtained



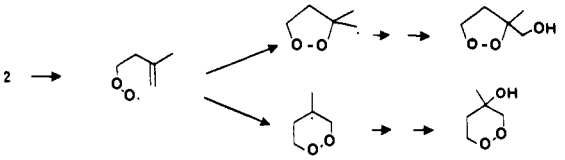
in Me_2SO solvent, where OH exchange is slow, supported the conclusion that only five-membered ring peroxides were formed in the radical cyclizations.

Reaction of **5** with DBPO under the standard reaction conditions le to consumption of the starting material. However, no stable products could be isolated by low-temperature chromatography. Although new peroxidic products were formed in the reaction, they decomposed on silica gel even at −20 °C. This is perhaps not surprising since expected products from **5** would be bicyclic endoperoxides with a hydroperoxy functional group attached directly to the bicyclic system.

The kinetic preference for cyclization to the five- rather than the six-membered ring has been documented in carbon and alkoxy radical cyclizations. In all carbon systems, cyclization to the five-membered ring occurs either when the initial radical is not stabilized or when the first formed products are trapped immediately by an efficient hydrogen atom donor.

Rieke and Moore[34] and Suzur et al.[35] have demonstrated that unsaturated alkoxy radicals, formed by photolysis of nitrites, cyclize to give five-membered ring compounds exclusively. Cyclization to a six-membered ring was not observed even when five-membered ring formation was excluded.

From our studies on **2, 3,** and **4** it would appear that peroxy radicals are subject to the same influences which cause carbon and alkoxy radicals to cyclize preferentially to five-membered rings. The peroxy radical derived from **2** would be the most likely of the radicals reported here to cyclize to a six-membered ring. Factors that might favor the six-membered ring formation in this case are (1) reduced steric hindrance for addition at the unsubstituted end of the alkene and (2) formation of a tertiary,



rather than a primary, radical intermediate. Only **10,** however, could be isolated from the reaction mixture. None of the six-membered ring compound could be found. It should be noted that the mechanism proposed for prostaglandin biosynthesis (Scheme I) involves an initial peroxy radical cyclization which preferentially yields a five- rather than a six-membered ring radical intermediate.

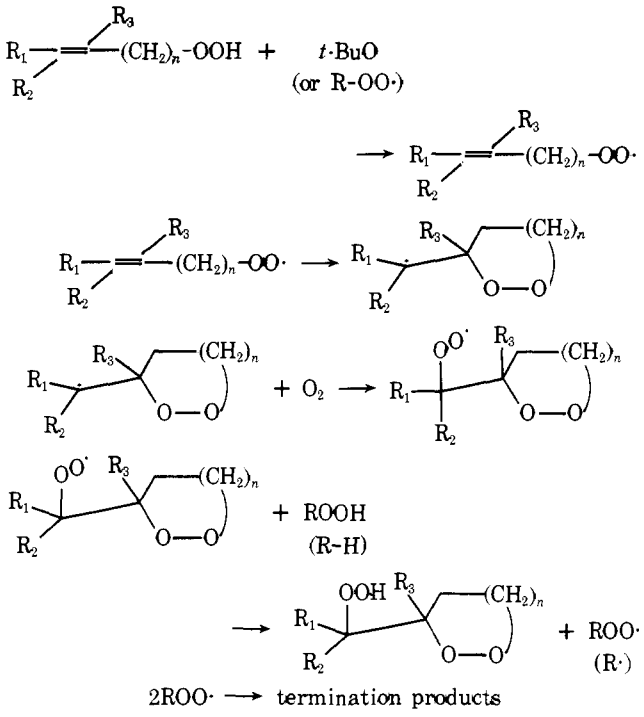
A generalized mechanism consistent with our observations is presented in Scheme II.

This scheme is consistent with our observations of product structure. Further, it is directly parallel to the known chemistry of hydroperoxide and hydrocarbon oxidations.

Other methods of initiation for the free radical cyclization have been studied. Of particular interest is the photochemical cyclization initiated by photolysis of acetophenone in the presence of the unsaturated hydroperoxide. For example, photolysis of a 0.004 M acetophenone, 0.01 M **2** solution in Freon 11 at 0 °C for 7 h led to consumption of **2.** Reduction of the reaction mixture with triphenylphosphine followed by purification in the usual way led to **10** which was isolated with a product yield somewhat better than that of the DBPO initiated reaction.

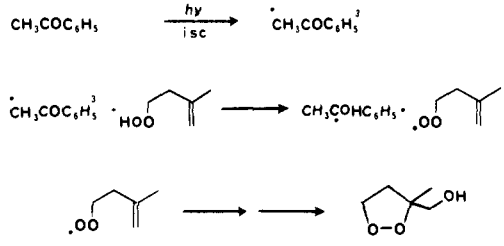
The mechanism of the ketone-sensitized photochemical decomposition of hydroperoxides is open to some question. Walling[36a] and Richardson[36b] have suggested that the sensi-

Scheme II



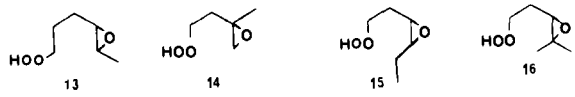
tized photodecomposition of hydroperoxides most probably occurs by initial hydrogen atom abstraction of the hydroperoxy hydrogen.[36] Our observations support this view. Abstraction of the hydroperoxy hydrogen of **2** by excited acetophenone leads to the peroxy radical which may cyclize and ultimately be converted to the cyclic peroxide **10** as shown in Scheme III.

Scheme III



Further work is in progress on this and other methods of initiating the peroxy radical cyclization (transition metals) and will be reported later.[37]

Acid-Catalyzed Cyclization of Oxirane Hydroperoxides. The hydroperoxides **1–4** were easily epoxidized with *m*-chloroperbenzoic acid. In this way, **13–16** were prepared. The oxirane hydroperoxides so generated were chromatographically stable on silica gel and could be isolated analytically pure after column chromatography. It was found convenient to carry out the epoxidation in a two-phase methylene chloride/aqueous sodium bicarbonate medium.[38] If standard epoxidation procedures were used (methylene chloride one phase), some of the epoxides were slowly converted to cyclic peroxides (vide infra) by the action of *m*-chlorobenzoic acid formed as a by-product of the epoxidation reaction.

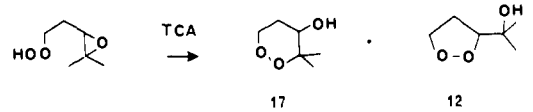


13 **14** **15** **16**

Reaction of **14, 15,** and **16** with catalytic amounts of trichloroacetic acid (TCA) in CCl_4 proceeded smoothly at 0 °C. For example, when 300 mg of **14** in CCl_4 was treated with a

14 **10**

catalytic amount of TCA at 0 °C, the cyclic peroxide **10** was obtained in nearly 70% yield. Compound **10** generated in this way was identical in every respect with **10** generated by the peroxy radical pathway described earlier. Similarly, **15** was converted to the cyclic peroxide **11** by treatment with catalytic TCA. The reaction of **16** with TCA led to a 3:2 mixture of cyclic peroxides **17** and **12.** The compounds were separated with difficulty by HPLC, and the ratio of **12** to **17** could be obtained by analysis of the NMR spectrum of the mixture.

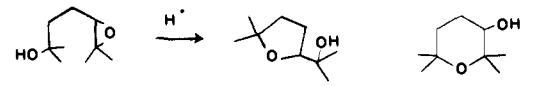


17 **12**

It is of interest to note that the pattern of alkyl substitution on the oxirane affects the ratio of five- to six-membered ring product. One could conclude from this that a species with considerable carbonium ion character is intermediate in the reaction. Of the compounds studied, **16** should most favor six-membered ring formation on the basis of ion stability. The carbonium ion leading to the six-membered ring is tertiary in this case whereas the corresponding ion formed from **14** or **15** is primary or secondary, respectively.

Although **13** is consumed when treated with catalytic amounts of TCA, no cyclized product could be isolated from the reaction mixture. The cyclic peroxide **8** is unstable to acid, however, and it probably would not have rvived the conditions of the reaction.

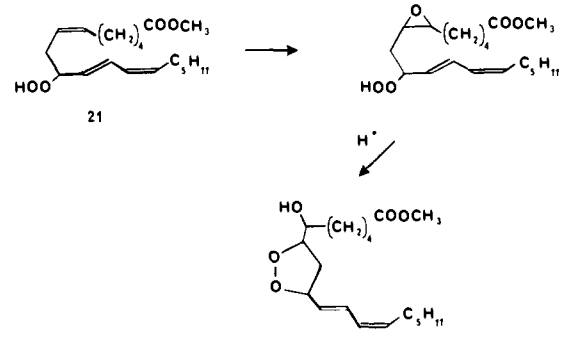
The epoxide cyclizations reported here are reminiscent of reactions leading to tetrahydrofurans and tetrahydropyrans from oxiranols. Mousseron-Canet et al.,[39] for example, observed a 9:1 mixture of compounds **19** and **20** in the acid-catalyzed reaction of **18.** It should also be noted that the intermolecular analogue of the oxirane hydroperoxide cyclization reaction was reported some 25 years ago.[40]



18 **19** **20**

9 : 1

The hydroperoxide **21**[41,42] was also subjected to the epoxidation-catalytic TCA reaction conditions. A product assigned the structure **22** was isolated from the product mixture and purified by preparative HPLC. The structure of **22** was supported by elemental analysis, proton NMR, and uv spectroscopy. The peroxidic nature of **22** was confirmed by ferrous thiocyanate visualization[43] of this compound on TLC plates. Several other products were formed in the reaction but none have, as yet, been purified and identified.



21 **22**

It should be noted that Corey[44] has proposed a mechanism for biosynthesis of prostaglandins in which one of the conjugated double bonds of a hydroperoxide analogous to **21** is epoxidized. An acid-catalyzed cyclization then converts this epoxide-hydroperoxide to an endoperoxide (PGH). Although we have found no evidence for prostaglandiproducts in the

epoxidation reactions of **21**, a bicyclic peroxide like PGH would most likely be unstable to our reaction conditions.

In summary, cyclic peroxides can be prepared by peroxy radical cyclization and oxirane hydroperoxide acid-catalyzed cyclization. The peroxy radical route to bicyclic endoperoxides has been implicated as a key step in the biosynthesis of prostaglandins. In fact, we have previously reported the isolation of prostaglandin analogues in the DBPO-initiated reactions of lipid hydroperoxides.[41] Further details of this investigation will be reported in a future full paper.

Experimental Section

NMR spectra were recorded with a Joel JNM-MH-100 spectrometer. Ir spectra were recorded on a PE-621 grating spectrometer. High performance liquid chromatographic analyses were carried out using Waters Associates Model ALC-202 for analytical separations and Model ALC/GPC-301 for preparative work. Uv-visible spectra were recorded on a Cary 15 spectrometer.

Solvents. Peroxides in ether solvents were destroyed by refluxing with lithium aluminum hydride followed by distillation. Ethyl acetate was purified by distillation from phosphorus pentoxide. Hydrocarbon solvents were purified by washing with sulfuric acid, water, saturated sodium bicarbonate, and water. After drying over anhydrous calcium chloride, the solvents were distilled from calcium hydride. A center cut was retained in each case and was stored over molecular sieves.

Syntheses. The synthesis of *trans*-hex-4-ene 1-hydroperoxide is illustrative and is presented below.

***trans*-Hex-4-enyl 1-Methanesulfonate.** *trans*-Hex-4-en-1-ol was prepared by the method of Crombie and Harper.[45] The alcohol (20 g, 0.2 mol) was combined with methanesulfonyl chloride (22.9 g, 0.2 mol), and the mixture was cooled to 0–5 °C. Pyridine (31.6 g, 0.4 mol) was added to the combined reagents dropwise over a period of 3.5 h, such that the internal temperature did not exceed 5 °C.

The reaction mixture was poured into 125 ml of ice-cold 10% hydrochloric acid, and the product was extracted into ether (75 ml). The extract was washed with two 20-ml portions of water and one 30-ml portion of saturated aqueous sodium bicarbonate. The solution was dried with anhydrous potassium carbonate, filtered, and stripped to a pale-yellow residue. The residue was distilled to give a clear colorless liquid (31.3 g, 0.176 mol 88%): bp 67 °C (0.07 mmHg); NMR (CCl_4) δ 1.6–2.2 (7 H, m), 2.95 (3 H, s), 4.19 (2 H, t), 5.45 (2 H, m).

***trans*-Hex-4-ene 1-Hydroperoxide (1).** The methanesulfonate (14.26 g, 0.08 mol) was dissolved in a mixture of 90 ml of methanol and 10 ml of water. The solution was cooled to 0–5 °C and combined with 30% hydrogen peroxide (36.2 g, 0.32 mol) and 50% aqueous potassium hydroxide (9.8 g, 0.044 mol) by magnetic stirring. The mixture was let warm to room temperature and stirred for 16 h.

The reaction mixture was then cooled to 0–5 °C and combined with 30 g of 50% potassium hydroxide. The resulting aqueous solution was extracted with benzene (50 ml), cooled to 0–5 °C, and neutralized (pH 7) with concentrated hydrochloric acid. This mixture was then extracted with four 30-ml portions of benzene. These four extracts were combined and extracted with 40 g of ice-cold 25% aqueous potassium hydroxide. The aqueous phase was separated, cooled to 0–5 °C, and neutralized (pH 7) with concentrated hydrochloric acid. The resulting mixture was extracted with four 20-ml portions of benzene. The benzene solution was dried (sodium sulfate) and the solvent stripped. The residue was distilled to give a clear colorless liquid (3.94 g, 42%): bp 45 °C (1.3 mmHg); NMR (CCl_4) δ 1.6–1.8 (5 H, m), 1.44–2.2 (2 H, m), 4.00 (2 H, t), S 4–5.5 (2 H, m), 8.84 (1 H, s).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.09; H, 10.39.

Iodometric titration: 0.985 equiv of iodine liberated/mole.

3-Methyl-but-3-ene 1-Hydroperoxide (2). 3-Methylbut-3-en-1-ol[46] was converted to the hydroperoxide via the methanesulfonate as described above. Purification was achieved by chromatography on silica. NMR (CCl_4) δ 1.85 (3 H, s), 2.35 (2 H, t), 4.05 (2 H, t), 4.75 (2 H), 9.32 (1 H).

Anal. Calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.69; H, 9.69.

***cis*-Hex-3-ene 1-Hydroperoxide (3).** *cis*-Hex-3-en-1-ol[46] was converted to the hydroperoxide via the methanesulfonate as described above. NMR (CCl_4) δ 0.96 (3 H, t), 2.04 (2 H, m), 2.36 (2 H, m), 3.92 (2 H, t), 5.34 (2 H, m), 9.00 (1 H, 9).

Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.81; H, 10.21.

4-Methylpent-3-ene 1-Hydroperoxide (4). 4-Methylpent-3-en-1-ol[47] was converted to the hydroperoxide via the methanesulfonate as described above. The amount of **6** could be reduced by carefully controlling the pH below 7 during the reaction of mesylate with hydrogen peroxide. **4** could be obtained free from **6** by chromatography on silica. NMR (CCl_4) δ 1.8 (6 H, d), 2.2 (2 H, m), 3.9 (2 H, t), 5.1 (1 H, m).

Δ^3-Cyclopentene Hydroperoxide (5). Δ^3-Cyclopentenol was converted to the hydroperoxide as described above. NMR (CCl_4) δ 2.52 (4 H, m), 4.94 (1 H, m), 5.77 (2 H, m).

Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 59.87; H, 8.11.

DBPO-Initiated Cyclization of Unsaturated Hydroperoxides. The cyclization procedure and workup are illustrated with *trans*-hex-4-ene 1-hydroperoxide (1).

Isolation of 3-(1-Hydroxyethyl)-1,2-dioxane (8). The hydroperoxide **1** (0.605 g, 5.21×10^{-3} mol) was dissolved in 500 ml of benzene (0.0104 M). DBPO (0.475 g, 2.03×10^{-3} mol) was added to this solution, and the mixture was stirred magnetically while in contact with the atmosphere for 48 h. The reaction mixture was cooled to 5–10 °C and triphenylphosphine (1.0144 g, 3.81×10^{-3} mol) was added. The mixture was stirred at 5–10 °C for 30 min after which the solvent was removed under reduced pressure at room temperature. A pale-yellow residue was obtained. To the residue was added 10 ml of cold diethyl ether resulting in an immediate white precipitate. The solid was removed by gravity filtration, and the solution was stripped to a residue. The residue was applied to a silica gel column (Davison 200–325 mesh) and was eluted with 300-ml portions of 0, 10, 25, 50, and 60% mixtures of ethyl acetate in hexane. The 60% ethyl acetate fraction was collected, and the solvents were evaporated. A clear colorless liquid (0.197 g, 1.49×10^{-3} mol, 29%) was obtained: NMR (CCl_4) δ 1.18 (3 H, 2 d), 1.83 (4 H, m), 3.02 (1 H, s), 3.76 (1 H, m), 4.03 (1 H, m, 4.20 (2 H, m) (see Figure 1); ir (CCl_4) 3595, 3445, 2950, 1447, 1252, 1067, 1040, 920, and 863 cm^{-1}.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.46; H, 9.01.

Isolation of 3-(1-Hydroperoxyethyl)-1,2-dioxane (7). *trans*-Hex-4-ene hydroperoxide (0.236 g, 2.03×10^{-3} mol) was treated with DBPO (0.120 g, 5.14×10^{-4} mol) in benzene solution (100 ml) as previously described. After 48 h at room temperature the solvent was stripped to give a yellow residue. This material was dissolved in 2 ml of 50% ethyl acetate in 2,2,4-trimethylpentane and was subjected to preparative HPLC (8 ft × ⅜ in. Porasil A, 50% ethyl acetate in 2,2,4-trimethylpentane, 5 ml/min^{-1}). One major component was observed and collected. The solvents were removed, and the residue was re-cycle chromatographed on Porasil A. The product was collected on the third pass. The solvents were removed giving a clear colorless liquid (0.069 g, 0.465 mol, 23%): NMR (CCl_4) δ 1.18 (3 H, 2 d), 1.82 (4 H, m), 3.96 (2 H, m), 4.12 (3 H, m); ir (CCl_4) 3540, 3420, 2950, 1240, and 863 cm^{-1}.

The cyclic peroxy alcohls **10**, **11**, and **12** were obtained analytically pure by methods similar to those described above. These compounds were also prepared by an alternative approach, the acid-catalyzed reaction of appropriate oxirane hydroperoxides. The spectral characteristics of these compounds are presented below.

Trichloroacetic Acid Catalyzed Reaction of Oxirane Hydroperoxides: 3-Methyl-3-(hydroxymethyl)-1,2-dioxolane (10). The hydroperoxide **2** (0.3 g 2.95×10^{-3} mol) was dissolved in 5 ml of methylene chloride. To the hydroperoxide was added *m*-chloroperbenzoic acid (3.1×10^{-3} mol) over 10 min and the mixture was stirred for 3 h. The reaction mixture was then cooled to 0 °C and 13 mg of TCA added, and this solution was stirred for another 3-h period at 0 °C. The product mixture was chromatographed in a jacketed column at 0 °C on 10 g of silica gel (pentane:ether); yield, 230 mg of **14** (66%). This material was identical in every respect with material obtained by the DBPO, triphenylphosphine reaction sequence on **2.** NMR (CCl_4) δ 1.2 (3 H, s), 2.1–2.7 (2 H, m), 3.46 (2 H, AB quartet), 4.16 (2 H, t); NMR (Me_2SOd_6) 1.45 (3 H, s), 2.0–2.5 (2 H, m), 3.25 (2 H, m), 3.96 (2 H, t), 4.7 (1 H, t).

Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.76; H, 8.30.

The absorption at δ 2.2 is representative for protons attached to the 4 position of a 1,2-dioxolane. All 1,2-dioxolanes we have isolated show these protons in the δ 2.0–2.5 region. This must be due to an aniso-

tropic effect from the peroxide linkage on the 4 protons.[48]

3-(1-Hydroxy-*n*-propyl)-1,2-dioxolane (11). The hydroperoxide **3** was converted to **11** via the oxirane hydroperoxide as described above. **11** was purified by HPLC on Porasil A. NMR (CCl_4) δ 1.00 (3 H, t), 1.44 (2 H, m), 2.56 (2 H, m), 3.34 (1 H, m), 4.04 (3 H, m).

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.32; H, 9.38.

Reaction of 4-Methylpent-3-ene 1-hydroperoxide (4) with *m*-Chloroperbenzoic Acid, TCA. **4** was treated with *m*-chloroperbenzoic acid followed by TCA as described above. HPLC of the reaction mixture (several recycles on Porasil A, 2-propanol/hexane solvent) led to separation of two cyclic peroxides. Both of the peroxides appeared to be somewhat unstable to the chromatographic procedure and considerable amounts of material were lost in the purification.

3-(2-Hydroxy-2-propyl)-1,2-dioxalane (12). Material isolated from HPLC had the following NMR: (CCl_4) δ 1.20 (GH, d), 2.64 (2 H, m), 4.12 (3 H, m).

4-Hydroxy-3,3-dimethyl-1,2-dioxane (17). Material isolated from HPLC had the following NMR: (CCl_4) δ 1.22 (GH, d), 1.90 (2 H, m), 3.64 (1 H, m), 4.34 (2 H, m).

A mixture of **12** and **17** were analyzed for C and H content.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.35; H, 8.89.

Reaction of Methyl 9-Hydroperoxy-6,10,12-octadecatrienoate (21) with *m*-Chloroperbenzoic Acid, TCA. The hydroperoxide **21** (0.157 g) was treated with *m*-chloroperbenzoic acid (0.093 g) in a two-phase solution of 6 ml of CH_2Cl_2 and 1.5 ml of aqueous 0.5 M sodium bicarbonate.[38] The methylene chloride phase was separated after 3 h and 0.012 g of monochloroacetic acid added. After 2 h at 25 °C, the product mixture was chromatographed (HPLC, 8 ft Porasil A). **22** was isolated by HPLC and had the following characteristics: uv 234.5 nm, ϵ 14 000; positive test to ferrous thiocyanate; NMR (CCl_4) δ 0.95 (3 H, m), 1.4 (12 H, m), 2.0–2.5 (6 H, m), 3.2–3.5 (1 H, m), 3.6 (3 H, s), 3.4–4.7 (1.6 H, m), 5.0–6.5 (3.8 H, m).

Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.91; H, 9.49.

Acetophenone-Sensitized Photolysis of Unsaturated Hydroperoxides. The photolysis of **2** is illustrative. **2** (107 mg) and 50.6 mg of acetophenone were dissolved in 100 ml of Freon 11. The solution was photolyzed for 7 h at 0 °C. From the photolysis, 31 mg of **2** was recovered unchanged. Triphenylphosphine reduction of the intermediate peroxide-hydroperoxide led to 25.8 mg of **10** (32% based on recovered hydroperoxide).

References and Notes

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(2) Abstracted in part from the Ph.D. Dissertation of M. O. Funk, Duke University, 1975.
(3) J. W. Hinman, *Annu. Rev. Biochem.*, **41**, 161 (1972).
(4) *Ann. N.Y. Acad. Sci.*, **180**, (1971).
(5) P. W. Ramwell and J. E. Shaw, *Recent Prog. Hormone Res.*, **26**, 139 (1970).
(6) S. Bergstrom, Ed., *Adv. Biosci.* **9**, (1973).
(7) J. E. Pike, *Sci. Am.*, **225**, 84 (1971).
(8) (a) B. Samuelsson, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **31**, 1442 (1972); (b) B. Samuelsson, H. Granstrom, and M. Hamberg, *Prostaglandins, Proc. Nobel Symp., 2nd, 1966*, 31–45 (1967); (c) D. H. Nugteren, R. K. Beerthuis, and D. A. VanDorp, *ibid.*, 45–50 (1967).
(9) M. Hamberg, J. Svenson, T. Wakabayashi, and B. Samuelsson, *Proc. Natl. Acad. Sci., U.S.A.*, **71**, 345 (1974).
(10) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci., U.S.A.*, **71**, 3400 (1974).
(11) M. Hamberg, P. Hedquist, K. Standberg, J. Svensson, and B. Samuelsson, *Life Sci.*, **16**, 451 (1975).
(12) E. F. L. J. Anet, *Aust. J. Chem.*, **22**, 2403 (1969).
(13) E. H. Nugteren, H. Vonkeman, and D. A. VanDorp, *Recl. Trav. Chim. Pays-Bas*, **86**, 1237 (1967).
(14) P. Haverkamp-Begeman, W. J. Woestenberg, and S. Leer, *J. Agric. Food Chem.*, **16**, 679 (1968).
(15) W. A. Pryor and J. P. Stanley, *J. Org. Chem.*, **40**, 3616 (1975).
(16) Aspects of this work have been previously published as a preliminary communication, M. O. Funk, R. Isaac, and N. A. Porter, *J. Am. Chem. Soc.*, **97**, 1281 (1975).
(17) For a review, see R. Hiatt, "Organic Peroxides", Vol. II. D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1971, p 1.
(18) H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76**, 2984 (1954).
(19) H. R. Williams and H. S. Mosher, *J. Am. Chem. Soc.*, **76**, 2987 (1954).
(20) S. Dykstra and H. S. Mosher, *J. Am. Chem. Soc.*, **79**, 3474 (1957).
(21) S. Wanzonek, P. D. Klimstra, and R. F. Kallie, *J. Org. Chem.*, **25**, 621 (1960).
(22) For a review, see J. A. Howard, "Advances in Free Radical Chemistry", Vol. 4, G. H. Williams, Ed., Academic Press, New York, N.Y., 1972, p 49.
(23) R. Hiatt, K. C. Irwin, and C. W. Gold, *J. Org. Chem.*, **33**, 1430 (1968).
(24) J. R. Thomas, *J. Am. Chem. Soc.*, **87**, 3935 (1965).
(25) D. G. M. Diaper, *Can. J. Chem.*, **46**, 3095 (1968).
(26) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Am. Chem. Soc.*, **82**, 1762 (1960).
(27) R. Hiatt and L. Zigmnd, *Can. J. Chem.*, **48**, 3967 (1970).
(28) R. Haitt, T. Mill, K. C. Irwin, and J. K. Castleman, *J. Org. Chem.*, **33**, 1428 (1968).
(29) J. A. Horward and K. U. Ingold, *Can. J. Chem.*, **47**, 3797 (1969).
(30) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1593 (1963).
(31) R. Hiatt, R. J. Smythe, and C. McColeman, *Can. J. Chem.*, **49**, 1707 (1971).
(32) H. D. Holtz, P. W. Solomon, and J. E. Mahan, *J. Org. Chem.*, **38**, 3175 (1973).
(33) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7587 (1972).
(34) R. D. Rieke and N. A. Moore, *J. Org. Chem.*, **37**, 413 (1972).
(35) J. M. Suzur, M. P. Bertrand, and R. Nonguler, *Tetrahedron Lett.*, 4197 (1969).
(36) (a) C. Walling and M. Gibian, *J. Am. Chem. Soc.*, **87**, 3413 (1965); (b) W. H. Richardson, G. Ranney, and F. C. Montgomery, *ibid.*, **96**, 4668 (1974).
(37) N. A. Porter, D. Gilmore, and J. Nixon, to be published.
(38) If one wishes to isolate the oxirane hydroperoxide a two-phase methylene chloride/aqueous bicarbonate system can be employed with success for the epoxidation; W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973).
(39) M. Mousseron-Canet, C. Levallois, and H. Huerre, *Bull. Soc. Chim. Fr.*, 658 (1966).
(40) M. R. Barusch and J. A. Payne, *J. Am. Chem. Soc.*, **75**, 1987 (1953).
(41) N. A. Porter and M. O. Funk, *J. Org. Chem.*, **40**, 3614 (1975).
(42) M. O. Funk, R. Isaac, and N. A. Porter, *Lipids*, 11, 113 (1976).
(43) M. H. Abraham, A. G. Davies, D. R. Llewellyn, and E. M. Thain, *Anal. Chim. Acta*, **17**, 499 (1957).
(44) E. J. Corey, G. W. J. Fleet, and M. Kato, *Tetrahedron Lett.*, 3693 (1973).
(45) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950).
(46) Aldrich Chemical Co.
(47) E. Caspi and K. R. Varma, *J. Org. Chem.*, **33**, 2181 (1968).
(48) D. H. Gibson and C. H. Depuy, *Tetrahedron Lett.*, 2203 (1969).