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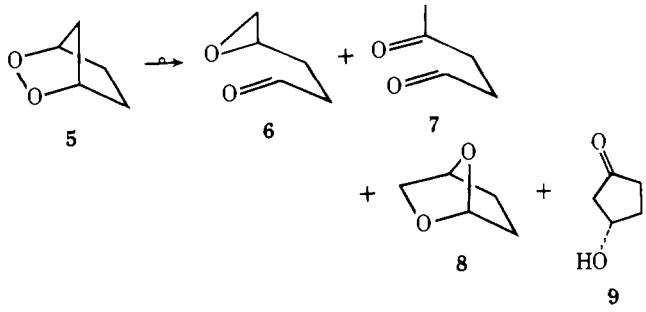
Prostaglandin Endoperoxides. 6. A Polar Transition State in the Thermal Rearrangement of 2,3-Dioxabicyclo[2.2.1]heptane[1]

Sir:

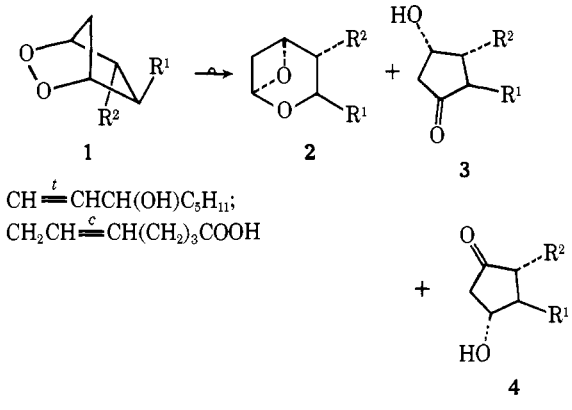
Prostaglandin (PG) endoperoxides[2,3] (e.g., **1**) are a branch point in the oxidative transformation of polyunsaturated fatty acids into a vast array of physiologically active metabolites such as thromboxane A_2 (**2**),[4] PGD_2 (**3**), and PGE_2 (**4**).[2,3] We recently reported the first nonenzymatic synthesis of bona fide, fully characterized derivatives of the 2,3-dioxabicyclo[2.2.1]-heptane heterobicyclic ring system,[1c] and a synthesis of the parent compound **5**.[1c] A thorough examination of the chemistry of **5** was initiated to provide a basis for interpreting the complex biochemistry of PG endoperoxides. We now report that (a) the model endoperoxide **5** rearranges thermally to afford **6–9**; (b) the relative yields of these products are strongly



solvent dependent; and (c) the rate of decomposition increases with solvent polarity and is exceptionally rapid in protic solvents. Solvent effects on the thermal reactions of **5** result primarily from an extraordinary dependence of the rate of rearrangement to levulinaldehyde (**7**) on solvent polarity.

Extraordinary reactivity was postulated for PG endoperoxides owing to the strained bicyclic structure of their peroxide nucleus **5**. Instability at room temperature was predicted.[5] More recently, PG endoperoxides, prepared enzymatically, were isolated.[3] As expected, these endoperoxides are thermally labile. In nonpolar organic solution (1:1 light petroleum–ether), 9α,11α-epidioxy-15(*S*)-hydroxy-13-*trans*-prostenoic acid decomposes with a half-life of 2.7 h at 20 °C. In aqueous medium, at pH 4–8, the half-life is only 30 min at 20 °C.[3b] PG-endoperoxide-like derivatives of **5** were also obtained nonenzymatically, by autoxidation of methyl linolenate, and were observed to decompose thermally with a half-life of 3.3 h at 80 °C.[6]

Thermal decomposition of **5** was monitored by ^1H NMR and GLC.[7] Products **7, 8,** and **9** were identified by spectral and GLC comparison with authentic samples, prepared by reported procedures.[8] The identity of the epoxy aldehyde (**6**), a new



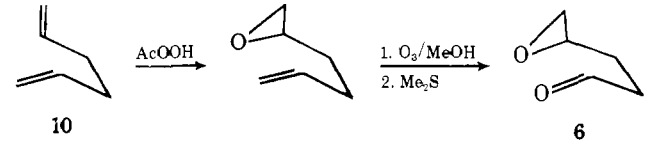


Table I. Thermal Decomposition of **5**[a]

Entry	Reaction solvent	D^b	Reaction temp °C	$t_{1/2}$,[c] h	Products, mol %[d] 6	7	8	9
A	Cyclohexane	1.94	73	5.7	97	2	1	0
B	CCl_4	2.13	73	4.1	87	10	3	0
C	Benzene-d_6	2.18	73	2.9	86	11	3	0
D	Chlorobenzene	4.85	73	2.4	85	15	0	0
X	CD_3COOD	6.63	73	0.22	0	100	0	0
E	$ClCD_2CD_2Cl$	7.94	73	2.1	54	42	4	0
F	2-Butanone	14.35	73	1.5	63	35	2	0
G	CD_3CN	28	73	1.3	40	59	1	0
Y	D_2O	74	40	0.12	0	72	0	28

[a] The concentration of **5** was ~0.5 M for each experiment. For entry F one run was conducted under air, another under oxygen, and a third deoxygenated by three freeze–pump–thaw cycles. The same rate of decomposition of **5** was observed for each run. Therefore, all other experiments were conducted under air. For entries A, X, and Y, solvents were freed of most catalytic impurities, especially metal ions, by stirring with Na_2EDTA for 1 week followed by a low temperature molecular distillation. Furthermore, all glassware, including ^1H NMR tubes and the receivers into which **5** was sublimed prior to use, were scrupulously cleaned with $Na_2Cr_2O_7$–H_2SO_4 followed by NH_4OH (1 day) and Na_2EDTA (1 day), rinsed with distilled water, and dried. Omission of the Na_2EDTA for solvent purification and washing of glassware did *not* change the rate observed for decomposition of **5**. [b] Corrected for temperature. [c] Half-life calculated from the corresponding first-order rate constants (see Table II). [d] Near-quantitative overall yields determined by GLC analysis with *n*-undecane or diglyme as internal standard.

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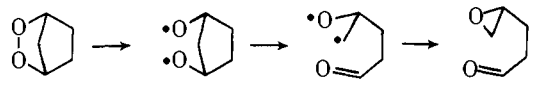
compound, was confirmed by unambiguous synthesis from 1,5-hexadiene (**10**).[8d]

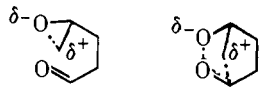
Product distributions obtained from thermal decomposition of **5** in various solvents are given in Table I. Solvents are listed in order of increasing dielectric constant. No interconversion of **6**, **7**, or **9** is observed under the reaction conditions, and the rate of disappearance of **5** exhibits first-order kinetics for at least 3 half-lives. The epoxy aldehyde **6** is a chemically sensitive compound which readily rearranges to **8**.[9] Thus, the small quantities of **8** obtained from **5** may well be an artifact, due to secondary isomerization of **6**, rather than a primary rearrangement product from **5**.

Simple homolysis of the peroxide bond in **5** followed or accompanied by β scission of a carbon-carbon bond might generate diradical **11**. Cyclization of **11** could produce epoxy al-



5 11 6

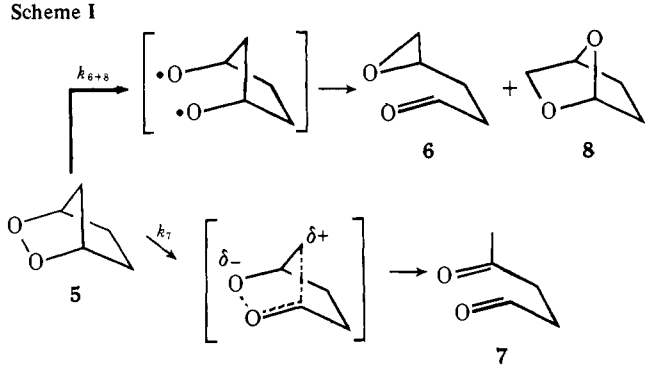
dehyde **6**. The novel rearrangements which give keto aldehyde **7** and hydroxy ketone **9** seem to be polar rather than diradical processes since they are favored by polar and protic solvents. However, certain "diradical rearrangements" involving 1,2 shifts of hydrogen, which have little or no analogy in simple radical chemistry, may be facilitated by a transition state which is "sufficiently polar to make the rearrangement essentially a carbonium ion process".[11] Thus, **7** could arise by 1,2-hydride shift to the positive carbon in **12** or **13**. We propose that the



12 13

first-order decomposition observed for **5** is a composite of parallel first-order reactions, one a dipolar, heterolytic process leading to **7** and the other a homolytic process which gives **6** and hence **8** (Scheme I). First-order kinetics for appearance

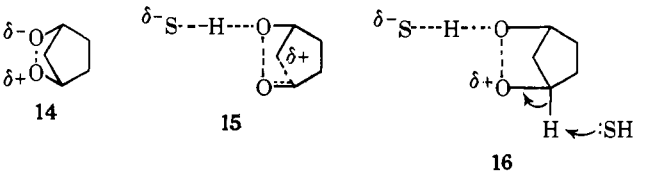
Scheme I



of **6** and **7** was confirmed for entries C, E, F, and G of Table **I**. The first-order rate constants k_{6+8} and k_7 for product appearance, calculated from the product ratios of Table I, and the rate constant k_{-5} for disappearance of **5**, are listed in Table II.[12] As expected for a homolytic reaction, the rate of formation of **6** and **8** shows only a small dependence on solvent polarity. Comparable rate enhancements are known for some dialkyl peroxide decompositions.[13] In contrast, k_7 is extraordinarily sensitive to solvent polarity in accord with a polar transition state. The rate accelerations found for decomposition of **5** in protic solvents are also unprecedentedly large.[14] Rates are an order of magnitude greater for table entries X and Y than observed in aprotic solvents of similar polarity. An attractive explanation for this effect presumes that protic solvents facilitate heterolysis by proton donation to the electron-rich oxygen in **13** or **14** as in **15** or **16**.

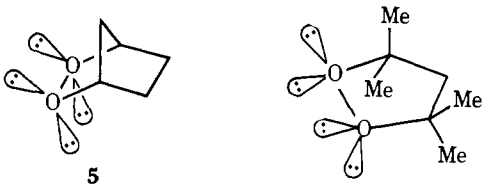
Table II. Partial Rate Constants for Parallel First-Order Reactions of **5**

Reaction solvent	D	Rate constants × 10^5, s^{-1}		
		k_{-5}	k_{6+8}	k_7
Cyclohexane	1.94	3.4	3.3	0.1
CCl_4	2.13	4.7	4.2	0.5
Benzene-d_6	2.18	6.6	5.9	0.7
Chlorobenzene	4.85	8.0	6.8	1.2
$ClCD_2CD_2Cl$	7.94	9.2	5.3	3.9
2-Butanone	14.35	13	8.5	4.6
CD_3CN	28	15	6.2	8.9



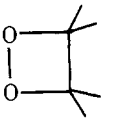
14 15 16

The rate of thermal decomposition of the 1,2-dioxolane **17** increases by only 30% in acetonitrile compared with benzene as solvent.[15] The corresponding rate increase for **5** is 130%. It is tempting to speculate that repulsive antisymmetric vicinal orbital interactions play a major role in determining the chemical reactivity of **5**. A large destabilization is expected for



5 17

5 with a C_1-O-O-C_4 dihedral angle $\theta = 0°$ compared with **17** ($\theta = 30°$) owing to unfavorable juxtaposition of the oxygen lone pairs in **5**. This would be reflected in a lower ionization potential (we estimate ~8.4 eV as observed for ascaridole) for **5** compared with **17** (9.26 eV).[16] It follows that the rigid bicyclic peroxide **5** is more basic and, hence, more susceptible to proton or Lewis acid[17] induced decomposition than more flexible peroxides. Lewis acid catalysis of the thermal decomposition of 1,2-dioxetane **18** is well documented.[18]



18

The facile disproportionation of the endoperoxide **5** to give hydroxy ketone **9** under nonalkaline conditions is extraordinary. Similar behavior was, however, observed previously in the rearrangement of PG endoperoxides into D and E prostaglandins in neutral aqueous solution.[3b] Proton abstraction from a bridgehead carbon in **16** is required to produce **9**. Since acetic acid is ineffective as a proton acceptor compared with water, only **7** is formed in acetic acid, while both **7** and **9** are produced in water. Other observations confirm the requirement of *both* proton donation and proton abstraction for facile disproportionation of the endoperoxide **5**. Thus, the aprotic amine **19** catalyzes rearrangement of **5** to **7** with no trace of **9**.[1e,19]

19 20

However, imidazole (**20**), which is an effective proton donor as well as acceptor, catalyzes rearrangement of **5** to a 1:1 mixture of **7** and **9**.[1e] Whatever the mechanism, it is now ap-

parent that the unusual proclivity toward disproportionation in neutral aqueous solution and the decreased thermal stability of PG endoperoxides in aqueous solution vs. nonpolar solvents is characteristic of the conformationally rigid, strained, bicyclic peroxide nucleus **5** of PG endoperoxides. In fact, the rates of decomposition in aqueous solution observed for the model endoperoxide **5** and PG endoperoxides are almost identical.

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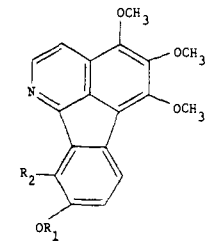
X-Ray Crystal Structure of Norrufescine

Sir:

We report herein the x-ray crystal structure of the azafluoranthene alkaloid norrufescine and thereby provide the first covalent bonding parameters for the azafluoranthene nucleus. Norrufescine ($C_{18}H_{15}NO_4$) occurs naturally in the stems of the Amazonian vines *Abuta imene* and *Abuta rufescens*.[1] Two azafluoranthene alkaloids, imeluteine (**1**) and rufescine (**2**), have been previously isolated and characterized.[2] Norrufescine



1, R_1 = CH_3, R_2 = OCH_3
2, R_1 = CH_3, R_2 = H
3, R_1 = H, R_2 = H

(**3**) differs from rufescine in that one of the four rufescine methoxy groups is replaced by a phenolic hydroxyl group. However there has been some ambiguity as to the position of this phenolic function.[2] This study has confirmed the predicted structure of norrufescine.

Small brown crystals of norrufescine were grown from a $CHCl_3$-methanol solution of this compound. The density of the crystals was not measured because only a very small amount of norrufescine was available. A crystal measuring 0.08 × 0.11 × 0.13 mm was used for x-ray measurements. Precession photographs revealed a monoclinic lattice. Systematic absences of hkl reflections for $h + k$ odd and of $h0l$ reflections for l odd indicated the space group to be either Cc or $C2/c$. The calculated density of norrufescine assuming the space group to be $C2/c$ is in good agreement with known densities of alkaloids with similar composition. This assumption of space group was subsequently confirmed by the successful refinement of the structure.

X-ray diffraction data were measured on a Picker FACS-I diffractometer equipped with a graphite monochromator and employing Mo Kα radiation (λ = 0.7093 Å). The unit cell parameters, which were determined by the least-squares fit of the angular positions of 12 reflections, are a = 27.18 (8), b = 8.57 (2), c = 16.07 (4) Å; β = 127.8 (1)°. The x-ray reflections were measured to the limit 2θ = 50° using the θ-2θ scan mode with a scan rate of 1° min^{-1}. The three reflections that were monitored after every 50 intensity measurements showed no significant decay during the data collection process.

The measured intensities, I, were corrected for Lorentz and polarization effects. Standard deviations, $\sigma(I)$, were calculated according to Stout and Jensen[3] assuming an instrumental instability factor of 0.05. Of the 2355 measured unique reflections 1166 had $I < 2.33\ \sigma(I)$ and were therefore considered to be unobserved.

The structure of norrufescine was uneventfully solved by direct methods using the program MULTAN.[4] The structure was refined by least-squares procedures in which the quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = I/\sigma^2(I) = 1/\sigma^2(F_o)$. The atomic scattering factors used were those of Cromer and Waber[5] for non-H atoms and those of Stewart, Davidson, and Simpson[6] for H atoms. The least-squares refinement, in which the thermal parameters of the non-H atoms were varied isotropically, converged at R = 0.156. This was followed by a refinement in which the thermal parameters were varied anisotropically. A difference Fourier map at this stage revealed the positions of the hydroxyl hydrogen and four of the five ring hydrogens. The methyl hydrogens could not be located. A final refinement in which non-H atoms were varied anisotropically and H atoms were varied isotropically con-

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