The Prostaglandin Endoperoxide Nucleus and Related Bicyclic Peroxides.[1] Synthetic and Spectroscopic Studies

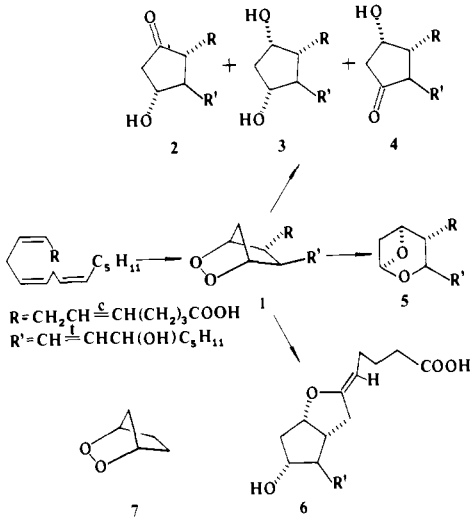
Daniel J. Coughlin,[2] R. S. Brown,[3] and Robert G. Salomon*[2]

Contribution from the Departments of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, and University of Alberta, Edmonton, Alberta, Canada T6G 2G2.
Received June 7, 1978

Abstract: Several derivatives of 2,3-dioxabicyclo[2.2.1]heptane, the strained bicyclic peroxide nucleus of prostaglandin endoperoxides, were prepared from 2,3-dioxabicyclo[2.2.1]hept-5-enes by selective reduction with diimide or chlorination. Stereospecific cis-exo delivery of hydrogen in the reduction was demonstrated by deuterium-labeling studies. The chlorination is accompanied by molecular rearrangement involving a novel 1,2 shift of an alkylperoxy group. A homologous series of saturated bicyclic peroxides was prepared from singlet oxygen adducts of cyclic 1,3-dienes by reduction with diimide. The bridgehead ^{13}C–H coupling constants observed for these bicyclic peroxides increase with decreasing ring size in parallel with increasing ring strain. With the exception of the highly strained bicyclo[2.2.1] peroxide, the first ionization energy of the bicyclic peroxides, measured by photoelectron spectroscopy, increases with increasing C–O–O–C dihedral angle. Photoelectron spectral data for a homologous series of monocyclic peroxides are also reported.

Introduction

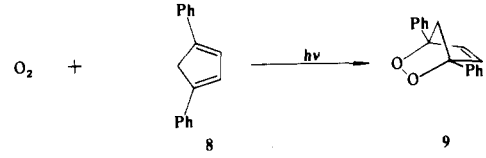
Prostaglandin endoperoxides are chemically sensitive intermediates in the transformation of essential fatty acids into a large array of biomolecules which exhibit potent and varied physiological activities. Prostaglandin endoperoxides[4] (e.g., **1**) are the immediate biological precursors of prostaglandins[4] (e.g., prostaglandin E_2 (**2**), prostaglandin $F_{2\alpha}$ (**3**), prostaglandin D_2 (**4**)), thromboxane A_2 (**5**),[5] and prostacyclin (**6**).[6] They are derivatives of the strained 2,3-dioxabicyclo[2.2.1]-heptane (**7**) heterobicyclic ring system. Prostaglandin endoperoxides have been isolated from enzymatic cyclooxygenation of polyunsaturated fatty acids.[4h,i] However, studies of the chemical reactions of these key biomolecules are hampered by the instability[7] and uncertain purity[8] of the minute samples available by bioconversion. Furthermore, the complexity of the molecular structures of the natural endoperoxides and their transformation products complicates identification, which has generally been indirect and hence only tentative. The mechanistic details of prostaglandin endoperoxide chemistry and biochemistry, therefore, remain essentially unknown.



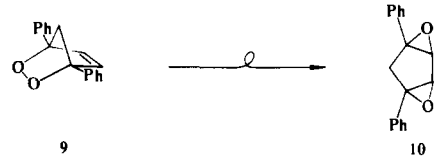
We recently found that diimide selectively reduces the carbon–carbon π bond of unsaturated dialkyl peroxides.[1c] This discovery allowed the first nonenzymatic synthesis of a bona fide, fully characterized derivative of 2,3-dioxabicyclo[2.2.1]heptane (**7**), the strained bicyclic peroxide nucleus of prostaglandin endoperoxides. This selective reduction now has been extended to provide an efficient synthesis of **7** itself,[9a] as well as a series of saturated bicyclo[*n*.2.2] peroxides from corresponding unsaturated peroxides which are readily available. Derivatives of the prostaglandin endoperoxide nucleus **7** are also available from reaction of molecular chlorine with 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptene (**9**). An unusual molecular rearrangement involving a novel 1,2 shift of an alkylperoxy group accompanies chlorination of **9**. We now present the details of these synthetic studies. Also the influence of structure on the ^{13}C NMR and photoelectron spectra of homologous series of mono- and bicyclic peroxides is reported.

Results

Chlorination of 1,4-Diphenyl-2,3-dioxabicyclo[2.2.1]hept-5-ene (9). Unsaturated bicyclic peroxides are readily available by cycloaddition of singlet oxygen with cyclic 1,3-dienes.[10] Thus, 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptene (**9**)[11] is prepared by addition of photochemically generated singlet oxygen to 1,4-diphenyl-1,3-cyclopentadiene (**8**).[12] The diene

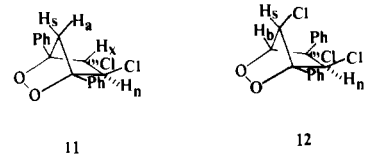


8 serves as both sensitizer and substrate for singlet oxygen. Since **9** readily rearranges to the diepoxide **10**,[11,13] purification



by recrystallization from hot solvent is unsatisfactory. Simple rinsing of the crude photooxygenation product with cold ethanol affords the unsaturated peroxide **9** in sufficient purity for synthesis of derivatives.

Chlorination of **9** with excess chlorine in chloroform produces a dichloro peroxide **11** as well as trichloro peroxide **12**



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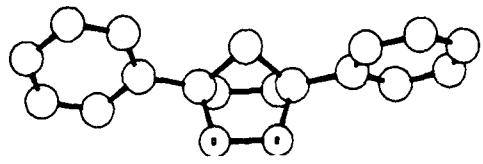


Figure 1. X-ray crystal structure of 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane (**13**).

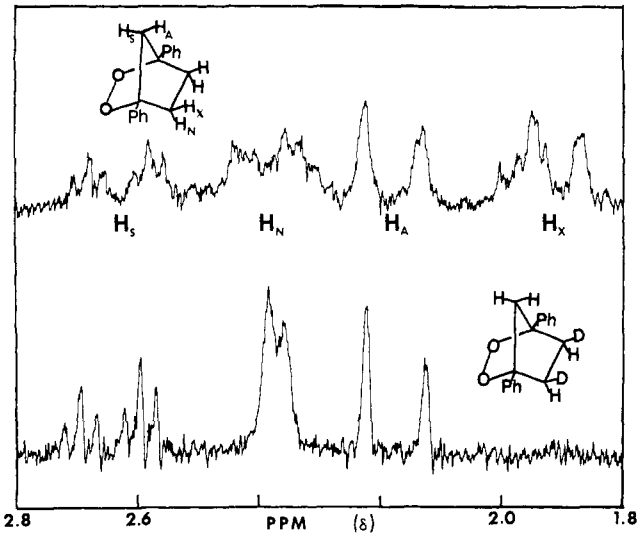


Figure 2. Upfield region of 100-MHz ^{1}H NMR spectra of **13** (top) and **14** (bottom).

in a 1.3:1 ratio. With carbon tetrachloride as solvent, **11** and **12** are produced in equal amounts and constitute about 90% of the products according to ^{1}H NMR analysis of the chlorination reaction mixture. Though separation of these products is difficult, analytically pure **11** and **12** are obtained by chromatography and recrystallization, albeit in only 26 and 11% yields, respectively. The ^{1}H NMR spectrum of dichloro peroxide **11** shows four one-proton multiplets centered at δ 2.58, 2.96, 4.55, and 4.66 corresponding to H_s, H_a, H_x, and H_n, respectively. The large geminal coupling J_{sa} = 11 Hz, a small vicinal coupling, J_{xn} = 2.8 Hz, and long-range W-plan coupling, J_{sn} = 2.8 Hz, which is characteristic of bicyclo[2.2.1]-heptane ring systems,[14] confirm the assigned relative geometries. The ^{1}H NMR spectrum of the trichloro peroxide **12** shows three one-proton multiplets centered at 4.56, 4.88, and 5.42, corresponding to H_n, H_s, and H_b, respectively. Vicinal coupling, J_{sb} = 4.3 Hz, is present, and long-range W-plan coupling, J = 2.4 Hz, confirms the configurations assigned for H_s and H_n. The configuration assigned to the chloro and phenyl substituents at C-5 assumes a trans relationship between the chloro groups at C-5 and C-6 (see Discussion section).

Reduction of Unsaturated Bicyclic Peroxides with Diimide. Selective reduction of the C–C π bond of unsaturated peroxides is achieved with diimide,[15] generated in situ by the reaction of potassium azodicarboxylate with acetic acid.[16] Thus, analytically pure saturated peroxide **13** is obtained from **9** in 76%

9 13, X=H; 14, X=D

yield. The C_1–O–O–C_4 dihedral angle in **13** is 0° and the O–O bond (1.501 ± 0.002 Å) is abnormally long according to X-ray crystal structure analysis (Figure 1).[17]

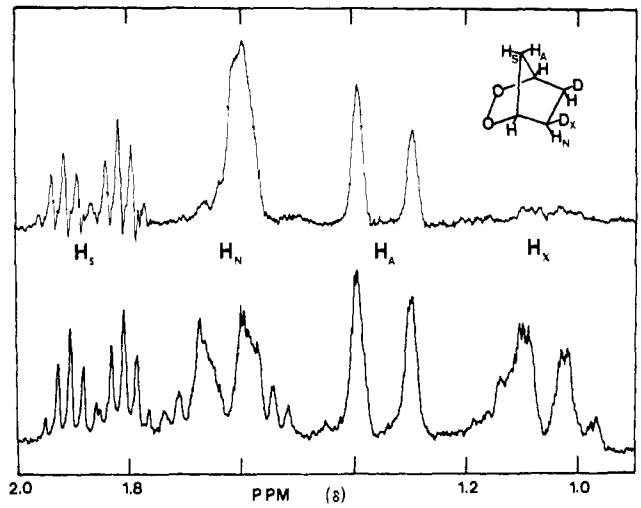
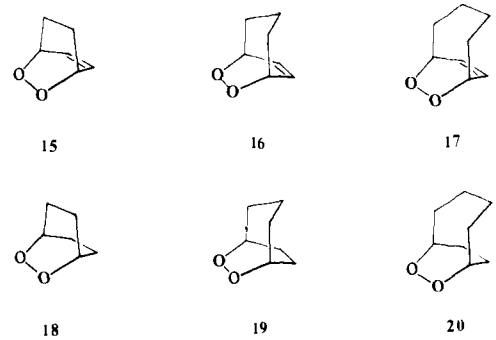


Figure 3. Upfield region of 100-MHz ^{1}H NMR spectra of **7** (bottom) and cis-exo dideuterated analogue **26** (top).

Reduction of **9** with dideuterio diimide occurs stereospecifically cis-exo to give **14.** Thus, the upfield portion of the ^{1}H NMR spectrum of **13** (Figure 2) in perdeuteriobenzene solution exhibits four multiplets centered at δ 1.90, 2.17, 2.40, and 2.64 which correspond to H_x, H_a, H_n, and H_s, respectively. Geminal coupling, J_{xn} = 8, J_{as} = 10 Hz, and long-range W-plan[12] coupling, J_{ns} = 2.5 Hz, support these assignments. The multiplet at δ 1.90 and 8-Hz coupling of H_n with H_x are absent in the ^{1}H NMR spectrum of **14,** though long-range W-plan coupling, J_{sn} = 2.5 Hz, is present (Figure 2). The mass spectrum of **14** (*m/e* (rel intensity) 254 (9), 224 (23), 222 (39), 221 (100), 105 (99), 77 (71), 30 (2)) shows fragmentation into $C_2D_2H_2$ and 1,3-diphenyl-1,3-propanedione. In the mass spectrum of **13** there is no fragment of *m/e* 30 and the parent peak appears at *m/e* 252.

Selective diimide reduction is also effective for the preparation of the parent 2,3-dioxabicyclo[2.2.1]heptane (**7**).[9a] Again, we find that reduction with deuterated diimide occurs stereospecifically cis-exo. Thus, the multiplet at δ 1.1 in the ^{1}H NMR spectrum of **7** in perdeuteriobenzene, which we assign to the exo hydrogens at positions 5 and 6, is essentially absent in the ^{1}H NMR spectrum of the product from reduction with deuterated diimide (Figure 3).

The singlet oxygen adducts **15**,[18] **16**,[19] and **17**[20] from 1,3-cyclohexadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene give the saturated bicyclic peroxides **18–20,** respectively, upon

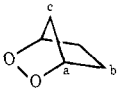
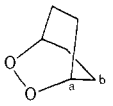
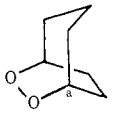
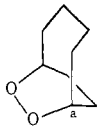
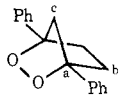
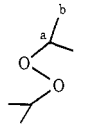


15 16 17

18 19 20

reduction with diimide. Thus, the new approach which we recently introduced[1c,21] for synthesis of saturated dialkyl peroxides by selective reductions with diimide ("diazene") is quite general. Many additional examples of the synthetic applications of our method are provided by recent work from other laboratories.[22]

Table I. ^{13}C NMR Spectra of Saturated Peroxides

peroxide	carbon type	chemical shift, Hz	multiplicity	J_{C-H}, Hz
7 	a	78.7	d	161
	b	29.1	t	136
	c	43.8	t	136
18 	a	71.7	d	150
	b	24.2	t	132
19 	a	76.8	d	144
		19.9	t	128
		20.4	t	128
		35.0	t	123
20 	a	76.2	d	141
		20.8	t	128
		24.6	t	123
		34.9	t	123
13 	a	91.3	s	-
	b	35.2	t	133
	c	52.6	t	138
	a	75.3	d	141
	b	20.5	q	126

^{13}C NMR spectra (see Table I) confirm the symmetrical structures of the bicyclic peroxides **13** and **18–20.** The bridgehead ^{13}C–H coupling constants increase with decreasing ring size from 141 Hz for **20** to 161 Hz for the prostaglandin endoperoxide nucleus **7**. Photoelectron spectra of the bicyclic peroxides **7** and **18–20** as well as a homologous series of monocyclic peroxides provide the first two vertical ionization energies of a variety of conformationally different dialkyl peroxides (see Table II).

Discussion

Cationic Rearrangement of a Bicyclic Peroxide. The process which gives the trichloro peroxide **12** from the unsaturated endoperoxide **9** apparently involves a deep-seated skeletal reorganization. A mechanism which can explain the genesis of **12** from **9** involves a key 1,2 shift of a peroxide group in the chloronium ion intermediate **21** (Scheme I). A driving force for the novel **21** → **22** rearrangement is provided by stabilization of the positive center in **22** by a phenyl substituent. A trans relationship is assumed for the chloro groups at C-5 and C-6 in analogy to the trans relationships in **11** generated by simple addition of chlorine to the unsaturated peroxide **9**.

Scheme I

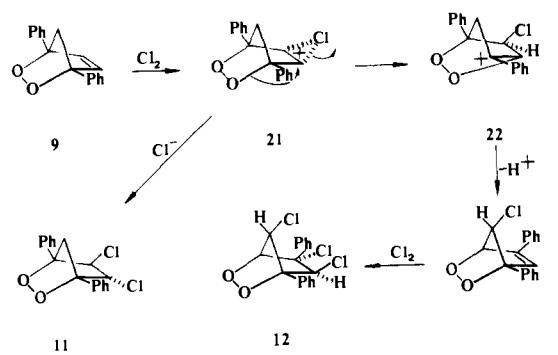
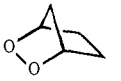
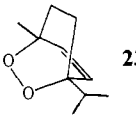
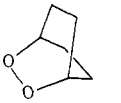
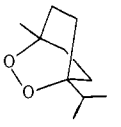
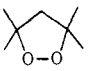
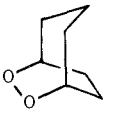
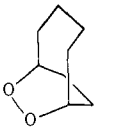
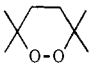
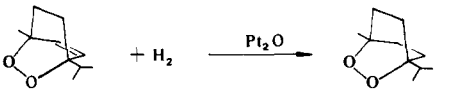


Table II. Vertical Ionization Energies for the Two Highest Occupied Orbitals of Some Dialkyl Peroxides

Compd		n_0^-, eV	σ^-, eV	ΔIP ($\sigma^- - n_0^-$)	θ,[a] deg
	**7**	8.99[b]	11.23	2.24	0
	**23**	8.42[c,d]	10.71	2.29	0
	**18**	8.82	10.84	2.02	15
	**24**	8.50[d]	10.36	1.86	15
	**29**	9.86	11.13	1.27	30[e]
	**33**	9.26[d]	10.47	1.20	30[e]
	**19**	8.97	10.37	1.40	50
	**20**	9.05	10.03	0.98	60
	**30**	10.0	10.2	0.2	75
	**34**	9.35[d]	9.76	0.41	75
	**31**	9.75	10.34	0.59	*f*
	**32**	9.29	10.60	1.29	*f*
diisopropyl peroxide		9.16	10.71	1.55	*f*
di-*tert*-butyl peroxide[g]		8.78	10.46	1.68	*f*

[a] Measured from Dreiding models[33] with probable errors of ±5°. [b] ν^+ ion = 880 ± 80 cm^{-1}. [c] ν^+ ion = 1008 ± 50 cm^{-1}. [d] Reference 27. [e] Reference 34. [f] Conformationally flexible. [g] Reference 30a.

Reduction of Unsaturated Bicyclic Peroxides with Diimide. In some cases, unsaturated bicyclic peroxides can be selectively reduced by catalytic hydrogenation to afford saturated bicyclic peroxides. Thus, dihydroascaridole (**24**) is available from as-



23 24

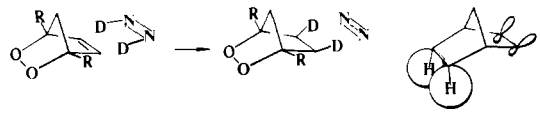
caridole (**23**) by this method.[23] However, unsaturated peroxides are generally reduced completely to saturated diols by catalytic hydrogenation.

Our discovery that diimide selectively reduces the carbon-carbon π bond of unsaturated peroxides[1c] provided a simple and effective synthesis of 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane (**13**), the first fully characterized synthetic derivative of the strained bicyclic peroxide nucleus **7** of prostaglandin endoperoxides. Thus, **13** is readily available from **9** in good yield and analytical purity. The unsubstituted peroxide **7** is also readily available by selective diimide reduction of **25**.[9]

9, R = Ph
25, R = H

13, R = Ph
7, R = H

Addition of hydrogen to both **9** and **25** occurs stereospecifically cis-exo since reduction with deuterated diimide affords **14** and **26** from **9** and **25**, respectively. Preferential attack of bicyclo[2.2.1]heptene (**27**) derivatives from the exo face of the



9, R = Ph
25, R = H

14, R = Ph
26, R = H

27

carbon-carbon π bond has been attributed to the effect of steric hindrance to endo attack by the endo hydrogens at C-5 and C-6,[24] and also to an unsymmetrical π bond which has greater electron density on the exo face.[25] In **9** or **25** the steric demands of nonbonding electron pairs on oxygen[26] take the place of steric effects of the endo hydrogens in **27**.

The unsaturated peroxides **25** and **15–17** are readily obtained from cyclic 1,3-dienes by cycloaddition of singlet oxygen.[18-20] Selective reduction of these cycloadducts with diimide readily affords saturated bicyclic peroxides **7** and **18–20**, a

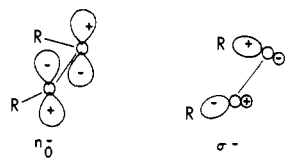
25, n = 1
15, n = 2
16, n = 3
17, n = 4

7, n = 1
18, n = 2
19, n = 3
20, n = 4

homologous series of bicyclic dialkyl peroxides. We recently reported preparation of a homologous series of monocyclic peroxides.[1d] These two series are valuable for determining the effects of geometric constraints and ring strain on the properties of dialkyl peroxides (see below). Such information is vital for understanding the novel chemistry of the strained bicyclic peroxide nucleus of prostaglandin endoperoxides. An X-ray crystal structural study of **13** has already revealed an abnormally long oxygen-oxygen bond.[17] The unusual length may result from repulsive antisymmetric vicinal orbital interactions.[27] The C_1-O-O-C_4 dihedral angle $\theta = 0°$ found in **13** maximizes unfavorable juxtaposition of lone-pair electrons on oxygen.

^{13}C NMR Spectra of Saturated Bicyclic Peroxides. Carbon-hydrogen coupling constants increase significantly for carbon atoms in a ring as the size of the ring decreases. This effect of ring strain is mainly due to increases in the s character of the carbon orbitals involved in bonding with hydrogen.[28] The ^{13}C NMR spectra of the saturated bicyclic peroxides are given in Table II. Assignment of the methylene carbon resonances of **13** was aided by the appearance of a triplet, $J_{CD} = 32$ Hz, for the 35.2-ppm resonance in the spectrum of the deuterated analogue **14**. The carbon-hydrogen coupling of the bridgehead carbons in the dioxabicyclic series ([4.2.2] (**20**), $J = 141$ Hz; [3.2.2] (**19**), $J = 144$ Hz; [2.2.2] (**18**), $J = 150$ Hz; [2.2.1] (**7**), $J = 161$ Hz) exhibits a significant increase with decreasing ring size. The larger ring peroxides **19** and **20** exhibit bridgehead coupling constants which are close or equal to that found for the α-C-H coupling constant, $J = 141$ Hz, of diisopropyl peroxide. The larger ring bicyclic peroxides **19** and **20** are, thus, strain free. It is interesting that conformation has no noticeable effect on the carbon-hydrogen coupling constants, since the conformation of the bicyclic peroxides is clearly different (more cisoid) from that of the acyclic peroxide. The carbon-hydrogen coupling constant and, hence, the ring strain of the [2.2.2] peroxide **18** is midway between that of the larger ring bicyclic peroxides and the highly strained bicyclo[2.2.1]heptane peroxide (**7**). For comparison, the bridgehead carbon-hydrogen coupling constant for bicyclo[2.2.2]octane was measured. The increase in J_{CH} from 134 Hz for this hydrocarbon to 142 Hz for bicyclo[2.2.1]heptane[29] is not even as large as the 11-Hz difference found betwene the corresponding peroxides **18** and **7**. Thus, the increased strain in the [2.2.1] compared to the [2.2.2] derivative may be even greater for the peroxides than for the hydrocarbons.

Photoelectron Spectra of Homologous Series of Mono- and Bicyclic Peroxides. PE investigations of some peroxides have been reported,[27,30] and, for the most part, they confirm theoretical predictions.[30,31] Of particular interest is the separation between the two highest peroxide orbitals, designated as an antisymmetric combination of the oxygen lone pairs (n_0^-) and antisymmetric combination of the C-O σ bonds (σ^-), respectively (**28**), as a function of C-O-O-C dihedral angle.



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Regardless of the sophistication, calculations[30,31] show that the splitting of the two highest MOs should have maximum (but not necessarily equal) values at $\theta = 0$ and 180°, and become degenerate at 90° where the two orbitals cross. Experimental support within the framework of Koopmans' theorem[32] is provided by the PE spectra of some reasonably well-defined *tertiary* dialkyl peroxides.[27,30a] However, owing to the lack of materials, no data are available for the homologous secondary or primary peroxides. Some of these are now provided in Table II listing the experimental ionization energies and dihedral angles[33] for compounds **7**, **18–20**, **29–34**, and diisopropyl

29, n = 1
30, n = 2
31, n = 3
32, n = 4

33, n = 1
34, n = 2

peroxide. The He(I) PE spectra of bicyclic peroxides **7**, **18**, **19**, and **20** are presented inFigure 5.

A plot of the observed splitting vs. dihedral angle[33] is displayed in Figure 4. The best fit straight line ($r = 0.96$) has a slope of −0.025 eV/deg and an intercept of 2.24 eV when $\theta = 0°$.

The entries (Table II) for dioxabicyclo[2.2.1]heptane (**7**) and ascaridole (**23**) show that the observed splittings of the first two bands (from n_0^- and σ^-) are 2.24 and 2.29 eV, respectively, even though the first band of the former is 0.5 eV higher than the latter, presumably owing to strain and/or substitution effects. Comparing dioxabicyclo[2.2.2]octane (**18**) and dihydroascaridole (**24**) shows splittings of 2.02 and 1.86 eV, for a dihedral angle of 15° in each. Similarly the two dioxacyclopentanes **29** and **33**, each having angles of 30°,[34] have splittings of 1.27 and 1.20 eV, respectively. From these data, one can conclude that the splitting of the first two ionizations

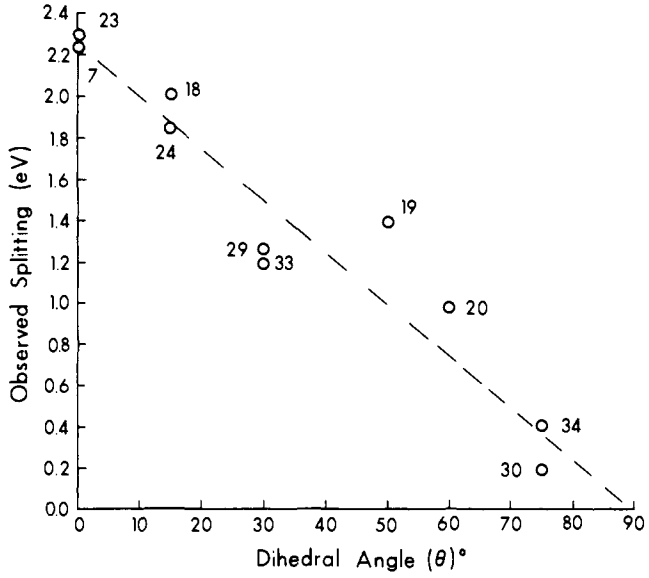
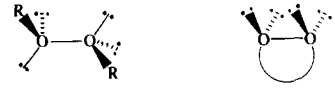


Figure 4. ΔIP vs. dihedral angle (θ) for some mono- and bicyclic dialkyl peroxides.

is a direct function of the dihedral angle and the substitution pattern has relatively little consequence. One does observe, however, that the first IP (n_O^-) is from 0.3 to 0.6 eV lower for the more highly substituted peroxide within a series as expected.

Another trend which is observed for the rigid peroxides relates to the half-width (fwhm) of the first two ionizations, which is in the order of 0.4–0.55 eV regardless of the structure. Multiple conformations in equilibrium would lead to an observed PE spectrum with considerably broadened peaks since each species of different θ would have different splittings. Dioxacycloheptane (**31**) from Dreiding models can adopt conformations yielding $0 < \theta < 120°$. The observed splitting is 0.59 eV (fwhm = 0.5 eV for each band), which from Figure 4 corresponds to a dihedral angle of $\theta = 68°$, or 110° if the graph of ΔIP for $90° < \theta < 180°$ mirrors that for $0° < \theta < 90°$. The sharpness of the two bands indicates that most of the species prefer conformations with one or both of these angles. Similarly dioxacyclooctane (**32**) from models can adopt many conformations allowing $0° < \theta < 170°$, but the observed splitting is 1.29 eV (fwhm (n_O^-) = 0.4 eV). Inspection of models shows that severe H–H cross-ring repulsions are experienced for $0° < \theta < 70°$, so that we conclude that the dihedral angle (Figure 4) is $\theta = 140°$ if the graph from 90 to 180° mirrors that from 0 to 90°.[36] In contrast, diisopropyl peroxide, which is conformationally mobile, shows two bands at 9.16 (fwhm = 0.65 eV) and 10.71 eV, the latter being significantly broadened probably owing to overlapping ionizations from a variety of conformations having different dihedral angles.

Acyclic dialkyl peroxides adopt an extended conformation **35** which minimizes repulsive interactions between nonbonding electron pairs on vicinal oxygen atoms. Incorporation of peroxide into a cyclic molecule limits conformational freedom and, for smaller rings, enforces an energetically unfavorable folded conformation **36**, in which vicinal oxygen lone pair interactions



35 36

are maximized. This is expected to raise the ground-state energy of the nonbonding electrons, and hence lower the first

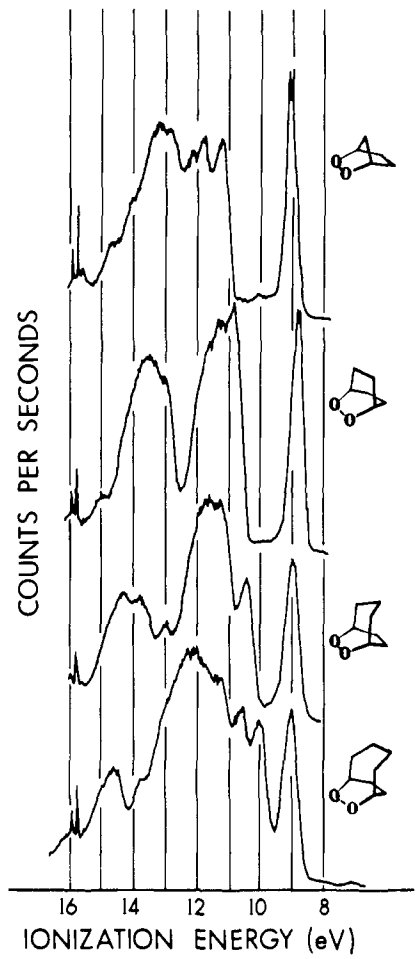
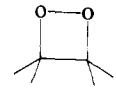


Figure 5. Photoelectron spectra of bicyclic peroxides **7**, **18**, **19**, and **20** with argon as internal calibrating gas.

ionization energy.[27,30] Since the prostaglandin endoperoxide nucleus **7** has a dihedral angle $\theta = 0°$,[17] an exceptionally low first ionization energy might be expected. Although a small decrease in n_O^- (see Table II) is observed on going from [4.2.2] peroxide **20** (9.05 eV) and the [3.2.2] peroxide **19** (8.97 eV) to the [2.2.2] peroxide **18** (8.82 eV), the prostaglandin endoperoxide nucleus **7** does not follow this trend. Rather, n_O^- for **7** (8.99 eV) is similar to that of **19** and **20**. Perhaps the angle strain in **7** raises n_O^- as has been suggested[27] for the 1,2-dioxetane **37** which also exhibits an unexpectedly high first



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ionization energy. Thus, the extraordinary proclivity of the prostaglandin endoperoxide nucleus **7** toward heterolytic decomposition[1f] *cannot* be ascribed to an abnormally low first ionization energy.

Conclusions

The first nonenzymatic syntheses of bona fide, fully characterized derivatives of 2,3-dioxabicyclo[2.2.1]heptane, the strained bicyclic peroxide nucleus of prostaglandin endoperoxides, were achieved by reduction or chlorination of 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]hept-5-ene. Diimide selectively reduces the C–C π bond of this unsaturated peroxide without reducing the sensitive O–O bond. A homologous series of bridgehead unsubstituted bicyclic peroxides (2,3-dioxabicyclo[2.2.1]heptane, 2,3-dioxabicyclo[2.2.2]octane, 6,7-

dioxabicyclo[3.2.2]nonane, and 7,8-dioxabicyclo[4.2.2]decane) was prepared similarly. Together with a homologous series of monocyclic peroxides, these bicyclic peroxides will be valuable for determining the effects of geometric constraints on the properties of dialkyl peroxides. ^{13}C NMR data confirm that 2,3-dioxabicyclo[2.2.1]heptane is highly strained. The ring strain of 2,3-dioxabicyclo[2.2.2]octane is midway between the [2.2.1] peroxide and the [3.2.2] and [4.2.2] peroxides which show no ^{13}C NMR evidence of ring strain.

The PE spectra of the symmetrical dialkyl peroxides having reasonably well-defined dihedral angles show that the splitting of the two highest occupied peroxy orbitals (n^- and $\sigma_{(C-O)}$) maximizes at 0° (or 180°) and minimizes at 90° for tertiary, secondary, and primary dialkyl peroxides. Though models suggest conformational mobility for dioxacycloheptane and dioxacyclooctane, PE data show that in the gas phase a single conformation predominates. An abnormally low first ionization energy due to repulsive antisymmetric interactions of the vicinal oxygen lone pair electrons is *not* observed for the prostaglandin endoperoxide nucleus in spite of a 0° dihedral angle.

Experimental Section

General. All melting points are uncorrected and were recorded on a Thomas-Hoover capillary melting point apparatus. Proton magnetic resonance spectra were recorded with a Varian A-60A or HA 100 FT spectrometer with tetramethylsilane as an internal standard and chloroform-d_1 as solvent unless otherwise specified. Carbon magnetic resonance spectra were recorded with a Varian XL-100 pulsed Fourier transform nuclear magnetic resonance spectrometer at 25.16 MHz. The solvent for ^{13}C NMR was $CDCl_3$ with tetramethylsilane as an internal reference, the deuterium of the solvent providing the internal lock signal. Mass spectra were recorded with a Du Pont Model 21-094 GC–MS instrument with an interfaced computer. Photoelectron spectra were run on a MacPherson Model 36 ESCA machine using argon as an internal calibrant. Each value reported is the average of at least two runs and has a precision of ±0.03 eV. Preparative thin layer chromatography was performed using precoated 2-mm silica gel plates (20 × 20 cm, Merck). Microanalyses were preformed by Chemalytics, Inc., Tempe, Ariz., and Spang Microanalytical Laboratory, Eagle Harbor, Mich.

Materials. Benzene solvent used for photooxygenation reactions was freshly distilled from potassium benzophenone ketyl. All other solvents were used without further purification. 1,4-Diphenyl-1,3-cyclopentadiene,[12] 2,3-dioxabicyclo[2.2.2]oct-7-ene,[18] 6,7-dioxabicyclo[3.2.2]non-8-ene,[19] 7,8-dioxabicyclo[4.2.2]dec-9-ene,[20] and potassium azodicarboxylate[37] were prepared by reported procedures.

1,4-Diphenyl-2,3-dioxabicyclo[2.2.1]hept-5-ene (9).[13] 1,4-Diphenyl-1,3-cyclopentadiene[12] (1.00 g, 4.58 mmol) was dissolved in dry benzene (250 mL) in a Pyrex photolysis vessel with a water-cooled cold finger. Oxygen was continuously bubbled through the solution using a fritted gas dispersion tube. The vessel was irradiated in a Rayonet photochemical reactor (Southern New England Ultraviolet) using 350-nm lamps, until the fluorescence of the solution disappeared (about 2 h). The benzene was then removed by rotary evaporation at room temperature, leaving a solid, yellow residue. The solid was then washed with cold 95% ethanol (3 × 5 mL) until the crystals appeared completely white. The yield of 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]-hept-5-ene (**9**) was 0.595 g (52%): mp 111–112 °C (lit.[13] 112 °C); ^1H NMR (60 MHz) δ 2.6 (2 H, dd, J = 2.3, 8.5 Hz), 6.78 (2 H, s), 7.12–7.73 (10 H, m); ^{13}C NMR δ 61.12 (C-7), 95.15 (C-1,4), 126.9 (C-para), 128.8 (C-meta), 129.13 (C-ortho), 133.36 (aromatic), 137.9 (C-5,6).

Chlorination of 9. Unsaturated peroxide **9** (0.7 g, 3.2 mmol) was dissolved in CCl_4 (15 mL) and Cl_2 gas was bubbled into the solution for 10 min. The resulting solution was rotary evaporated and the residual yellow oil was chromatographed on 45 g of silica gel with CCl_4 as eluting solvent. Two products were isolated which gave positive tests for peroxides with ferrous thiocyanate reagent,[38] with **11** R_f 0.16 (0.25-mm silica gel plate, CCl_4 as eluting solvent) and **12** R_f 0.08 (0.25-mm silica gel plate, CCl_4). Dichloro peroxide **11**, mp 140.5–141.0 °C, was obtained in 26% yield (0.26 g) after recrystallization from ethanol: ^1H NMR (benzene-d_6) δ 2.58 (dd, 1 H, J = 11, 2.8 Hz), 2.96 (d, 1 H, J = 11 Hz), 4.55 (d, 1 H, J = 2.8 Hz), 4.66 (t, 1 H, J = 2.8 Hz), 7.05–7.15 (m, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 321 (57), 307 (20), 306 (20), 305 (76), 304 (29), 303 (100), 289 (20), 288 (11), 287 (33), 285 (17), 269 (22), 268 (13), 267 (18), 225 (15), 224 (24), 218 (13), 217 (17), 215 (13), 202 (11), 192 (15), 106 (22), 105 (88), 91 (18), 77 (46), 51 (16).

Anal. Calcd for $C_{17}H_{14}Cl_2O_2$: C, 63.57; H, 4.39. Found: C, 63.96; H, 4.42.

The trichloro peroxide (**12**), mp 141.7–142.3 °C, was obtained in 11% yield (0.125 g) after recrystallization from ethanol: ^1H NMR (benzene-d_6) δ 4.56 (d, 1 H, J = 2.4 Hz), 4.88 (dd, 1 H, J = 2.4, 4.3 Hz), 5.42 (d, 1 H, J = 4.3 Hz), 7.13 (10 H).

Anal. Calcd for $C_{17}H_{13}Cl_3O_2$: C, 57.41; H, 3.69. Found: C, 57.21; H, 3.68.

1,4-Diphenyl-2,3-dioxabicyclo[2.2.1]heptane (13). Peroxide **9** (0.10 g, 0.39 mmol) was placed in a 25-mL round-bottom flask equipped with a magnetic stirrer. To the flask were added potassium azodicarboxylate[37] (0.784 g, 3.9 mmol) and methanol (5 mL), forming a yellow slurry. Acetic acid (0.472 g, 0.45 mL, 8 mmol) dissolved in methanol (5 mL) was added dropwise to the stirred slurry over the course of 20 min, care being taken to keep the vigorous gas evolution under control. After complete addition of the acid, the slurry was stirred until it became white and gas evolution ceased. The mixture was poured into a separatory funnel and water (30 mL) was added slowly, causing vigorous evolution of CO_2. The aqueous solution was then extracted with ether (2 × 30 mL), and the ether layers were combined and washed with saturated sodium bicarbonate solution (40 mL) and water (40 mL). The ether layer was dried (Na_2SO_4) and the ether removed by rotary evaporation. The product, 1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane (**13**), was recrystallized from ethanol affording 0.075 g (76%) of product: mp 109.7–110 °C; ^1H NMR (100 Hz, benzene-d_6) δ 1.90 (d, 2 H, J = 8 Hz, H-exo), 2.17 (d, 1 H, J = 10 Hz, H-anti), 2.40 (dt, 2 H, J = 8, 2.5 Hz, H-endo), 2.64 (dt, 1 H, J = 10, 2.5 Hz, H-syn), 7.02–7.3 (m, 10 H, H-aromatic); ^{13}C NMR δ 35.21 (t, $J_{^{13}C-H}$ = 133 Hz, C-5,6), 52.60 (t, $J_{^{13}C-H}$ = 138 Hz, C-7), 91.25 (s, C-1,4), 126.8, 128.6, 127.7, 134.9 (all C-aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 252 (13), 224 (16), 220 (36), 219 (90), 115 (14), 105 (100), 103 (11), 91 (30), 77 (78), 65 (11), 51 (27), 28 (18), 18 (13).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.66; H, 6.42.

5,6-*exo*-Dideuterio-1,4-diphenyl-2,3-dioxabicyclo[2.2.1]heptane (14). Compound **14** was prepared analogously to **13** substituting MeOD, CH_3COOD, and D_2O for their protium counterparts: ^1H NMR (benzene-d_6) δ 2.17 (d, 1 H, J = 10 Hz, H-anti), 2.40 (d, 2 H, J = 2.5 Hz, H-endo), 2.64 (dt, 1 H, J = 10, 2.5 Hz, H-syn), 7.02–7.3 (m, 10 H, aromatic); ^{13}C NMR (nonaromatic, proton decoupled) δ 35.1 (t, $J_{^{13}C-D}$ = 20 Hz, C-5,6), 52.96 (C-7), 91.29 (C-1,4); mass spectrum (70 eV) *m/e* (rel intensity) 254 (9), 224 (23), 222 (39), 221 (100), 105 (99), 77 (71), 30 (2).

5,6-*exo*-Dideuterio-2,3-dioxabicyclo[2.2.1]heptane (26). All reaction vessels were flame dried and reactions were protected from atmospheric moisture with a blanket of dry nitrogen. Potassium azodicarboxylate was washed with MeOD and then filtered and dried under a stream of dry nitrogen. Methylene chloride was freshly distilled from P_2O_5. Cyclopentadiene was freshly distilled and dried by azeotropic removal of water. A solution of cyclopentadiene (2.2 g) and tetraphenylporphorine (8 mg) in methylene chloride (75 mL) was irradiated with a General Electric DWY 650-W lamp at −60 °C while oxygen was bubbled through the reaction mixture for 5 h.[9a] The resulting solution was transferred through a polyethylene tube (2 mm i.d.) into a magnetically stirred suspension of potassium azodicarboxylate (34 g) in methylene chloride (120 mL) maintained at −78 °C. Simultaneously, a solution of DOAc (20 g) in methylene chloride (60 mL) was added dropwise to the azodicarboxylate. After completion of the addition, which required about 10 min, the mixture was allowed to warm slowly. A vigorous evolution of gases, indicating generation of diimide, commenced when the temperature reached about −35 °C and was complete before the temperature rose above −15 °C. After the mixture reached room temperature, it was filtered with a sintered glass Buchner funnel. Solvent was removed by evaporation at 0 °C under aspirator vacuum and the oily residue was transferred under reduced pressure (0.1 mm) into a receiver maintained at −78 °C. The peroxide was fractionally sublimed to give a light yellow solid (1.6 g, 47%), mp 57–61 °C. The ^1H NMR spectrum of the deuterated peroxide **26** in benzene-d_6 is compared with the spectrum of the perhydro peroxide **7** in Figure 2.

2,3-Dioxabicyclo[2.2.2]octane (18). Compound **18** was prepared from 2,3-dioxabicyclo[2.2.2]oct-5-ene[18] using the procedure above.

The crude saturated peroxide product (2.7 g) was purified on 135 g of silica gel and eluted with CCl_4 (500 mL), 10% $CHCl_3$–90% CCl_4 (500 mL), 20% $CHCl_3$–80% CCl_4 (500 mL), and finally 40% $CHCl_3$–60% CCl_4 (~2 L) until the eluted solution showed no trace of peroxide with ferrous thiocyanate reagent. The product, 2,3-dioxabicyclo[2.2.2]octane (**18**), was eluted primarily with the 40:60 $CHCl_3$–CCl_4 solution to give saturated peroxide, mp 118 °C, in 40% yield after recrystallization from pentane followed by sublimation (0.4 mm): ^{1}H NMR (60 MHz) δ 1.45–2.40 (m, 8 H), 3.86–4.08 (m, 2 H); ^{13}C NMR δ 24.26 (t, $J_{^{13}C\text{-}H}$ = 132 Hz, C-5,6,7,8), 71.71 (d, $J_{^{13}C\text{-}H}$ = 150 Hz, C-1,4).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.25; H, 8.85.

6,7-Dioxabicyclo[3.2.2]nonane (19). Potassium azodicarboxylate[37] (15.5 g, 0.08 mol) was placed in a 250-mL Morton flask equipped with a high-speed mechanical stirrer. The flask was placed in a water bath which was kept at 15–20 °C throughout the reaction. Methanol (25 mL) was added and the slurry stirred vigorously. Acetic acid (10.0 g, 0.16 mol) was dissolved in methanol (10 mL) and 1 mL of this solution was added slowly to the potassium azodicarboxylate. 6,7-Dioxabicyclo[3.2.2]non-8-ene[19] (0.5 g, 4 mmol) in methanol (10 mL) was then added immediately to the slurry. The remaining acetic acid–methanol solution was added over the course of 30 min. After complete addition of the acid solution, the mixture was stirred until it became white. Water (100 mL) was added slowly, and the solution was saturated with potassium chloride. The solution was then transferred to a separatory funnel and the reaction flask rinsed with methylene chloride (2 × 25 mL), the methylene chloride portions being added to the separatory funnel. Another 50-mL portion of methylene chloride was added to the separatory funnel and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL) and dried (Na_2SO_4). Rotary evaporation gave a waxy, solid residue which was separated by preparative thick layer chromatography, R_f 0.5–0.68 (2-mm silica gel, ethyl acetate eluting solvent, positive test for peroxide with ferrous thiocyanate).[38] The product was extracted from the silica gel with methylene chloride. Solvent was removed and the solid residue sublimed twice (0.4 mm) at room temperature. The sublimed product, 6,7-dioxabicyclo[3.2.2]nonane (**19**), 0.197 g (38% yield), mp 112–113 °C, had the following spectral characteristics: ^{1}H NMR (60 MHz) δ 1.4–2.38 (m, 10 H), 4.17–4.45 (m, 2 H); ^{13}C NMR δ 19.89 (t, $J_{^{13}C\text{-}H}$ = 128 Hz, C-3), 20.43 (t, $J_{^{13}C\text{-}H}$ = 128 Hz, C-8,9), 34.95 (t, $J_{^{13}C\text{-}H}$ = 123 Hz, C-2,4), 76.84 (d, $J_{^{13}C\text{-}H}$ = 144 Hz, C-1,5).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.53; H, 9.38.

7,8-Dioxabicyclo[4.2.2]decane (20). Compound **20** was prepared from 7,8-dioxabicyclo[4.2.2]dec-9-ene[20] as above, and was purified by preparative TLC: R_f 0.60–0.73 (2-mm silica gel plate, ethyl acetate); mp 96–97 °C after sublimation at room temperature; yield 19%; ^{1}H NMR (60 MHz) δ 1.41–2.35 (br m, 12 H), 4.26–4.53 (br m, 2 H); ^{13}C NMR δ 20.83 (t, $J_{^{13}C\text{-}H}$ = 128 Hz, C-3,4), 24.62 (t, $J_{^{13}C\text{-}H}$ = 123 Hz, C-9,10), 34.87 (t, $J_{^{13}C\text{-}H}$ = 123 Hz, C-2,5), 76.18 (d, $J_{^{13}C\text{-}H}$ = 141 Hz, C-1,6).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.12; H, 9.72.

Acknowledgment. This research was assisted financially by Grants GM-21249 and RR-07113 from the National Institutes of Health, and by a grant from G. D. Searle and Co. to R.G.S. and by the University of Alberta and the National Research Council of Canada to R.S.B.

References and Notes

(1) For previous papers in this series see (a) R. G. Salomon and R. D. Gleim, *J. Org. Chem.*, **41**, 1529 (1976); (b) M. F. Salomon, R. G. Salomon, and R. D. Gleim, *ibid.*, **41**, 3983 (1976); (c) D. J. Coughlin and R. G. Salomon, *J. Am. Chem. Soc.*, **99**, 655 (1977); (d) M. F. Salomon and R. G. Salomon, *ibid.*, **99**, 3500 (1977); (e) R. G. Salomon and M. F. Salomon, *ibid.*, **99**, 3501 (1977); (f) R. G. Salomon, M. F. Salomon, and D. J. Coughlin, *ibid.*, **100**, 660 (1978).
(2) Case Western Reserve University.
(3) University of Alberta.
(4) (a) P. F. Beal, G. S. Fonken, and J. E. Pike, Belgian Patent 659 984 (1964); (b) B. Samuelsson, *J. Am. Chem. Soc.*, **87**, 3011 (1965); (c) M. Hamberg and B. Samuelsson, *ibid.*, **88**, 2349 (1966); (d) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **242**, 5329, 5336, 5344 (1967); (e) B. Samuelsson, *Prog. Biochem. Pharmacol.*, **3**, 59 (1967); (f) **5**, 109 (1969); (g) B. Samuelsson, *Fed. Proc., Fed Am. Soc. Exp. Biol.*, **31**, 1442 (1972); (h) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 899 (1973); (i) D. H. Nugteren and E. Hazelhof, *Biochim. Biophys. Acta*, **326**, 448 (1973); (j) C. Pace-Asciak and M. Nashat, *ibid.*, **388**, 243 (1975); (k) R. R. Gorman, F. F. Sun, O. V. Miller, and R. A. Johnson, *Prostaglandins*, **13**, 1043 (1977); (l) F. B. Ubatuba and S. Moncada, *ibid.*, **13**, 1055 (1977).
(5) (a) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975); (b) G. B. Kolata, *Science*, **190**, 770 (1975).
(6) *Chem. Eng. News*, **54** (52), 17 (1976).
(7) For example, 9α,11α-epidioxy-15(*S*)-hydroxy-13-*trans*-prostenoic acid has a half-life of 2.7 h at 20 °C in light petroleum–ether (1:1, v:v) and in aqueous medium the half-life is only 30 min at 20 °C. See ref 4i.
(8) Evidence which suggests that these preparations contain impurities which catalyze their decomposition was obtained recently: W. A. Pryor and J. P. Stanley, *J. Org. Chem.*, **40**, 3615 (1975).
(9) (a) The analytically pure peroxide **7** which we obtained by this reaction, after careful fractional sublimation, has mp 63–65 °C rather than mp 41–43 °C reported by W. Adam and H. J. Eggelte, *J. Org. Chem.*, **42**, 3987 (1977); for other approaches to the synthesis of 2,3-dioxabicyclo[2.2.1]heptanes see ref 1d and (b) N. A. Porter and D. W. Gilmore, *J. Am. Chem. Soc.*, **99**, 3503 (1977); (c) R. A. Johnson, E. G. Nidy, L. Baczynskyj, and R. R. Gorman, *ibid.*, **99**, 7738 (1977); (d) R. M. Wilson and F. Geiser, *ibid.*, **100**, 2225 (1978); also see ref 1e.
(10) (a) G. O. Schenck and D. E. Dunlap, *Angew. Chem.*, **68**, 248 (1956); (b) K. H. Schutte-Elte, B. Willhalm, and G. Ohloff, *ibid.*, **81**, 1045 (1969); (c) W. R. Adams and D. J. Trecker, *Tetrahedron*, **27**, 2631 (1971); (d) G. O. Schenck, W. Muller, and H. Pfennig, *Naturwissenschaften*, **41**, 374 (1954).
(11) W. Müller, Thesis, Gottingen, 1956.
(12) N. L. Drake and J. R. Adams, *J. Am. Chem. Soc.*, **61**, 1326 (1939).
(13) K. Gollnick and G. O. Schenck, "1,4-Cycloaddition Reactions", J. Hamer, Ed., Academic Press, New York, 1967, p 255.
(14) L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Elmsford, N.Y., 1959; S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969).
(15) H. O. House, "*Modern Synthetic Reactions*", W. A. Benjamin, Menlo Park, Calif., 1972, pp 248–256.
(16) E. E. Van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3725 (1961).
(17) D. A. Langs, G. T. DeTitta, D. J. Coughlin, and R. G. Salomon, in preparation.
(18) (a) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969); (b) C. Kaneko, A. Sugimoto, and S. Tanaka, *Synthesis*, 876 (1974).
(19) A. C. Cope, T. A. Liss, and G. W. Wood, *J. Am. Chem. Soc.*, **79**, 6287 (1957).
(20) Y. Kayama, M. Oda, and Y. Kitahara, *Chem. Lett.*, 345 (1974).
(21) Apparently unaware of our previous report on selective reduction of unsaturated peroxides with diimide (ref 1c), others reported a variety of peroxides including **18** which they prepared by this method: W. Adam and H. J. Eggelte, *Angew. Chem., Int. Ed. Engl.*, **16**, 713 (1977).
(22) (a) W. Adam, A. J. Bloodworth, H. J. Eggelte, and M. E. Loveitt, *Angew. Chem., Int. Ed. Engl.*, **17**, 209 (1978); (b) W. Adam and I. Erden, *ibid.*, **17**, 210, 211 (1978); (c) W. Adam and I Erden, *J. Org Chem.*, **43**, 2737 (1978).
(23) H. Paget, *J. Chem. Soc.*, 829 (1938); C. G. Moore, *ibid.*, 234 (1951).
(24) E. E. Van Tamelen and R. J. Timmons, *J. Am. Chem. Soc.*, **84**, 1067 (1962).
(25) (a) W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 7233 (1977); (b) S. Inagaki, H. Fujimoto, and K. Fukui, *ibid.*, **98**, 4054 (1976).
(26) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley, New York, 1965, pp 373–374.
(27) R. S. Brown, *Can. J. Chem.*, **53**, 3439 (1975).
(28) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, pp 332–362.
(29) K. Tori, R. Muneyuki, and H. Tanida, *Can. J. Chem.*, **41**, 3142 (1963); N. H. Werstiuk, R. Taillefer, R. A. Bell, and B. Sayer, *ibid.*, **51**, 3010 (1973).
(30) (a) C. Batich and W. Adam, *Tetrahedron Lett.*, 1467 (1974); (b) K. Osafune and K. Kimura, *Chem. Phys. Lett.*, **25**, 47 (1974).
(31) (a) W. H. Fink and L. C. Allen, *J. Chem. Phys.*, **46**, 2261 (1967); (b) U. Kaldor and I. Shavitt, *ibid.*, **44**, 1823 (1966).
(32) T. Koopmans, *Physica (Utrecht)*, **1**, 104 (1934).
(33) Dihedral angles were measured from Dreiding models and are only approximate since torsional effects and vicinal O–O interactions are ignored.
(34) A Drieding angle of 30° for the dioxacyclopentanes is likely to be an underestimate since vicinal orbital interactions may distort the five-membered ring somewhat more. For 1,2,4-trioxacyclopentane microwave spectroscopy[35] reveals a C–O–O–C dihedral angle of 50°.
(35) C. W. Gilles and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **94**, 6337 (1972).
(36) While empirical data which would allow precise interpolation of the expected splitting as a function of angle is not available for angles larger than 90°, the substantial splitting observed for **32** provides good evidence that the peroxide angle is greatly in excess of 100°.
(37) J. Theile, *Justus Liebigs Ann. Chem.*, **271**, 127 (1892).
(38) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1681 (1975).