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(16) Temperatures of kinetic measurements and melting points are corrected. The NMR spectra were measured in carbon tetrachloride with a Varian EM-390 spectrometer. The NMR data are reported on the δ scale in parts per million as (δ, coupling, area).
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Cyclic Peroxides by Intramolecular Peroxymercuration of Unsaturated Hydroperoxides

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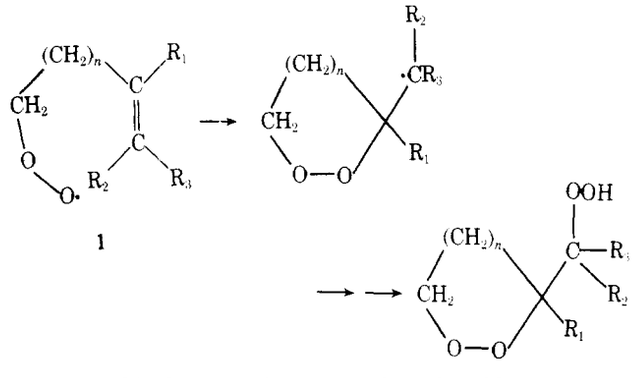
Unsaturated hydroperoxides undergo cyclization when treated with mercuric nitrate or trifluoroacetate. The β-mercurated cyclic peroxide products are isolated by high-pressure liquid chromatography as the alkyl mercuric bromides. Yields of analytically pure cyclic peroxides range from 60 to 90%. Treatment of the β-mercurated peroxides with molecular bromine gives the β-bromo cyclic peroxides in 80–90%, while reaction of the β-mercurated peroxides with borohydride leads to the parent cyclic peroxides in yields that range from 10 to 100%.

Cyclization reactions of unsaturated hydroperoxides have provided a synthetic approach for the preparation of a variety of cyclic peroxides. Thus, unsaturated hydroperoxides undergo cyclization,[1,2] presumably via a peroxy radical such as **1**, when subjected to autoxidation conditions. Cyclization of



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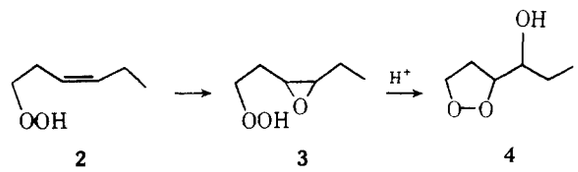
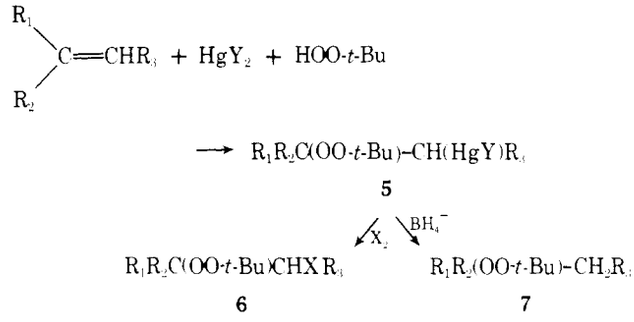
unsaturated hydroperoxides can also be induced by generating an electron deficient site from the olefin functionality. For example, the hydroperoxide **2** is converted[2] to a β-hydroxy cyclic peroxide **4** via the oxirane–hydroperoxide **3**. The dis-



2 **3** **4**

covery that compounds like **4** have interesting pharmacological properties[3] prompted us to explore other methods of generating cyclic peroxides from unsaturated hydroperoxides. In particular, we sought to extend the established method of intermolecular olefin peroxymercuration to our unsaturated hydroperoxides.

Peroxymercuration of olefins has been effectively employed as a method for the preparation of β-substituted peroxides.[4-6] A variety of substituted olefins react with mercuric salts such as the acetate, trifluoroacetate, or nitrate in the presence of hydroperoxides to yield the β-mercurated peroxide **5**. These

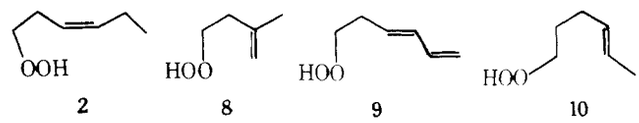


5 **6** **7**

compounds can be efficiently converted into the corresponding β-halogeno or β-hydrido peroxides by halogenodemercuration[4] or hydridodemercuration.[5] We report here that intramolecular peroxymercuration is affected by reacting hydroperoxides such as **2** with mercuric(II) compounds. The versatile β-mercurated cyclic peroxides so generated are a source of several new cyclic peroxide compounds.

Results and Discussion

The Synthesis of β-Mercuri Cyclic Peroxides. The unsaturated hydroperoxides **2**, **8**, **9**, and **10** react with 1 equiv of



2 **8** **9** **10**

$Hg(NO_3)_2 \cdot H_2O$ in dichloromethane at 22 °C. The products formed are isolated as the mercuric bromides, and the cyclic peroxides so generated are isolated and purified by high-

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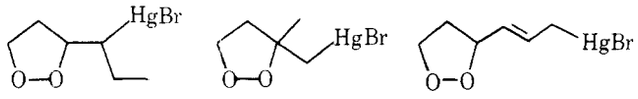
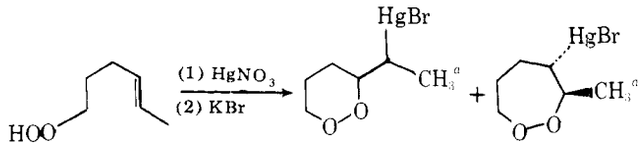
pressure liquid chromatography (LC). Yields of LC purified β-mercurated cyclic peroxides exceed 55% in all cases investigated. The structure assignment of the mercurated cyclic peroxides is supported by ^1H and ^{13}C NMR spectroscopy and elemental analysis.

2, **8**, and **9** are converted solely into the five-membered ring cyclic peroxides **11**, **12**, and **13** with none of the possible six-



11 **12** **13**

membered ring isomer being detected by LC or NMR. **10** yields a mixture of two cyclic peroxides, **14** and **15**, upon re-

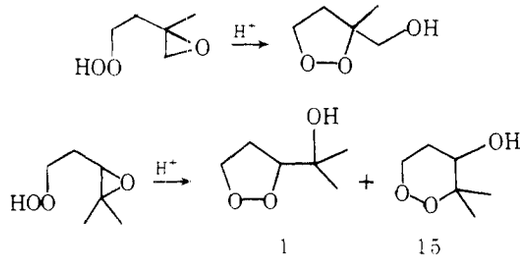


10 **14** **15**

action with $Hg(NO_3)_2 \cdot H_2O$. These isomers can be readily separated by LC, and the ratio of **14**/**15** as judged by NMR of the crude reaction mixture and by LC isolation is 3:1, the six-membered ring product being favored. The ^1H (and ^{13}C) NMR spectra of **14** and **15** are strikingly similar, each showing a 3 H multiplet from δ 3.8 to 4.6 (α to peroxide), a 1 H multiplet at δ 2.6 (α to HgBr), and a doublet at δ ~1.4 (α-CH_3^a). The structures of **14** and **15** can be unequivocally assigned, however, by double irradiation experiments. Thus, for **14** the CH_3^a methyl doublet (δ 1.42) is shown to be coupled with the hydrogen α to HgBr and for **15** the CH_3^a doublet (δ 1.30) is coupled to a proton α to the peroxide linkage.

Although there are two possible diastereomers of **14** and **15**, we find only one of the diastereomers for both **14** and **15** as products of the cyclization. Further evidence is presented in the discussion of bromodemercuration that also suggests that the initial cyclization led to only one diastereomer of **14** and **15** (presumably by trans addition).

Comment should be made about the ring size preference for cyclization. The preferred formation of five-membered ring peroxides from **2**, **8**, and **9** is as expected from the rules of cyclization as described by Baldwin.[7,8] Baldwin suggests that the rules for opening three-membered rings to form cyclic structures seem to lie between those for tetrahedral and trigonal systems, generally exo modes being preferred. Thus, nucleophilic attack of the hydroperoxide on the mercurinium–olefin complex should lead to exo cyclization as is observed for **2**, **8**, and **9**. The rules for the Hg(II) cyclization of **10** are less definite, however, and our observation that both the 6-exo and 7-endo cyclization products are formed indicates that these cyclization modes are competitive. In this regard, we note that electronic effects may well modify any predictions for nucleophilic cyclization at electron deficient three-membered rings. As previously reported,[2] the 5-exo preference of acid-catalyzed oxirane–hydroperoxide cyclization may be altered by substituents on the oxirane. 6-Endo

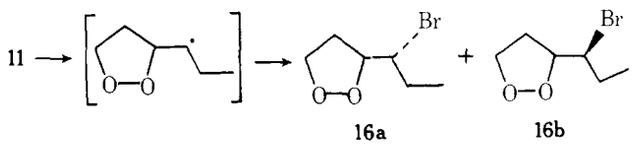


1 15

product formation, in apparent violation of the rules, can dominate for suitably substituted oxiranes.

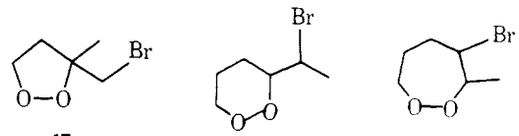
Bromo- and Hydridodemercuration. The four β-mercurated cyclic peroxides **11**, **12**, **14**, and **15** were subjected to reaction conditions for conversion to the β-bromo[4] cyclic peroxides. Thus, treatment of the β-mercurated cyclic peroxides with molecular bromine in methylene chloride leads to β-bromo cyclic peroxides (LC pure) in greater than 74% isolated yield. The β-bromo products derived from **11**, **14**, and **15** are mixtures of two diastereomers which can be separated in each case by LC. Whereas the peroxymercuration reaction leads, as expected, to only one diasteromer, the demercuration, which proceeds by a radical mechanism, leads to a 1:1 mixture of diastereomers.

The example of bromodemercuration of **11** is illustrative. **11** is assigned the threo structure since the peroxymercuration presumably occurs by trans addition.[9] Bromodemercuration of **11** in methylene chloride leads to **16**, a 1:1 mixture of the



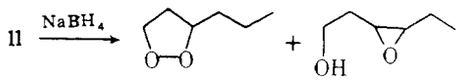
16a **16b**

threo and erythro β-bromo peroxides. These diastereomers can be separated by LC. When the bromodemercuration is carried out in pyridine, one stereoisomer is formed exclusively under our conditions. This is in accord with the earlier report[10] that bromodemercuration in pyridine proceeds by retention of configuration via a nonradical mechanism. The β-bromo peroxides **17**, **18**, and **19** could be prepared by bromodemercuration of **12**, **14**, and **15**, respectively.



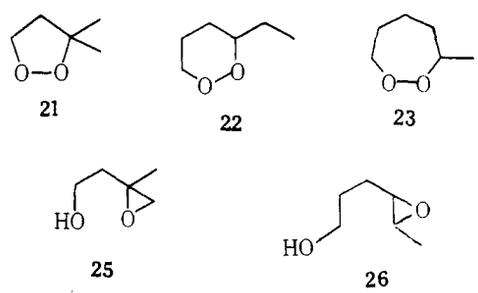
17 **18** **19**

Reaction of compounds **11**, **12**, **14**, and **15** with basic sodium borohydride leads to mixtures of cyclic peroxides and epoxy alcohols. When **11** is subjected to hydridodemercuration, for example, the peroxide **20** and the epoxy alcohol **24** are formed



20 **24**

in a 3:1 ratio. Similarly, the alkylmercuri bromides **12**, **14**, and **15** lead to the cyclic peroxides **21**–**23** and the epoxy alcohols **25** and **26**.



21 **22** **23**

25 **26**

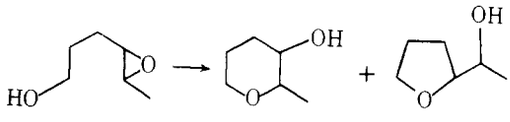
The ratio of peroxide to epoxy alcohol formed is dramatically dependent on the structure of the starting β-mercurated peroxide, as is shown in Table I. The conditions of the hydridodemercuration are identical for every experiment, and the peroxide/epoxy alcohol ratio varies from 20:80 for **14** to 100:0 for **15**. Under the conditions of the reaction, **26**, the epoxy al-

Table I. Products Formed from Sodium Borohydride Reduction of β-Mercurated Cyclic Peroxides

reactant	peroxide (yield, %)	epoxy alcohol (yield, %)
11	20 (75)	24 (25)
12	21 (90)	25 (10)
14	22 (<10)	26 (90[a])
15	23 (100)	26 (0[a])

[a] Yield of epoxy alcohol plus tetrahydrofuran and tetrahydropyran derived from the epoxide under the hydridodemercuration conditions.

cohol derived from **14** and **15**, partially rearranges to tetrahydropyran and tetrahydrofuran products **27** and **28**. In fact, if one attempts to prepare **26** by *m*-chloroperbenzoic epoxidation of the olefin, only **27** and **28** are isolated. The



26 **27** **28**

epoxide **26** can be isolated, however, by neutral epoxidation of the olefin with H_2O_2/benzonitrile.[11,12]

The mechanism for sodium borohydride demercuration has been thoroughly investigated,[5,13,14] and alkyl radicals are established intermediates in the reaction. The intermediate alkyl radical can abstract hydrogen from a suitable donor (R–Hg–H has been suggested as an intermediate[14]) to yield the peroxide. In competition with hydrogen abstraction is intramolecular radical attack (S_Hi) on the peroxide linkage by the alkyl radical, a reaction that ultimately leads to epoxy alcohol products as shown for the reaction of **11** in Figure 1.

Two observations support the mechanism presented in Figure 1. The percentage yield of peroxide formed is dependent on the rate of addition of borohydride to the β-mercurated peroxide. Thus, rapid addition of the borohydride solution (see Experimental Section) leads reproducibly to the product mixtures shown in Table I. If borohydride is added slowly (10–15-min addition), the epoxy alcohol becomes a dominate product in all of the reactions. Thus, when borohydride is added slowly, the in situ concentration of R–Hg–H is low and the competing H atom transfer leading to peroxide product is slow compared to the S_Hi pathway leading to epoxy alcohol. Rapid addition of borohydride leads to a high in situ R–Hg–H concentration and favors the H atom transfer pathway that leads to peroxide products.

A second observation eliminates consideration of a mechanism involving nucleophilic attack of borohydride on the peroxide bond followed by alkoxide displacement of bromide. This mechanism requires that cis epoxide should be formed exclusively from **11**. In fact, both cis and trans epoxy alcohols **24** are formed with the trans product being the major product (an observation that is in accord with the radical mechanism). Finally, we should note that Bloodworth[5] has published a detailed description of the reaction of acyclic β-mercurated cyclic peroxides with borohydride, and he has presented strong evidence in support of the free-radical mechanism for this reaction.

The variation in peroxide product yield is striking. Borohydride reduction of **14** leads to under 10% of the peroxide under the best reaction conditions. **15**, on the other hand, leads only to cyclic peroxide under borohydride reaction. We suggest that the peroxide–epoxy alcohol yields shown in Table I may well reflect the ease of S_Hi radical attack on the cyclic peroxide bond. We shall defer a more detailed discussion of the implications of these observations vis-à-vis the stereochemistry of the S_Hi and S_H2 reactions until a more detailed kinetic investigation of this system is concluded.

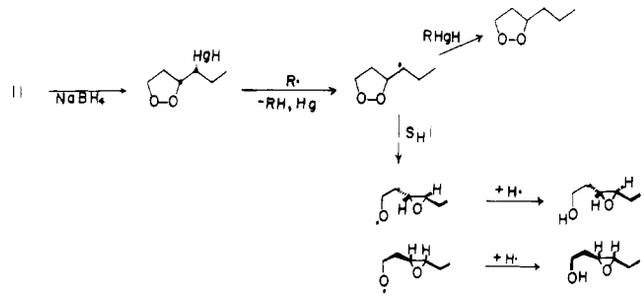


Figure 1. Reaction of **11**.

Experimental Section

Proton NMR spectra were recorded using a Jeol JNM-MH-100 spectrometer. Carbon NMR spectra were recorded using a Jeol JNM-FX-60 Fourier transform spectrometer. A Waters Associates Model ALC-GPC-301 was used for high-performance liquid chromatographic separations. A Varian Aerograph Model 700 gas chromatograph was used for preparative gas chromatography.

Solvents. Burdick and Jackson Laboratories, Inc. (Muskegon, Mich.), "Distilled in Glass" chromatographic grade hexane, chloroform, and isopropyl alcohol were used for LC without further purification. Fisher Certified methylene chloride and pentane were also used without further purification for reactions and chromatography.

Syntheses. The unsaturated hydroperoxides **2**, **8**, and **10** were prepared as previously described by the method of Porter.[2] **2** and **8** were synthesized from commercially available alcohols,[15] while **10** was made from the alcohol prepared by the procedure of Crombie and Harper.[16] *trans*-Hexa-3,5-diene 1-hydroperoxide (**9**) was synthesized by the method of Mosher[17] from the precursor alcohol. *trans*-Hexa-3,5-dien-1-ol was prepared by $LiAlH_4$ reduction of methyl 3,5-hexadienoate. The procedure for conversion of the mesylate of *trans*-hexa-3,5-dien-1-ol to **9** is given below.

3,5-Hexadiene 1-Hydroperoxide (9). A 4.4-g (0.025-mol) amount of crude mesylate was combined with 3 mL of H_2O and 30 mL of methanol at ambient temperature with magnetic stirring. The stirred solution was cooled to 0–5 °C, followed by the slow dropwise addition of 163 g (0.10 mol) of 30% H_2O_2. Aqueous KOH (50%; 1.5 g, 0.013 mol) was slowly added. The system was flushed with N_2, brought to ambient temperature, and stirred for 16 h. After 16 h, the reaction vessel was immersed in an ice bath and taken to 0–5 °C. Aqueous KOH (50%; 9.89 g, 0.04 mol) was slowly added, after which time the solution was transferred to a separatory funnel and extracted with benzene. The aqueous phase was cooled to 0–5 °C, neutralized with concentrated HCl, and then extracted with benzene. The combined organic extractions were dried over Na_2SO_4, filtered, and stripped of solvent. The hydroperoxide product was purified by chromatography on a 1 × 35 cm silica gel column, 60–200 mesh, grade 950, at −10 °C. A hexane/ethyl ether eluent gradient was employed. Spectra of the purified product indicated the presence of a single hydroperoxide isomer (0.57 g, a 20% yield of chromatographed product from starting mesylate): ^1H NMR ($CDCl_3$) δ 2.2–2.4 (q, 2 H), 3.9–4.1 (t, 2 H), 4.9–5.1 (m, 2 H), 5.4–5.7 (m, 1 H), 5.9–6.4 (m, 2 H); J_{H_3,H_4} = 16 Hz (trans). The corresponding alcohol, 3,5-hexadienol, was submitted for C, H analysis. Anal. Calcd for $C_6H_{10}O_2$: C, 73.49; H, 10.29. Found: C, 73.34; H, 10.59.

Reaction of Unsaturated Hydroperoxides with Mercuric Nitrate. The synthesis of 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**) from *cis*-hex-3-ene 1-hydroperoxide (**2**) is illustrative of the cyclization procedure and is described in detail below.

***threo*-3-(1-Bromomercuripropyl)-1,2-dioxolane (11).** Hydroperoxide **2** was purified by LC (8 ft × ⅜ in, Porasil A, 5% isopropyl alcohol in hexane, 6.0 mL min^{-1}) immediately prior to use.[2] The purified hydroperoxide (0.238 g, 2.05 mmol) was dissolved in methylene chloride (35 mL) and added dropwise under N_2 over a 15-min period to a stirred suspension of mercuric nitrate (0.738 g, 2.15 mmol) in methylene chloride (75 mL) at 22 °C. The suspension was stirred for 15 additional minutes after completion of the addition. H_2O (8 mL) was then added, followed by the addition of 0.256 g (2.25 mmol) of KBr. A white precipitate immediately appeared upon addition of the salt. This precipitate ultimately dissolved into the organic phase with continued stirring. The mixture was transferred to a separatory

Table II. Spectral Data for β-Mercuribromo Peroxides

compd	yield, % (LC pure)	^{1}H NMR, δ	^{13}C NMR, ppm
11[a]	65	1.0–1.3 (t, 3 H), 1.8–2.1 (p, 2 H), 2.2–3.1 (m, 3 H), 3.9–4.4 (m, 2 H), 4.6–4.9 (m, 1 H)	16.53, 27.00, 42.15, 65.66, 69.80, 83.49
12[a]	68	1.45 (s, 3 H), 2.2–2.5 (m, 4 H), 4.0–4.3 (m, 2 H)	27.61, 46.54, 48.49, 70.74, 85.52
14[a]	49	1.42 (d, 3 H), 1.5–2.1 (m, 4 H), 2.6–2.9 (q, H), 4.05–4.3 (m, 2 H), 4.4–4.7 (m, 1 H)	15.88, 23.92, 30.90, 52.75, 72.81, 85.03
15[a]	16	1.3 (d, 3 H), 1.9–2.4 (m, 4 H), 2.6–2.9 (m, 1 H), 3.9–4.8 (m, 4 H)	20.67, 29.20, 32.12, 64.81, 74.35, 83.04
13[a]	58	2.2–2.9 (m, 4 H), 4.05–4.2 (t, 2 H), 4.4–4.7 (q, 1 H), 5.2–6.1 (m, 2 H); vinyl–vinyl J = 16 Hz	36.79, 41.34, 70.17, 80.73, 126.70, 133.20

[a] Satisfactory combustion analytical data for C and H (±0.3%) were provided for these compounds (Ed.).

Table III. Spectral Data for β-Bromo Cyclic Peroxides

compd	yield, %	LC order of elution	^{1}H NMR, δ	^{13}C NMR, ppm
16b, (erythro)	40	first	1.1 (t, 3 H), 1.4–2.2 (m, 2 H), 2.5–2.8 (m, 2 H), 3.8–4.2 (m, 3 H), 4.4–4.6 (m, 1 H)	12.34, 27.13, 38.17, 57.83, 70.25, 81.79
16a (threo)[a]	40	last	1.05 (t, 3 H), 1.5–2.3 (m, 2 H), 2.5–2.9 (m, 2 H), 3.7–4.5 (m, 4 H)	11.53, 28.67, 40.64, 59.21, 70.01, 82.11
17[a]	67		1.5 (s, 3 H), 2.3–2.9 (m, 3 H), 3.5 (s, 2 H), 4.05–4.15 (m, 2 H)	22.09, 38.50, 44.35, 70.74, 83.90
18a (erythro)	37	first	1.65 (d, 3 H), 1.8–1.9 (m, 4 H), 3.8–4.1 (m, 4 H)	22.21, 22.94, 25.46, 47.96, 72.65, 84.59
18b (threo)	37	last	1.65 (d, 3 H), 1.7–1.95 (m, 4 H), 3.9–4.2 (m, 4 H)	21.60, 23.63, 25.42, 47.59, 72.69, 84.39
19a (trans)	38	first	1.3 (d, 3 H), 1.9 (m, 2 H), 2.2–2.3 (m, 2 H), 3.6–4.4 (m, 4 H)	19.13, 29.16, 35.86, 58.48, 75.17, 87.17
19b (cis)	38	last	1.2 (d, 3 H), 1.9 (m, 2 H), 2.2–2.3 (m, 2 H), 3.8–4.5 (m, 4 H)	17.91, 24.93, 32.04, 60.34, 74.15, 83.25

[a] See Table II, footnote *a*.

funnel. The organic phase was collected, washed once with water (10 mL), dried over anhydrous sodium sulfate, filtered, and stripped in vacuo to a clear and colorless oil.

The product was then purified by preparative LC (8 ft × 3/8 in, Porasil A, 9:9:2 hexane/chloroform/methylene chloride, 5.0 mL min^{-1}). The endoperoxide fraction was stripped to a clear and colorless liquid (65%).

The spectral and analytical data of the β-mercurated cyclic peroxides are presented in Table II.

Reaction of 3,5-Hexadiene 1-Hydroperoxide with Mercuric Nitrate. The procedure for cyclization of this diene was changed so that mercuric salt would never be in excess to the diene. **9** (114 mg, 1.00 mmol) was suspended in 30 mL of CH_2Cl_2 with magnetic stirring under positive N_2 pressure at ambient temperature. Solid $Hg(NO_3)\cdot H_2O$ (359 mg, 1.00 mequiv) was added with stirring as a fine powder under CH_2Cl_2. After some 30 min of stirring, 10 mL of H_2O was added followed at once by 119.0 mg (1.00 mmol) of KBr. After vigorous stirring, the mixture was filtered into a separatory funnel and the phases were separated. The water layer was washed with CH_2Cl_2 (5 mL × 2). All CH_2Cl_2 phases were combined over Na_2SO_4, dried, filtered, and stripped of solvent. The product, a white solid, was purified by column chromatography; a 1 × 35 cm silica gel column, 60–200 mesh, grade 950, at 10 °C was employed. Elution was affected with a hexane/CH_2Cl_2 solvent gradient. Spectra of the purified product revealed the presence of a single endoperoxide mercuric bromide, 228 mg (58%), from starting hydroperoxide.

Bromodemercuration. The typical procedure for bromodemercuration is presented below for 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**).

3-(1-Bromopropyl)-1,2-dioxolane (16). The endoperoxide **11** (0.135 g, 0.34 mmol) was dissolved in 5 mL of methylene chloride and then added dropwise over a 15-min period to a magnetically stirred solution of Br_2 (0.164 g, 1.0 mmol) in methylene chloride (5 mL) under N_2 in subdued lighting. The solvent and excess bromine were removed in vacuo after 4 h of stirring. The resulting residue was extracted with petroleum ether (30 mL) and dried over anhydrous sodium sulfate. The solution was filtered and stripped to a pale-yellow oil. The product was purified by preparative LC (8 ft × 38 in, Porasil A, 3% isopropyl alcohol in hexane, 6.0 mL min^{-1}). Two stereoisomers (threo and erythro) of equal yield were collected. Anal. (for the mixture of threo and erythro isomers) Calcd for $C_6H_{11}O_2Br$: C, 36.96; H, 5.65. Found: C, 36.84; H, 5.71.

The assignment of the more polar diastereomer as the stereoisomer **16a** (threo configuration) was based on the results of bromodemercuration performed in pyridine as described later.

The spectral data for the β-bromo peroxides are presented in Table III.

Bromodemercuration in Pyridine. The preferential formation of the bromo endoperoxides with retained configuration was performed by the procedure described here in detail for endoperoxide **14**.

Reaction of *erythro*-3-(1-Bromomercuriethyl)-1,2-dioxane (14) with Bromine in Pyridine. 14 (0.163 g, 4.12 mmol) was dissolved in 12 mL of pyridine. Br_2 (0.098 g, 6.15 mmol) was added to pyridine (2.5 mL), which was then added dropwise over a 5-min period to the magnetically stirred endoperoxide solution. The mixture was stirred in subdued lighting for 20 h. Diethyl ether (150 mL) was then added to the reaction mixture. The resulting solution was washed twice with a total of 100 mL of 10% HCl. The acid washes were extracted once with 100 mL of diethyl ether. The ether fractions were combined and washed once more with 25 mL of 10% HCl followed by a 25-mL wash with a saturated sodium bicarbonate solution. The ether solution was then dried over anhydrous sodium sulfate. The dried ether was filtered and stripped to a clear, colorless viscous oil (0.07 g, 88% crude). The proton NMR spectrum of the product was identical without exception with that of the less polar diastereomer, the erythro isomer **18a**. The NMR spectrum did not indicate the presence of any of stereoisomeric threo compound **18b**.

Hydridodemercuration. The typical procedure for hydridodemercuration is presented below in detail for 3-(1-bromomercuripropyl)-1,2-dioxolane (**11**).

3-Propyl-1,2-dioxolane (20). The endoperoxide **11** (0.704 g, 1.78 mmol) was dissolved in 6 mL of methylene chloride and 15 mL of H_2O. Sodium borohydride (55 mg, 1.46 mmol) was dissolved in 5.5 mL of 2 N NaOH and transferred to a 10-mL syringe which was then cooled in an ice bath. The endoperoxide solution was cooled to −2 °C and stirred vigorously under a nitrogen atmosphere. The basic borohydride solution was added to the endoperoxide solution over a 15-s

Table IV. NMR Spectral Data for Cyclic Peroxides

compd	^{1}H, δ	^{13}C, ppm
20	0.95 (t, 3 H), 1.3–1.5 (m, 4 H), 2.0–2.3 (m, 1 H), 2.5–2.8 (m, 1 H), 4.0–4.2 (m, 3 H)	14.04, 19.70, 35.73, 40.77, 69.66, 80.36
21[a]	1.3 (s, 6 H), 2.3 (t, 2 H), 4.0 (5, 2 H)	25.83, 47.02, 70.09, 82.11
22	0.95 (t, 3 H), 1.4–2.0 (m, 4 H), 3.9–4.2 (m, 2 H)	
23[a]	1.1 (d, 3 H), 1.5–1.9 (m, 6 H), 3.8–4.2 (m, 3 H)	19.41, 22.50, 30.62, 37.52, 75.29, 80.57

[a] See Table II, footnote *a*.

period followed by stirring for an additional 4 min. Methylene chloride (75 mL) was then added, and the resulting mixture was immediately filtered into a separatory funnel. The organic layer was collected, washed once with H_2O (15 mL), and dried over anhydrous sodium sulfate. The dried solution was then filtered and the solvent removed on a rotary evaporator with a bath temperature of 0 °C. The recovered liquid, clear and colorless, was chromatographed in a jacketed column at −20 °C on 15 g of silica gel (pentane/methylene chloride), yield 0.111 g (55%).[18]

The spectral data for the cyclic peroxides are presented in Table IV.

Registry No.—**2,** 60653-71-6; **8,** 55175-91-2; **9,** 67393-81-1; **10,** 60653-70-5; **11,** 67393-65-1; **12,** 67393-66-2; **13,** 67393-82-2; **14,** 67393-67-3; **15,** 67393-68-4; **16a,** 67393-75-3; **16b,** 67393-74-2; **17,** 67393-76-4; **18a,** 67393-77-5; **18b,** 67393-78-6; **19a,** 67393-79-7; **19b,** 67393-80-0; **20,** 67393-69-5; **21,** 67393-70-8; **22,** 67393-71-9; **23,** 67393-72-0; *cis*-**24,** 67393-83-3; *trans*-**24,** 67393-84-4; **25,** 59954-67-5; **26,** 67393-73-1; *trans*-hexa-3,5-dien-1-ol mesylate, 67393-85-5.

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Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction. 4. Experimental and Theoretical Examination of the Reaction of Acrylonitrile with 1-(Phenylthio)-2-methoxy-1,3-butadiene. Determination of the Conformations of the Four Cyclohexene Adducts by ^{1}H NMR Spectroscopy

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The importance of secondary orbital interactions in controlling regiochemistry in the Diels–Alder reaction has been assessed by determining the composition of the adduct mixture formed by the reaction of (*Z*)-1-(phenylthio)-2-methoxy-1,3-butadiene with acrylonitrile. All four possible regio- and stereoisomers were separated by high-pressure liquid chromatography and their structures and approximate conformational preferences were determined by 250-MHz proton magnetic resonance spectroscopy. It was also determined that the product composition remains invariant with time under the reaction conditions. As predicted by frontier molecular orbital theory, the ratio of ortho (phenylthio and cyano groups) to meta regioisomers is greater (three to four times) in the (cis) products of endo addition than in the (trans) products of exo addition, thus indicating that secondary orbital interactions, which can only occur in the transition states for endo addition, play a substantial role in controlling regiochemistry.

The origin of the regioselectivity, which is so crucial to the magnificent synthetic utility of the Diels–Alder reaction, has intrigued organic chemists since the discovery of the reaction by Diels and Alder.[2] Of the many theories which have been proposed to explain this regioselectivity, the frontier molecular orbital (FMO) approach has been the most successful. In the application of FMO theory, several investigators[3–6] have used just the primary orbital interactions to predict the preferred regioisomer; however, we have observed numerous cases in which this approach failed to predict the regioselectivity that was observed.[7] In these cases the preferred regioisomer can be predicted by including secondary orbital interactions[8] in the theory.

An obvious test of the influence of secondary orbital in-

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