

sition metal ions in CP acetic acid. In a series of "non-Fe" titrations, 3 to 4% of the peroxy ester reacted in 5 min. On this basis, concentrations of hydroperoxide and peroxy ester were corrected as follows. The approximate peroxy ester concentration obtained from the difference in titers for "non-Fe" and "Fe" titrations, was multiplied by 1.03 to give the corrected peroxy ester concentration. This value was then subtracted from the total peroxide concentration (based on "Fe" titration) to give the corrected hydroperoxide concentration. Corrected values are listed in Table I.⁷

Reaction of *tert*-Butyl Hydroperoxide with Acetic Acid. Reaction mixtures were formulated by weight into volumetric flasks and were conducted in half-filled⁸ glass-stoppered flasks maintained at $30 \pm 0.1^\circ$ in a thermostat. Except for expt 1, total peroxide concentration remained constant during the course of reaction. In Experiments 2-6, sulfuric acid catalyst, diluted 50:50 with acetic acid, was added just prior to or just after the initial titration.

tert-Butyl peroxyacetate was isolated from final reaction mixtures of expt 1 and 2 as follows. Water (400 ml) was added to a 100-ml aliquot and the solution was extracted with 70 ml of diethyl ether and then with 30 ml of 30-60° petroleum ether. Combined extracts were washed sequentially with 50 ml of 10% Na₂CO₃ solution, 25 ml of 10% Na₂CO₃ solution, and 50 ml of water. After drying with MgSO₄, solvents were removed and the residue was distilled under reduced pressure, peroxy ester being collected at 29-30° (5 mm), n_D^{25} 1.4030 (lit.⁵ 1.4035), peroxide assay 96.8%. Recovery was about 60% of the theoretical amount of peroxy ester in the aliquots.

Preparation of *tert*-Butyl Peroxyacetate. A catalytic amount (0.4 g) of potassium acetate was added to a water-cooled stirred solution of *tert*-butyl hydroperoxide (14.1 g, 96% assay, 0.15 mol) and acetic anhydride (20 g, 0.196 mol, 30% excess) in 20 ml of 30-60° petroleum ether. Reaction was mildly exothermic. After standing overnight at room temperature, the reaction mixture was diluted with 80 ml of 30-60° petroleum ether, washed successively with 100 ml of water, 50 ml of 10% Na₂CO₃ solution, and 50 ml of water, dried with MgSO₄, and distilled under reduced pressure. Peroxy ester was collected at 30-30.5° (5 mm), yield 14.6 g (73%), peroxide assay 98.4%. The nmr spectrum agreed with literature data.⁵

Reaction of α -Cumyl Hydroperoxide with Acetic Acid. When a 0.984 *M* solution of α -cumyl hydroperoxide in glacial acetic acid was maintained at $30. \pm 0.1^\circ$, the hydroperoxide concentration slowly decreased. "Non-Fe" and "Fe" titers were identical, indicating the absence of peroxy ester. Pseudo-first-order kinetics were observed at least up to 30% reaction. The rate constant, obtained graphically, was $6.3 \pm 0.3 \times 10^{-7} \text{ sec}^{-1}$. As the reaction proceeded, the solution became yellow in color and finally yellowish brown and the odor of phenol was apparent during titrations. A similar reaction mixture, but 0.035 *M* in potassium acetate (in an attempt to reduce solution acidity), gave similar results. We assume the development of color was the result of oxidation of phenol to quinoidal products by the hydroperoxide. (Similar colors were observed when a solution of phenol and *tert*-butyl hydroperoxide in acetic acid was let stand at room temperature.) The presence of phenol in the reaction mixture was established by making an aliquot basic with sodium hydroxide, extracting several times with ether to remove α -cumyl hydroperoxide, acidifying with acetic acid, and treating with bromine followed by sodium bisulfite in the usual manner. The product, 2,4,6-tribromophenol (mp 95.5°), was obtained in 58% yield, based on hydroperoxide reacted.

Preparation of α -Cumyl Peroxyacetate. A catalytic amount (0.2 g) of potassium acetate was added to a cooled stirred solution of α -cumyl hydroperoxide (16.0 g, 95% assay, 0.1 mol) and acetic anhydride (12.8 g, 0.125 mol) in 40 ml of 38-50° petroleum ether. The reaction was stirred at room temperature until the potassium acetate dissolved and then let stand at room temperature for 1 hr. (Reaction time was limited to minimize decomposition of the peroxy ester in the presence of acetic acid.) Product work-up was similar to that described for *tert*-butyl peroxyacetate. Peroxy ester was collected at 54-57° (0.1 mm), yield 15.5 g (80%), peroxide assay 92%. Redistillation at 56-57° (0.1 mm) or at 48-49° (0.05 mm) gave a somewhat purer product (peroxide assay 94%), nmr (CCl₄) δ 1.58 [s, 6, (CH₃)₂], 1.75 (s, 3, CH₃CO), 7.3 (m, 5, C₆H₅).⁹

A 0.195 *M* solution of α -cumyl peroxyacetate in acetic acid at $30 \pm 0.1^\circ$ decomposed smoothly, following first-order kinetics up to at least 50% reaction. The rate constant was $4.5 \pm 0.05 \times 10^{-5} \text{ sec}^{-1}$, confirming results of Yablokov and coworkers.⁴

Registry No.—*tert*-Butyl hydroperoxide, 75-91-2; acetic acid, 64-19-7; *tert*-butyl peroxyacetate, 107-71-1; α -cumyl hydroperox-

ide, 80-15-9; 2,4,6-tribromophenol, 118-79-6; α -cumyl peroxyacetate, 34236-39-0.

References and Notes

- (1) From the M.S. thesis of A.K.B., Northeastern University, 1969.
- (2) C. Ruchardt and R. Hecht, *Chem. Ber.*, **97**, 2716 (1964) prepared *tert*-butyl peroxyformate from *tert*-butyl hydroperoxide and formic acid, noting that the reaction was applicable to other hydroperoxides but not to other carboxylic acids for preparative purposes.
- (3) Since the completion of our work, patents have issued on the acid-catalyzed esterification of certain hydroperoxides with carboxylic acids: (a) R. J. Harvey and C. N. Winnick, U. S. Patent 3595898 (1971); (b) V. L. Antonovskii and O. K. Lyashenko, Ger. Offen. 1937037 (1971); *Chem. Abstr.*, **74**, 140973 (1971).
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- (5) D. Swern, A. H. Clements, and T. M. Luong, *Anal. Chem.*, **41**, 412 (1969).
- (6) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).
- (7) Use of the correction gave more consistent equilibrium constants. Without the correction, *K* values were 0.28, 0.26, 0.24, 0.33, and 0.36 for Experiments 2 through 6, respectively; cf., Table I.
- (8) It was felt that the presence of oxygen would minimize possible induced chain decomposition reactions of the peroxides.
- (9) α -Cumyl peroxyacetate has previously been prepared by the reaction of the hydroperoxide with ketene¹⁰ and with acetyl chloride-pyridine.⁴ In both cases, the product was not distilled, possibly because of thermal decomposition, which was reported to be rapid at 90°. We found that the peroxy ester could be distilled, provided the bath temperature was kept below 70° during distillation. At bath temperatures of 80-90°, exothermic thermolysis occurred during attempted distillations.
- (10) D. Harman, U. S. Patent 2,608,570 (1952).

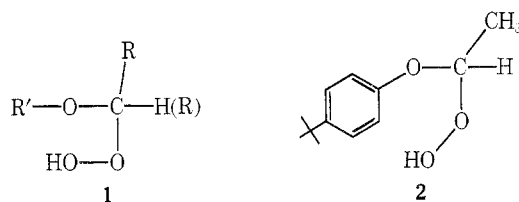
Preparation and Thermal Reactivity of α -(*p*-*tert*-Butylphenoxy)ethyl Hydroperoxide¹

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Compounds of type 1 where R' is alkyl are well known and routes to their synthesis are established,² but compounds where R' is aryl are unreported. An α -phenoxyalkyl hydroperoxide has been proposed³ as a possible intermediate in various enzyme-catalyzed hydroxylations of phenols. The synthesis and study of the thermal reactivity of a model compound 2 [α -(*p*-*tert*-butylphenoxy)ethyl hydroperoxide] was undertaken to test the plausibility of such an intermediate.

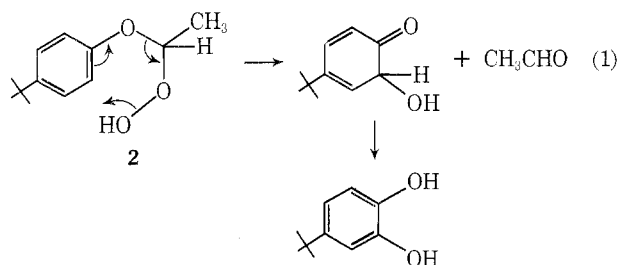


Synthetic attempts, employing the *in situ* trapping by *p*-*tert*-butylphenol⁴ of carbonyl oxides formed during the ozonolysis of various alkenes (2,3-dimethyl-2-butene, 2-ethyl-1-butene, 1,1-diphenylethylene, α -methylstyrene, and methylenecyclohexane), yield little or no peroxidic material which can be attributed to a compound such as 2. Similar attempts to trap the carbonyl oxides from *trans*-1,4-dibenzoyl ethylene and 2-ethylidenecyclohexanone are unproductive in yielding in these cases α -keto- α -phenoxyalkyl hydroperoxides. The results indicate that phenols (dissolved in inert solvents) unlike alcohols (normally employed as solvents) do not efficiently trap carbonyl oxides.⁵

The acid-catalyzed addition of 98% hydrogen peroxide to *p*-*tert*-butylphenyl vinyl ether did produce compound 2 in

yields of 15–20% (depending upon exact conditions). Under the moderately long reaction times required significant amounts of parent phenol, apparently formed by hydrolysis of the vinyl ether or hydroperoxide, are observed. An attempted synthesis of **2** using 50% hydrogen peroxide and the conditions of Milas, *et al.*,⁸ yielded none of the desired hydroperoxide, but under more rigorous reaction conditions, *i.e.*, temperatures of *ca.* 50°, traces of **2** are indicated along with large amounts of parent phenol.

A requirement for the proposed mechanism³ for enzymic ortho-hydroxylations is that compounds like **2** undergo a facile "Cope-type" rearrangement as shown in eq 1. Thermodynamic calculations, using the method of group addi-



tivity,⁹ indicate that the first step of eq 1 is exothermic by at least 70 kcal/mol. However, it was observed that compound **2** in a variety of solvents fails to thermally (80–175°) rearrange to give any detectable catechol or catechol-derived products (limits of detection are 1–2% reaction). Analyses *via* tlc indicate that in every case the major decomposition product of compound **2** is the parent phenol with traces of three minor products also noted. Control experiments show that the catechol and *o*-quinone products are readily detectable (see Experimental Section) and that under the reaction conditions *p*-*tert*-butyl catechol is converted to *p*-*tert*-butyl-*o*-quinone which is stable and reacts no further.

The catalytic effect of vanadium(IV) on this rearrangement was investigated since certain transition metals, particularly vanadium, chromium, tungsten, and molybdenum, are efficient catalysts for the presumably electrophilic transfer of oxygen from alkyl hydroperoxides to olefins.^{10–12} Product distributions from these reactions are very similar to those cited above except that *ca.* 2–3% of a quinone-like material is now observed. Mass spectral analysis shows that this material is not the expected *o*-quinone but suggests it to be a quinone formed by the dimerization of reaction products. A similar product distribution is observed when *tert*-butyl hydroperoxide and *p*-*tert*-butylphenol are reacted under similar conditions in the presence of vanadium. Thus, the small amount of observed quinone obtained from **2** is apparently formed by an intermolecular process.

These results demonstrate that the anticipated "Cope-type" rearrangement of compounds such as **2** does not occur readily and, therefore, this type of step in the proposed enzyme mechanism³ for the ortho-hydroxylation of phenols is questionable. This does not, however, invalidate the possibility that carbonyl oxides (such as "vinylogous ozone"³) are the oxidizing agents which hydroxylate the substrates by a pathway not involving an intermediate like **2** in various enzymic reactions.¹³

Experimental Section

(I) Ozonolysis Experiments. Solutions (usually at 0°, although some experiments were performed at –78° and at room temperature) of *p*-*tert*-butylphenol (0.66 *M*) and alkene (0.33 *M*) in methylene chloride were treated with a stoichiometric amount of ozone.

Table I
Conditions Required for Essentially Complete Thermal Decomposition of **2**

	Solvent	Temp, °C	Time, hr
Without V(IV)	Benzene	80	>24
	Water	100	~2
	1-Butanol	100	~2
	Nitromethane	100	~5
	DMF	100	~0.5
	Diglyme	100, 150	>0.5
	<i>p</i> -Dioxane	100	>4
	<i>n</i> -Octane	100, 125	>48
	<i>n</i> -Dodecane	150, 175	~2
With 10 ⁻⁴ <i>M</i> V(IV)	Benzene	80	~1
	<i>n</i> -Octane	80	~2

Upon warming the solutions to room temperature, product mixtures were analyzed *via* tlc (80:20 hexane–ether) on silica gel containing an ultraviolet indicator. Aromatic compounds were observed under ultraviolet light (254 nm) and peroxidic materials were detected by spraying plates with a 1% solution of KI. Compounds of interest were those aromatic in nature exhibiting a strong rapid peroxidic activity.

(II) Catalyzed Addition of Hydrogen Peroxide to *p*-*tert*-Butylphenyl Vinyl Ether. The reaction of an excess of potassium *tert*-butoxide with β -bromo-*p*-*tert*-butylphenetole^{14,15} in *tert*-butyl alcohol gives *p*-*tert*-butylphenyl vinyl ether (78%).¹⁶ To a stirring solution of 5 ml of anhydrous ether and 0.2 ml (8.7 mmol) of 98% hydrogen peroxide¹⁷ (kindly supplied by FMC Corporation) in a moisture-protected vial at –45° was added dropwise 1.1 ml (5.7 mmol) of *p*-*tert*-butylphenyl vinyl ether; 5 ml of anhydrous ether which contained 1.5 μ l of concentrated sulfuric acid was then added over a 15-min period; the system was allowed to warm to room temperature and remain as such with stirring for 45 hr. Tlc as in (I) showed the presence of compound **2** (R_f 0.41–0.43). The ethereal solution was washed with saturated (NH₄)₂SO₄ solution and saturated NaCl solution, dried (MgSO₄), and finally purified *via* silica gel chromatography (80:20 hexane–ether) giving after vacuum drying 0.171 g (22% based on an 80% reaction of vinyl ether) as a clear viscous oil α -(*p*-*tert*-butylphenoxy)ethyl hydroperoxide (**2**): uv max (95% C₂H₅OH) 273 nm (ϵ 8900); ir (CCl₄) 840 (O–O) and 3350–3550 cm⁻¹ (OO–H); nmr (DCCl₃) δ 1.28 (s, 9, (CH₃)₃C), 1.47 (d, 3, J = 5.5 Hz, CH₃–CH), 5.65 (q, 1, J = 5.5 Hz, CH₃–CH), 7.11 (m, 4, aromatic H's), and 8.65 ppm (s, 1, OOH); active oxygen content,¹⁸ 7.7%. (calcd, 7.6%). *Anal.* Calcd for C₁₂H₁₈O₃: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.35; H, 8.81; O, 22.64.

(III) Thermal Studies. (a) Solutions of **2** (0.05 *M*) in the following solvents (H₂O, 1-butanol, nitromethane, DMF, diglyme, benzene, *p*-dioxane, *n*-octane, and *n*-dodecane) were heated under a N₂ atmosphere at or near reflux. Aliquots *vs.* time were analyzed as in (I) for loss of hydroperoxide and formation of *p*-*tert*-butylcatechol (detected by 1% FeCl₃/1% K₃Fe(CN)₆ spray; dark blue color development) and/or *p*-*tert*-butyl-*o*-quinone (detected by characteristic pale yellow color). (b) To solutions as above (either benzene or *n*-octane) was added enough vanadium (as VO(AcAc)₂ in benzene) to make each 10⁻⁴ *M* in V(IV). Solutions were heated to 80° and analyzed as in (a). (c) Similar solutions of V(IV) in *n*-octane were prepared with *tert*-butyl hydroperoxide (0.05 *M*) and *p*-*tert*-butylphenol (0.05 *M*) in place of **2** and were treated as in (b). Table I summarizes the time required for essentially complete thermal decomposition of **2** under the various conditions.

Registry No.—**2**, 52827-71-1; *p*-*tert*-butylphenol, 98-54-4; hydrogen peroxide, 7722-84-1; *p*-*tert*-butylphenyl vinyl ether, 21476-78-8.

References and Notes

- (1) This research was supported by grants from the National Science Foundation and the National Institute of Arthritis, Metabolism, and Digestive Diseases (AM 13448).
- (2) R. Hiatt in "Organic Peroxides," Vol. 2, D. Swern, ed., Wiley-Interscience New York, N.Y., 1971, p 1.
- (3) G. A. Hamilton in "Molecular Mechanisms of Oxygen Activation," O. Hayaishi, ed., Academic Press, New York, N.Y., 1974, Chapter 10, p 405.
- (4) A phenol substituted with a bulky alkyl group was utilized to limit the an-

- anticipated oxidative-coupling reactions of the catechol and quinone materials which might form as a result of the rearrangement of **2**.
- (5) The synthesis of a compound like **2** was also attempted unsuccessfully by autoxidation of *p*-*tert*-butylphenyl isopropyl ether,⁶ prepared by the procedures of White, *et al.*⁷ Although only a limited number of autoxidation conditions were tried, no compound like **2** could be isolated.
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- (15) Prepared according to procedures in "Organic Syntheses," Coll. Vol. I, H. Gilman, Ed., Wiley, New York, N.Y., 1961, p 435.
- (16) M. F. Shostakovskii and A. V. Kalabina, *Izv. Fiz.-Khim. Nauch.-Issled. Inst. Irkutsk. Gos. Univ.*, **5**, 81 (1961); *Chem. Abstr.*, **58**, 6728c (1963).
- (17) CAUTION: High strength hydrogen peroxide forms highly explosive mixtures with many organic compounds. Adequate safety precautions were always taken when handling and using this material.
- (18) Active oxygen content determined according to the following procedure (see Mair, *et al.*,¹⁹ for further discussion). An accurately weighed sample of hydroperoxide in 50 ml of isopropyl alcohol, 10 ml of glacial acetic acid, and 1 ml of saturated KI solution was heated on a steam bath for 15 min, cooled, and titrated with standard aqueous Na₂S₂O₃.
- (19) R. D. Mair and R. T. Hall in "Organic Peroxides," Vol. 2, D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1971, p 535.

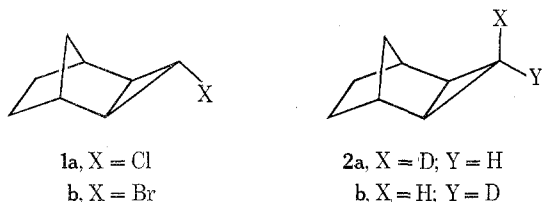
On Cyclopropyl Radical Intermediates in the *exo*-Tricyclo[3.2.1.0^{2,4}]octane System

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Prompted by the recent reports of Hatem and Waegell on the stereoselectivities of 1-halocyclopropyl radicals generated by halogen abstraction from *gem*-dihalocyclopropanes,¹ we report on the unique behavior of *exo*-tricyclo[3.2.1.0^{2,4}]octan-3-yl radical intermediates. Our original interest in replacing the chloro substituent in *anti*-3-chloro-*exo*-tricyclo[3.2.1.0^{2,4}]octane (**1a**)² with deuterium



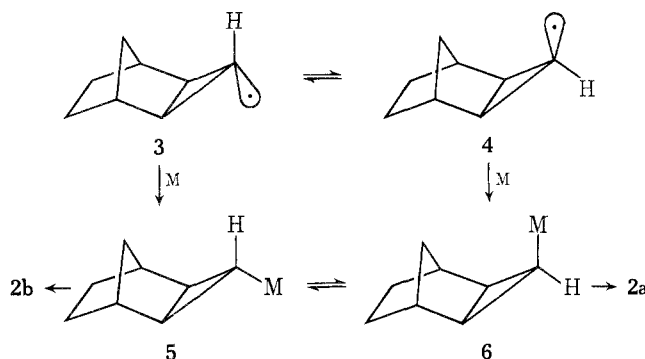
was stimulated by the need for development of a method for *syn* and *anti* C-3 deuterium placement on this ring system in connection with a different mechanistic study; however, initial experiments revealed that the chemistry of replacement of chloro by deuterio by treatment of **1a** with alkali metals in deuterated solvents is of considerable intrinsic interest, allowing one to view the steric interaction in *anti*- and *syn*-tricyclooctyl radicals **3** and **4**. Treatment of *anti*-3-chlorotricyclooctane (**1a**) with sodium in *tert*-butyl alcohol-*O-d*-tetrahydrofuran generated tricyclooctane **2** with a *syn* C-3 deuterio:*anti* C-3 deuterio ratio (**2a**:**2b**) of 2.11 ± 0.05 . Similar results were obtained when **1a** was allowed to react with potassium or lithium in *tert*-butyl alcohol-*O-d*-THF or with lithium in diethyl ether followed by deuterolysis (Table I). Since it is plausible that alkyl ha-

Table I
Reduction of Halotricyclooctanes **1a** and **1b**

Run	Halide	Reagent and Conditions	2a:2b
1	1a	Na/ <i>t</i> -BuOD-THF, reflux	2.11 ± 0.05
2	1a	K/ <i>t</i> -BuOD-THF, reflux	1.25
3	1a	Li/ <i>t</i> -BuOD-THF, reflux	1.70
4	1a	(1) Li, Et ₂ O, 0°, (2) D ₂ O	2.1 ± 0.3
5	1b	(1) <i>n</i> -BuLi, Et ₂ O, 0° (2) D ₂ O	≤0.06
6	1a	(1) LiNaph, THF, -78°, (2) D ₂ O	≥100:1
7	1a	(1) LiNaph, THF, -78°, (2) 0°, (3) D ₂ O	≥30:1

lides react with alkali metals in one-electron processes,³ and since it is established that cyclopropyllithium derivatives⁴ maintain configuration under moderate reaction conditions, it seems reasonable to suggest that the stereochemistry of replacement of chloro by deuterio is determined according to the sequence of steps outlined in Scheme I.

Scheme I



This scheme explains the stereoselectivity in terms of (a) the preequilibrium of radicals created in the initial electron transfer step, (b) the rate of trapping of the initially formed radical **3**, and (c) equilibration of the organometallics **5** and **6**. Reinforcement for the view that the *anti*-cyclopropyllithium substrate, once formed, is configurationally stable, was obtained by treatment of bromotricyclooctane **1b** with *n*-butyllithium, followed by deuterolysis, which afforded entirely *anti*-3-deuterio-*exo*-tricyclo[3.2.1.0^{2,4}]octane with no detectable quantity of *syn*-3-deuterio substrate (Table I). The generation of a cyclopropyllithium substrate with retention of configuration would be anticipated by analogy to similar reactions.^{4b-d}

At this point an attractive, alternative approach to the generation of cyclopropyl radicals **3** and **4** and then cyclopropyllithium reagents under conditions which would prevent epimerization of the organolithium reagents was the treatment of chlorotricyclooctane with lithium naphthalenide⁵ at a low temperature. The treatment of **1a** with lithium naphthalenide in THF at -78°, followed by neutralization with D₂O, generates *syn*-3-deuterio **2a** and *anti*-3-deuterio **2b** in a ratio of >100:1 (Table I). Since this high ratio of *syn*-3-deuterio to *anti*-3-deuterio could be the result of *anti* radical **3** coupling more rapidly with lithium naphthalenide than *syn* radical **4**, due to steric hindrance to approach of naphthalene radical anion, coupling products were searched for very carefully and none (<0.1%) detected. The results of lithium naphthalenide treatment not only provide insight into the chemistry of tricyclooctyl rad-