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A Synthesis of Mixed Dialkyl Peroxides via Reaction of an Alkyl Hydroperoxide with Alkyl Trifluoromethanesulfonates

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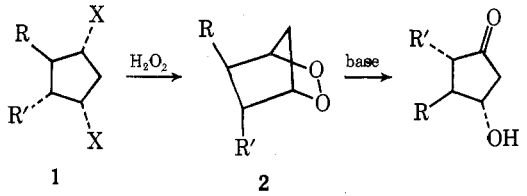
Mixed peroxides containing the *tert*-butyl group and secondary or primary alkyl groups are easily prepared under exceptionally mild conditions by reaction of primary or secondary trifluoromethanesulfonates with either potassium *tert*-butyl peroxide (method I) or with *tert*-butyl hydroperoxide in the presence of sodium bicarbonate (method II). Method I gives high yields of primary tertiary peroxides and moderate yields of secondary tertiary peroxides. The preparation of 1,3-cyclopentane bis triflates in good yields from 1,3-cyclopentanediols, models of the prostaglandin F nucleus, and conversion to 1,3-cyclopentane bis-*tert*-butyl peroxides are readily achieved. Loss of stereochemistry occurs with either method in the *cis*- and *trans*-cyclopentane-1,3-diol system, but method II is preferred in this system as it gives complete bisalkylation with no accompanying elimination.

In connection with studies on the synthesis of prostaglandin endoperoxides[1] (e.g., **2a**), we are seeking a mild, high-yield method for the synthesis of secondary alkyl peroxides. The prostaglandin endoperoxide nucleus is a strained bicyclic secondary peroxide which is extremely sensitive to base-catalyzed decomposition in comparison with common secondary peroxides. Thus, the usual harsh, alkaline method for preparation of bis secondary alkyl peroxides by reaction of secondary alkyl methanesulfonates with hydrogen peroxide in the presence of potassium hydroxide[2a,9] is incompatible with the survival of the prostaglandin endoperoxide nucleus. The ultimate goal of these studies is the synthesis of prostaglandin endoperoxides by treating suitably substituted 1,3-cyclopentane bis alkylating agents (e.g., **1a**) with hydrogen peroxide



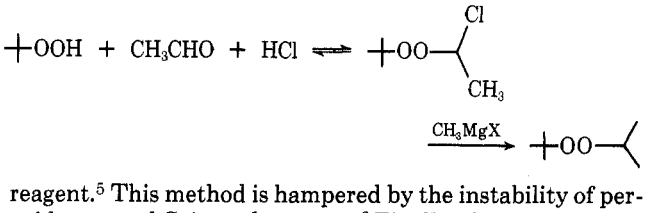
1 2

a, R = CH=CHCH(OH)C_5H_{11}; R′ = $(CH_2)_6COOH$; X = OH
b, R = R′ = H; X = OTf

or related peroxy nucleophiles. Thus, preparation of appropriately substituted cyclopentane derivatives must be feasible in any new method.

We report here development of new methods for synthesis of secondary or primary alkyl *tert*-butyl mixed peroxides by alkylation of either *tert*-butyl hydroperoxide in the presence of sodium bicarbonate or potassium *tert*-butyl peroxide with secondary or primary alkyl trifluoromethanesulfonates (triflates). These reactions give fair to good yields (30–60%) in secondary cases and an excellent yield with a primary triflate (83%). Furthermore, we report preparation of 1,3-bis(*tert*-butyl)peroxycyclopentane by these methods. Hence, further extensions of these reagents and procedures may be useful for the synthesis of prostaglandin endoperoxides.

In order to evaluate and develop various methods for synthesis of secondary peroxides, we chose preparation of the simple peroxide isopropyl *tert*-butyl peroxide as a model. Several methods have been employed to prepare this and related dialkyl peroxides. The most widely used synthesis involves reaction of alkyl bromides with sodium or potassium *tert*-butyl hydroperoxide.[3] The yields are low (33% for isopropyl bromide) and the purification somewhat tedious. Reaction of *tert*-butyl hydroperoxide with dialkyl sulfates and potassium hydroxide succeeds quite well in the methyl and ethyl cases,[1] but is only fair (38%) in the isopropyl case.[3a] Alkylation of cumyl hydroperoxide with 2-diazopropane gives a fair yield (41%),[4] but preparation of secondary diazo compounds other than isopropyl is difficult and yields are poor. *tert*-Butyl isopropyl peroxide was recently prepared in 25% overall yield from *tert*-butyl hydroperoxide by reaction of *tert*-butyl-2-chloroethyl peroxide with a methyl Grignard



reagent.[5] This method is hampered by the instability of peroxides toward Grignard reagents.[6] Finally, the recent preparation of secondary alkyl *tert*-butyl peroxides by peroxymercuration of olefins followed by demercuration with sodium

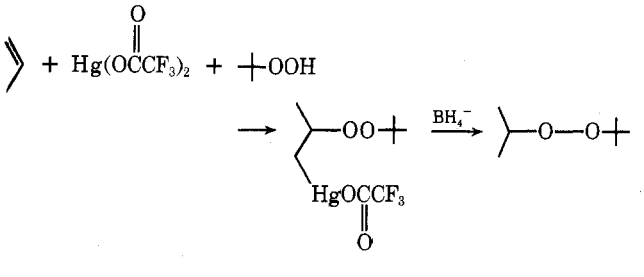
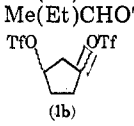
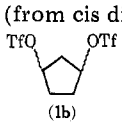
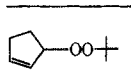
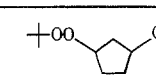
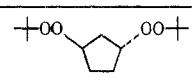


Table I. Synthesis of Mixed Dialkyl Peroxides with Alkyl Triflates

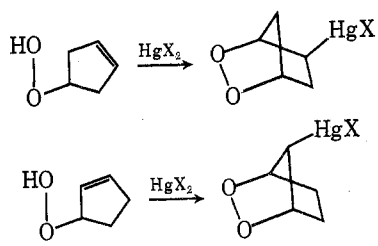
Triflate	Registry no.	Reaction type[a]	Reaction time, h	Product(s)	Yield %	Registry no.
Me_2CHOTf	41029-44-1	$NaHCO_3$/*t*-BuOOH	3	$Me_2CHOO(t\text{-Bu})$	56	15879-99-9
Me_2CHOTf		KOO-*t*-Bu	0.5	$Me_2CHOO(t\text{-Bu})$	33	
Me_2CHCH_2OTf	60306-25-4	$NaHCO_3$[b]/*t*-BuOOH	38	$Me_2CHCH_2OO(t\text{-Bu})$ (42%) + $(t\text{-BuO})_2$ (58%)	37	60306-29-8 110-05-4
Me_2CHCH_2OTf		KOO-*t*-Bu[b]	3	$Me_2CHCH_2OO(t\text{-Bu})$	81	
Me(Et)CHOTf	60306-26-5	$NaHCO_3$/*t*-BuOOH	18	Me(Et)CHOO(*t*-Bu)	33	31469-04-2
Me(Et)CHOTf		KOO-*t*-Bu	0.5	Me(Et)CHOO(*t*-Bu)	48	
 (1b)	60306-27-6	$NaHCO_3$/*t*-BuOOH	1	See Table II	50	
(from cis diol)		KOO-*t*-Bu	1	See Table II	40	
 (1b)	60306-28-7	$NaHCO_3$/*t*-BuOOH	1	See Table II	49	
(from trans diol)		KOO-*t*-Bu	1	See Table II	53	

[a] Reaction temperature 25 °C. [b] Reaction temperature 40 °C.

Table II. Reaction Products from *cis*- and *trans*-1,3-Cyclopentanediols

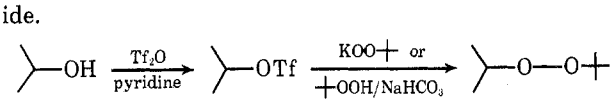
Starting diol	Reaction type	Products, % 		
Cis	$NaHCO_3$/*t*-BuOOH	0	66	34
Cis	KOO-*t*-Bu	43	9	49
Trans	$NaHCO_3$/*t*-BuOOH	0	62	38
Trans	KOO-*t*-Bu	29	23	48

borohydride is quite mild and gives fair yields (ca. 40% for the two-step process).[7] The use of intramolecular peroxymercuration[8] to prepare endoperoxides from 3- or 4-hydroperoxycyclopentenes is under investigation in our laboratories.



Results

We reasoned that a powerful alkylating agent, such as alkyl trifluoromethanesulfonate (triflate), might be capable of alkylating a hydroperoxide in the absence of strong bases which are required to generate alkylperoxy anions for reactions with less powerful alkylating agents, e.g. alkyl mesylates or alkyl halides. In fact, isopropyl triflate readily alkylates *tert*-butyl hydroperoxide in a few hours at room temperature. Cleanest reactions were obtained in the presence of sodium bicarbonate which neutralizes triflic acid by-product. In the case of isopropyl *tert*-butyl peroxide, the distilled product was not completely pure. The impurity, which we could not separate, appears to be di-*tert*-butyl peroxide. Pure isopropyl *tert*-butyl peroxide is obtained by an alternate procedure involving reaction of isopropyl triflate with potassium *tert*-butyl peroxide.



These new methods for preparation of mixed peroxides were extended to several additional examples, including isobutyl and secondary butyl triflates, and the bis triflates (**1b**) prepared from *cis*- and *trans*-cyclopentane-1,3-diol. The results and experimental conditions are summarized in Tables I and II. All of the peroxides except those obtained from the cyclopentanediols were reported previously. The structures of the latter are supported by their ^1H NMR spectra, elemental analyses, and mass spectra (see Experimental Section). In addition, the bis peroxides were reduced with lithium aluminum hydride[11] to the corresponding diols which were acetylated to give mixtures of *cis*- and *trans*-1,3-diacetoxycyclopentane, identified by gas–liquid phase chromatographic comparison with authentic samples.

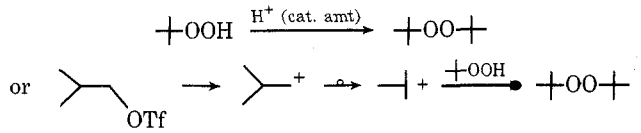
Discussion

These new methods for the synthesis of mixed dialkyl peroxides are quite mild and easy to execute. For monotriflates, the use of potassium *tert*-butyl peroxide is preferred over the *tert*-butyl hydroperoxide–sodium bicarbonate method for both speed of reaction and purity of the product. One complication which is encountered in either method, however, is the instability of some secondary triflates. Isopropyl triflate is stable in solution for several weeks at 0 °C, but 2-butyl triflate, which was obtained in poorer yields (48%), decomposes fairly rapidly at room temperature even in solution (15% after 0.5 h). Elimination of triflic acid to form olefins was a problem with some other triflates whose synthesis was attempted. Thus, reaction of cyclohexanol with triflic anhydride and pyridine gave a mixture of the desired triflate and cyclohexene which was converted entirely to cyclohexene in a few minutes by stirring with sodium bicarbonate. Attempted synthesis of cyclopentyl triflate gave only cyclopentene.

For the synthesis of isobutyl *tert*-butyl peroxide, the reaction of potassium *tert*-butyl peroxie with isobutyl triflate is a major improvement over previously available methodology. Thus, the mixed peroxide is obtained in 83% yield (isolated by distillation) by the new method while the reaction of sodium *tert*-butyl peroxide with isobutyl bromide gives only

a 30% yield.[3] The primary triflate is less reactive than the secondary ones, and a modest amount of heat (40 °C) is necessary to make the reaction proceed at a convenient rate. However, in contrast to secondary alkyl triflates, primary triflates are thermally stable, not prone to elimination, and are readily prepared in excellent yields. This new synthetic method should be easily applicable to long chain primary alkyl triflates, as contrasted by the dialkyl sulfate method which has only been used in the methyl and ethyl cases.[3]

Using the *tert*-butyl hydroperoxide–sodium bicarbonate method, some di-*tert*-butyl peroxide was formed from the reaction of isobutyl triflate with *tert*-butyl hydroperoxide.



This bis tertiary peroxide could arise either from *tert*-butyl hydroperoxide (perhaps catalyzed by traces of triflic acid)[12] or from the rearrangement of isobutyl triflate (or isobutyl carbonium ion) during the reaction.[10a] However, no rearrangement of isobutyl triflate occurs during its synthesis.

Preparation of the bis peroxide of cyclopentane-1,3-diol is a particularly significant result as it shows that the new method may prove applicable to a prostaglandin system. Synthesis of the bis triflate (**1b**) from either *cis*- or *trans*-cyclopentane-1,3-diol proceeds very smoothly in good yield, and no traces of olefin due to elimination of triflic acid can be detected by ^{1}H NMR of the crude bis triflate. The enhanced stability of the bis triflate over cyclopentyl triflate, which we were unable to prepare, indicated an inhibiting effect of the second substituent on elimination. The bis triflates from either the cis or trans diol isomer have nearly identical ^{1}H NMR spectra.

Examination of Tables I and II shows that good yields are obtained using either the *tert*-butyl sodium bicarbonate or the potassium *tert*-butyl peroxide methods, but elimination to form *tert*-butyl 3-cyclopentenyl peroxide was a competing reaction when the latter method was employed. Elimination generally accompanies common methods for the synthesis of dialkyl peroxides by nucleophilic displacement of halide or methanesulfonate with hydroperoxide, superoxide, or alkyl peroxide anions.[2] Thus, for bis alkylation with 1,3-cyclopentyl bis triflates (**1b**), which are models of the prostaglandin nucleus, the nonalkaline reaction with a hydroperoxide in the presence of sodium bicarbonate is superior. The bis triflate is readily prepared in good yield from the diol. The bis peroxides were easily purified by molecular distillation or column chromatography on Florisil.

The bis peroxides prepared by each of the methods described here consisted of similar mixtures of cis and trans isomers starting with either pure diol isomer. The cis bis peroxide was favored by the nonalkaline procedure while trans bis peroxide predominated when the alkaline potassium *tert*-butyl peroxide method was used and considerable elimination occurred. It is tempting to speculate that elimination from the cis bis triflate (or monotriflate monoperoxide) is favored over elimination from the corresponding trans isomer. That is, elimination selectively destroys a precursor of the cis bis peroxide. We have not determined whether the loss of stereointegrity observed in the transformation of cyclopentane diols to the bis peroxides occurs in the preparation of the bis triflates or during the conversion of the latter into the final products.

These studies are being extended to alkylation of hydrogen peroxide and related peroxy nucleophiles with triflates for the preparation of symmetrical dialkyl peroxides in general and prostaglandin endoperoxides in particular.

Conclusion

Mixed dialkyl peroxides are obtained by alkylation of an alkyl hydroperoxide with alkyl trifluoromethanesulfonates *under nonalkaline reaction conditions.* This new method was applied to 1,3-cyclopentane bis(trifluoromethanesulfonate), a model of the prostaglandin F nucleus. Under identical conditions, 1,3-cyclopentanediol bis(methanesulfonates) do not react at all with *tert*-butyl hydroperoxide. Cyclopentyl-1,3-bis(*tert*-butyl) peroxide is obtained in good yield uncontaminated with elimination product. This contrasts with the elimination which generally accompanies common methods for the synthesis of dialkyl peroxides by nucleophilic displacement of halide or methanesulfonate under alkaline conditions with hydroperoxide, superoxide, or alkyl peroxide anions. Thus, reaction of **1b** with potassium *tert*-butyl peroxide gives major quantities of elimination product in addition to the desired bis peroxide. The conversion of alcohol to peroxide via the triflate proceeds with loss of stereochemistry. In some cases, even the relatively basic nucleophile, potassium *tert*-butyl peroxide, gives much better yields of dialkyl peroxides with alkyl triflates than with less reactive alkylating agents. For monotriflates, purer products are usually obtained by reaction with the potassium *tert*-butyl peroxide than by reaction with the hydroperoxide in the presence of bicarbonate.

Experimental Section

Microanalyses were preformed by Chemalytics, Tempe, Ariz. ^{1}H NMR spectra were taken in carbon tetrachloride unless otherwise noted and recorded on a Varian A-60 spectrometer. Mass spectra were taken on a 21-490 Du Pont GC/mass spectrometer with interfaced computer, using 10 ft × 0.125 in. 15% FFAP column at 40 °C unless otherwise noted. Ir spectra were measured as neat films on a Perkin-Elmer Infracord spectrometer.

tert-Butyl hydroperoxide was purified by the method of Bloodworth et al.[7c] Potassium *tert*-butyl peroxide was prepared by the method of Kornblum and De La Mare.[13] Methylene chloride was dried by stirring over phosphorus pentoxide followed by distillation. Tetrahydrofuran was dried by distillation from the blue potassium ketyl of benzophenone. Pyridine was dried by standing over KOH several days followed by distillation and storage over molecular sieves.

Preparation of Triflates. General Procedure.[10a] A mixture of dry alcohol (10 mmol) and pyridine (10 mmol) in dry methylene chloride (3 ml) was added dropwise over 40 min to an ice-cooled, stirred solution of trifluoromethanesulfonic anhydride[10a] (10 mmol) in methylene chloride (7 ml) under nitrogen. The solution was stirred for an additional 15 min, and then washed with water (10 ml) and dried ($MgSO_4$). The solution was filtered and examined by NMR.

1. Isopropyl triflate[10a] was prepared according to the general procedure. The crude triflate was purified by bulb-to-bulb distillation at 1 mm (25 °C) and was stored in solution in the refrigerator. The triflate could also be prepared by bubbling propene into a stirred suspension of triflic acid in carbon tetrachloride.[10b]

2. *sec*-Butyl triflate was prepared according to the general procedure using an ice/salt bath and careful slow addition to triflic anhydride. After workup, the solution was examined by NMR and the yield (48%) determined by NMR with chloroform as an internal standard. The product is quite unstable and should be used immediately. NMR (CH_2Cl_2) δ 1.00 (3 H, t, J = 7 Hz), 1.33 (3 H, d, J = 7 Hz), 1.3–2.2 (2 H, m), 4.9–5.4 (1 H, m, partly buried under CH_2Cl_2).

3. Isobutyl triflate was prepared according to the general procedure. After the usual workup, the product was distilled, bp 36–37 °C (10 mm) (83%). The triflate is stable for several weeks at 0 °C. NMR δ 1.04 (6 H, d, J = 7 Hz), 1.77–2.43 (1 H, m), 4.26 (2 H, d, J = 6.5 Hz).

4. 1,3-Bis triflate of cyclopentane (1b) was prepared by the general procedure using 2 mmol of pyridine and 2 mmol of triflic anhydride for every 1 mmol of *cis*-[15] or *trans*[16]-cyclopentane-1,3-diol. After the usual workup, the solvent was removed and the product (79% from cis, 72% from trans) was examined by NMR ($CDCl_3$, cis): δ 2.16–2.35 (4 H, m), 2.5 (2 H, distorted quartet, J = 5 Hz), 5.25–5.85 (2 H, m). The NMR spectra of the products from both the cis and

trans starting materials were virtually the same. The crude triflates were used immediately after preparation.

Reactions of Triflates with Potassium *tert*-Butyl Peroxide. General Procedure. To the triflate (25 mmol) in dry methylene chloride (50 ml) in a Morton flask under nitrogen was added in one portion (dried in vacuo) potassium *tert*-butyl peroxide[14] (50 mmol, 100 mmol for bis triflates) with efficient stirring. Reaction times and temperatures are given in Table I. After NMR analysis showed that no more triflate remained, the crude reaction mixture was washed with 5% KOH (2 × 50 ml) and water (50 ml), and dried (Na_2SO_4).

1. Isopropyl *tert*-butyl peroxide, prepared according to the general procedure by stirring at room temperature for 0.5 h, had bp 45–50 °C (120 mm) [lit.[3a] 52 °C (125 mm)]; NMR δ 1.12 (6 H, partly buried d), 1.16 (9 H, s), 4.06 (1 H, heptet, J = 7 Hz). The material was identical with an authentic sample[3a] by NMR and ir.

2. *sec*-Butyl *tert*-butyl peroxide, prepared according to the general procedure by stirring at room temperature for 0.5 h, had bp 38–42 °C (35 mm) [lit.[7c] 42–44 °C (6 mm)]; NMR δ 0.91 (3 H, t, J = 7 Hz), 1.10 (3 H, d, partly buried), 1.17 (9 H, s), 1.17–1.70 (2 H, m), 3.83 (1 H, hextet, J = 6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 42 (30), 43 (30), 45 (29), 56 (100), 57 (24), 58 (28), 73 (78), 75 (23), 146 parent peak (52).

3. Isobutyl *tert*-butyl peroxide, prepared according to the general procedure by stirring under reflux for 3 h, had bp 63–64 °C (80 mm) [lit. 53 °C (50 mm[3a])]; NMR δ 0.93 (6 H, d, J = 6.5 Hz), 1.17 (9 H, s), 1.5–2.35 (1 H, m), 3.61 (2 H, d, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 42 (27), 43 (62), 55 (21), 56 (100), 57 (24), 73 (56), 146 parent peak (49).

4. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane derived from cis starting diol[15] was prepared in the usual manner at room temperature for 1 h. By NMR analysis, the crude product contained 57% bis peroxide and 43% 3-*tert*-butylperoxycyclopentene (for preparation see below). An olefin-free pure sample could be obtained by careful chromatography on Florisil, eluting with carbon tetrachloride, the olefin (contaminated with bis peroxide) eluting first: NMR δ 1.17 (18 H, s), 1.7–2.0 (6 H, m), 4.32–4.68 (2 H, m).

5. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane derived from trans diol[16] was prepared in the usual manner at room temperature for 1 h. NMR analysis indicated 71% bis peroxide and 29% monoperoxide olefin. After removal of olefin by chromatography, the NMR of the bis peroxide was indistinguishable from that of the cis derived bis peroxide.

Reduction of Cyclopentane 1,3-Bis(*tert*-butyl) Peroxide. The bis peroxide (0.25 mmol) in dry THF (1 ml) was added in one portion to a stirred suspension of lithium aluminum hydride (75 mg, 2 mmol) in dry THF under nitrogen. The mixture was stirred under reflux for 18 h. The reaction was cooled, water (75 μl) added, then 15% sodium hydroxide solution (75 μl), followed by water (225 μl). The white solid was removed by filtration and washed well with THF (3 × 10 ml). The THF was concentrated to obtain the crude diol which was acetylated by addition of pyridine (2 ml) and acetic anhydride (2 ml). After standing for 2 days, the solvents were removed under reduced pressure and the residue was taken up in ether (10 ml) and washed with saturated sodium bicarbonate (10 ml) and saturated cupric sulfate (10 ml). The ether layer was dried ($MgSO_4$) and concentrated to give the crude 1,3-cyclopentane bis acetate (75–100% yield over two steps). The bis acetate was analyzed by VPC (15 ft × 0.125 in. 15% FFAP, 150 °C). Samples of four 1,2 and 1,3 bis acetoxycyclopentanes were prepared by acetylation of the known diols.[15-17] Their relative retention times under these VPC conditions were, trans 1,2,[17] 1.0; cis 1,2,[17] 1.1; trans 1.3,[16] 1.5; cis 1,3,[15] 1.6. Results of the analyses are given in Table II.

3-*tert*-Butylperoxycyclopentene.[18] To 3-chlorocyclopentene[19] (25 mmol) in dry methylene chloride (50 ml) in a Morton flask under nitrogen was added in one portion potassium *tert*-butyl peroxide (50 mmol) with efficient stirring. The mixture was stirred for 3 days, washed with 5% KOH (2 × 50 ml) and water (50 ml), and dried ($MgSO_4$). Removal of solvent gave product (1.64 g, 42%) whose NMR indicates that it is quite pure: δ 1.18 (9 H, s), 1.73–2.12 (2 H, m), 2.12–2.55 (2 H, m), 4.8–5.1 (1 H, m), 5.80 (1 H, d of t, J = 6, 2, 2 Hz), 6.02 (1 H, d with additional fine coupling, J = 6 Hz).

Reaction of Triflates with Sodium Bicarbonate and *tert*-Butyl Hydroperoxide. General Procedure. The triflate (20 mmol, 10 mmol if bis triflate) in dry methylene chloride (30 ml) was placed in a Morton flask under nitrogen. Sodium bicarbonate (5 g) was added followed by purified[7c] *tert*-butyl hydroperoxide (25 mmol). The reaction was stirred vigorously until NMR analysis indicated no more triflate remaining. Reaction times and temperatures are given in Table I. The reaction mixture was washed with cold 5% KOH (50 ml) and water (50 ml) and dried (Na_2SO_4).

1. Isopropyl *tert*-butyl peroxide was prepared by the general procedure at room temperature for 3 h. Even after distillation, the product was impure, being contaminated with about 20% excess *tert*-butyl absorption in the NMR.

2. *sec*-Butyl *tert*-butyl peroxide was prepared by the general procedure at room temperature for 18 h. After distillation the product was still impure, showing about 40% extra *tert*-butyl absorption in the NMR. By VPC analysis (5 ft × 0.25 in., 15% FFAP, 50 °C column, 100 °C injector and detector), the extra *tert*-butyl was not due to di-*tert*-butyl peroxide. A pure sample of *sec*-butyl *tert*-butyl peroxide was collected by preparative VPC and identified by NMR and ir comparison with the sample prepared by the potassium *tert*-butyl peroxide route above.

3. Isobutyl *tert*-butyl peroxide was prepared by the general procedure at reflux for 38 h. After distillation the product was still impure, showing an additional *tert*-butyl peak 1 cycle upfield from the product *tert*-butyl peak. This new peak corresponds to di-*tert*-butyl peroxide. VPC analysis (5 ft × 0.25 in. 15% FFAP, 50 °C) also indicated the presence of di-*tert*-butyl peroxide whose presence was confirmed by GC/mass spectral analysis of the mixture (di-*tert*-butyl peroxide retention time 2.0 min, isobutyl *tert*-butyl peroxide retention time 4.2 min).

4. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane was prepared by the general procedure from either the bis triflate derived from *cis*- or *trans*-cyclopentane-1,3-diol using carbon tetrachloride as the reaction solvent. No cyclopentene-3-*tert*-butyl peroxide was formed from either starting material. Purification can be achieved by passage through Florisil eluting with carbon tetrachloride. Very pure samples were obtained from reactions with either cis or trans starting materials via molecular distillation at 50 °C (0.05 mm). Elemental analysis was performed on the purified bis peroxide from the cis diol. Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 62.85; H, 10.46.

Mass spectrum of the same material (direct inlet, 70 eV) *m/e* (rel intensity) 39 (48), 41 (53), 42 (43), 43 (62), 45 (22), 55 (33), 57 (100), 58 (41), 59 (46), 73 (71), 83 (23), 101 (21), 117 (20), 146 (28), 190 (22), 246 parent peak (6). Low voltage: 190 (100), 246 parent peak (27).

NMR analysis of the two products from cis and trans diol indicated that they were identical. Under very careful conditions the two different *tert*-butyl absorptions due to the cis and trans mixture of bis peroxide products can be discerned. The cis isomer comes at 0.8 cycles higher field than the trans isomer. By NMR, from either the cis or the trans starting material, the mixture consists of 62% cis and 38% trans bis peroxide.

Attempted reaction of the bis triflate from the cis diol starting material with sodium bicarbonate and *tert*-butyl hydroperoxide in methylene chloride rather than carbon tetrachloride as a solvent led to rapid decomposition after solvents were removed from the crude product.

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Registry No.—Trifluoromethanesulfonic anhydride, 358-23-6; *sec*-butyl alcohol, 78-92-2; isobutyl alcohol, 78-83-1; *cis*-cyclopentane-1,3-diol, 16326-97-9; *trans*-cyclopentane-1,3-diol, 16326-98-0; potassium *tert*-butylperoxide, 14970-33-3; *cis*-1,3-bis(*tert*-butyl) peroxide of cyclopentane, 60306-30-1; *trans*-1,3-bis(*tert*-butyl) peroxide of cylopentane, 60306-31-2; 3-*tert*-butylperoxycyclopentene, 38362-74-2; 3-chlorocyclopentene, 96-40-2; *tert*-butyl hydroperoxide, 75-91-2.

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Reaction of Sulfinate Esters with Grignard and Organocopper Lithium Reagents. A Useful Route to Chiral Sulfoxides[1]

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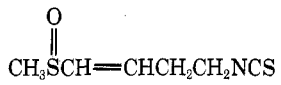
The reaction of sulfinate esters with various Grignard reagents was found to give a complex mixture of sulfoxide and sulfides. The use of organocopper lithium reagents in place of the Grignard effects the conversion of sulfinate esters to sulfoxides in higher yields and cleaner product mixtures. (−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate and (−)-menthyl (−)-(*S*)-benzenesulfinate were treated with organocopper lithium reagents. The reactions were found to proceed with inversion of configuration at sulfur to give sulfoxides of high optical purity.

The sulfoxide moiety, because of its pyramidal structure, can give rise to asymmetry in a molecule. The first known natural product in which optical activity results from chirality of an atom other than carbon is sulforaphen (**1**),[2] isolated from the black radish.



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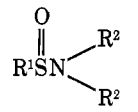
Sulfoxides can be prepared in various states of optical purity by a number of techniques. Asymmetric oxidation of sulfides with several reagents (optically active peracids,[3a-h] iodine in the presence of a chiral catalyst,[3i] or microbes[4]) provides sulfoxides, usually of low optical purity. Alternatively, sulfoxides can be optically enriched by incorporation into inclusion compounds with a chiral host molecule,[5] or by partial oxidation[6] or reduction[7a,b] with chiral reagents. In addition, the use of special techniques such as circularly polarized light[7c] and "chiral" electrodes[7d] have also produced respectable optical yields of chiral sulfoxides. Finally, sulfoxides of high optical purity can be prepared in variable yields by reaction of a variety of sulfinyl compounds (e.g., sulfinamides **2**,[8] heterocycles **3**,[9] or sulfinate esters **4**[10]) with organometallic reagents.



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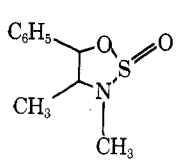

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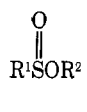

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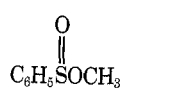
The most widely used synthetic procedure, dating from 1924,[10a] involves the reaction of a sulfinate ester **4** with a Grignard reagent. This reaction was later employed by Andersen[10b,c] to prepare optically active aryl sulfoxides; Mislow subsequently confirmed[10d,e] that the reaction was highly stereospecific, furnishing products of high optical purity.

While this valuable synthetic technique in certain instances can give sulfoxides in high yield, close scrutiny of the literature reveals that yields depend greatly on the structure of the target sulfoxide.[11] It appeared that careful examination of the reaction of a simple sulfinate ester such as methyl phenylsulfinate[12] (**5**) might provide some insight to the causes of this problem. Thus **5** and two cyclic sulfinate esters [1,2-oxathiolane 2-oxide (**6**) and 1,2-oxathiane 2-oxide (**7**)[13]] were treated with a number of Grignard reagents. The reaction of sulfinate esters with organocopper lithium reagents was also examined to evaluate their utility for sulfoxide formation.



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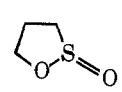

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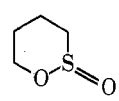

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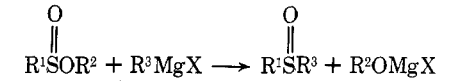
Results and Discussion

It was found that these compounds can react with Grignard reagents to give sulfoxides, but the conditions must be very carefully selected, otherwise considerable quantities of sulfides and other impurities are produced. These impurities can often remain tenaciously with the sulfoxide making separation difficult and thus severely limiting the synthetic utility of the reaction. The results obtained are summarized in Table I.

Reduction of Sulfinates to Sulfoxides by Grignard Reagents. In each case it was possible to characterize some sulfoxide in the reaction mixture, but the yields varied greatly with the structure of both sulfinate ester and Grignard reagent.



From the results of Table I, it is obvious that the sulfoxide, once generated, can react further. In the case where an equivalent amount of Grignard reagent was used, care was