The Stereoselectivity of Reactions of Electrophilic Species with 2-Lithio-1,3-dithiane 1-Oxide

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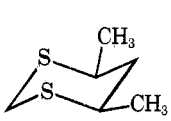
The stereoselectivity of the reactions of 2-lithio-1,3-dithiane 1-oxide (**12**) and its 2-methyl (**19**) and 2-phenyl (**20**) analogues with electrophilic reagents was determined. Reaction of **12** with DCl and with benzophenone occurs preferentially cis to the sulfoxide oxygen by a factor of 3–4:1. Reaction of **12** with methyl iodide yields almost equal amounts of *trans*- (**3b**) and *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). Lithio derivatives **19** and **20** exhibit a more pronounced tendency for protonation from the axial direction; the ratios are 8–10:1 and >20:1, respectively. Methylation of **20** with CH_3I occurs predominantly from the axial direction (84:16). Metalation of 1,3-dithiane 1-oxide (**1**) with lithium diisopropylamide in tetrahydrofuran occurs by preferential abstraction of the C(2)-equatorial proton (k_{eq}/k_{ax} = 2.7). The stereochemical courses observed for protonation of **19** and methylation of **20** were independent of the stereochemistry of the substrates which were metalated. A steric model is proposed to account for the trends in stereoselectivity between **12**, **19**, and **20** and between electrophiles. The stereoselectivity is based on an intrinsic preference for axial attack and developing van der Waals repulsions in the transition state between the C(4) and C(6) axial protons and either the C(2) substituent (favoring axial attack) or the incoming group (favoring equatorial attack).

The preceding paper[1] reported syntheses of stereochemically homogeneous samples of *trans*-2-deuterio- (**7a**), *cis*-2-deuterio- (**7b**), *trans*-2-methyl- (**3b**), *cis*-2-methyl- (**4b**), *trans*-2-phenyl- (**3c**), and *cis*-2-phenyl-1,3-dithiane 1-oxide (**4c**). Additionally, NMR criteria were proposed which, together with the method of their synthesis, allowed stereochemical assignments to be made to *trans*- and *cis*-2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxides (**3d** and **4d**, respectively). This group of compounds forms the basis of the study to be described in this paper. The study is concerned with the stereochemistry of metalation of 1,3-dithiane 1-oxide (**1**) and the stereoselectivity of the reactions of its 2-lithio derivative (**12**) with electrophilic species. The generation and some reactions of **12** had been reported, but the sterochemical details could not be defined on the basis of the information previously available.[2] Since **12** may be useful as a nucleophilic carbonyl equivalent in synthetic transformations, it was considered of interest to examine in more detail the stereochemical aspects of its formation and reactions. Such a study might be relevant, as well, to previous investigations in other systems. Metalation of the anancomeric 1,3-dithiane derivative **13** (with *n*-butyllithium) proceeds with a slight preference for abstraction of the equatorial proton at C(2) (k_{eq}/k_{ax} = 8.6 ± 1.3). The reactions of the lithio derivative are highly stereoselective, proceeding with >99% equatorial attack by DCl, methyl iodide, and carbonyl compounds.[3] With the cyclic sulfoxides *cis*- (**14**) and *trans*-4-*tert*-butylthiane 1-oxide (**15**),



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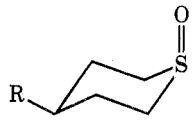
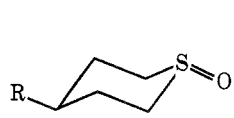


14, R = $(CH_3)_3C$
16, R = C_6H_5



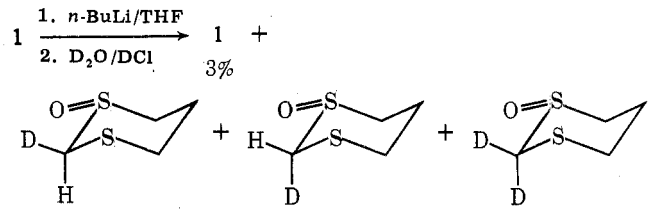
15, R = $(CH_3)_3C$
17, R = C_6H_5

the stereoselectivity of anion reactions is influenced by the configuration of the sulfoxide group. Methylation of the 2-lithio derivative of **14** occurs from the axial direction, and that of **15** from the equatorial direction; i.e., both reactions introduce a methyl group trans to the sulfoxide oxygen.[4] The rates of hydrogen-deuterium exchange have been determined for *cis*- (**16**) and *trans*-4-phenylthiane 1-oxide (**17**).[5] In **16**, the C(2) axial proton exchanges eight times faster than the C(2) equatorial proton in methanol or water. In **17**, the C(2) equatorial proton exchanges about 60 times faster than the C(2) axial proton.

In acyclic sulfoxides, such as benzyl methyl sulfoxide ($PhCH_2S(O)CH_3$), the diastereotopic methylene protons exchange at different rates.[6,7] The lithio derivative prepared by metalation exhibits different stereochemical courses on reaction with DCl (retention) and with methyl iodide (inversion).[8]

Results

Preliminary studies indicated that metalation of **1** with *n*-butyllithium in tetrahydrofuran was complete within 15 min at −50 to −70 °C. Direct quenching of the lithio derivative with DCl in D_2O was apparently accompanied by intermolecular exchange processes since the isolated product contained about 20% of dideuterated material under these conditions. Accordingly, the results given in eq 1 are for "inverse

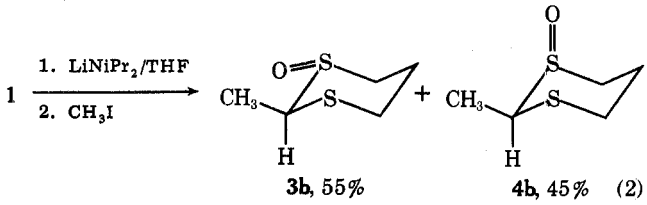


7a, 19% **7b**, 77% **18**, 1% (1)

quenching" wherein a solution of **12** was added to a cooled solution of D_2O–DCl in tetrahydrofuran. Isotopic compositions were determined by mass spectrometry[9] and the stereoselectivity determined by NMR analysis of the signals corresponding to the C(2) axial and equatorial protons at 3.64 and 4.02 ppm, respectively.[10] The ratio of axial to equatorial deuterium incorporation was 4:1.

When the hydrogen–deuterium exchange of **1** was carried out in methanol-O-*d* containing 0.08 M sodium methoxide, no selectivity was observed. A mixture containing 26% **1**, 28% **7a**, 28% **7b**, and 18% **18** resulted.

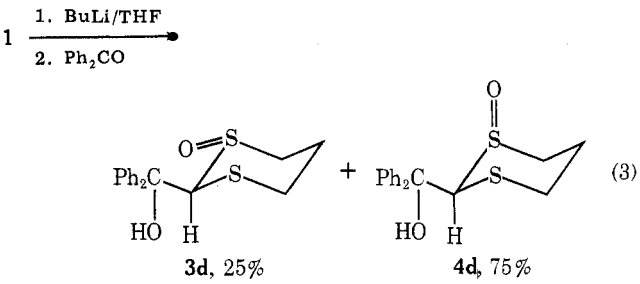
Methylation of **12** (generated by metalation of **1** with lithium diisopropylamide in tetrahydrofuran) with methyl iodide at −60 °C gave a mixture determined by liquid chromatography[11] to consist of 55% *trans*- (**3b**) and 45% *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**) (eq 2). Isolation of the pure products



3b, 55% **4b**, 45% (2)

by preparative TLC gave **3b** in 50% yield and **4b** in 40% yield, confirming the ratio obtained by LC analysis and demonstrating >90% conversion.[12]

Reaction of **12** with benzophenone afforded a mixture of the diastereomeric tertiary alcohols **3d** and **4d** (eq 3). The ratio



(3)

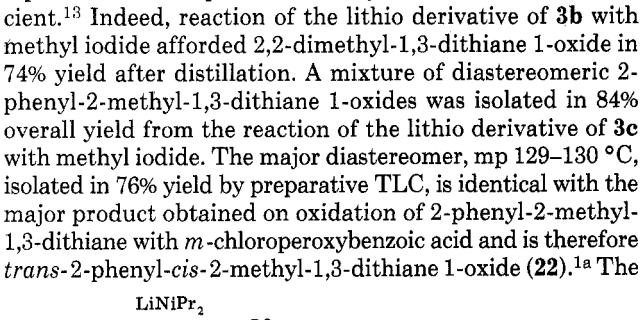
3d, 25% **4d**, 75%

was temperature dependent, with the cis compound **4d** dominating by 3:1 at −70 °C (NMR analysis). If the reaction mixture was allowed to stand at 25 °C for 1 h prior to workup, then the **4d**:**3d** ratio decreased to 1:1.

Metalation of 2-substituted 1,3-dithiane 1-oxides is more efficient with lithium diisopropylamide than with *n*-butyllithium. When the lithio derivatives of *trans*- (**3b**) or *cis*-2-methyl-1,3-dithiane 1-oxides were prepared in this way and quenched with HCl, identical (within experimental error) mixtures of **3b** and **4b** were produced. LC analysis indicated a **3b**:**4b** ratio of 88:12 from **3b** and 91:9 from **4b.** Thus, it appears that **3b** and **4b** produce the same lithio derivative (**19**) on metalation. Protonation of this lithio derivative occurs preferentially cis to the sulfoxide oxygen, as was the case with **12,** but with slightly greater stereoselectivity.

Highly stereoselective protonation of 2-lithio-2-phenyl-1,3-dithiane 1-oxide (**20**) was observed. Metalation of *trans*-2-phenyl-*cis*-2-deuterio-1,3-dithiane 1-oxide (**21**) with lithium diisopropylamide in tetrahydrofuran at −68 °C, followed by addition of aqueous HCl, gave **3c** as the exclusive product in quantitative yield. Under equilibrium conditions (0.008 M sodium methoxide in refluxing methanol), and starting with either pure **3c** or its cis diastereomer **4c,** the **3c**/**4c** ratio as determined by LC was 89:11.

The ready metalation of 2-substituted 1,3-dithiane 1-oxides, indicated by these experiments, suggested the possibility of preparing 2,2-disubstituted 1,3-dithiane 1-oxides in spite of a previous brief report that dialkylation of **1** was not efficient.[13] Indeed, reaction of the lithio derivative of **3b** with methyl iodide afforded 2,2-dimethyl-1,3-dithiane 1-oxide in 74% yield after distillation. A mixture of diastereomeric 2-phenyl-2-methyl-1,3-dithiane 1-oxides was isolated in 84% overall yield from the reaction of the lithio derivative of **3c** with methyl iodide. The major diastereomer, mp 129–130 °C, isolated in 76% yield by preparative TLC, is identical with the major product obtained on oxidation of 2-phenyl-2-methyl-1,3-dithiane with *m*-chloroperoxybenzoic acid and is therefore *trans*-2-phenyl-*cis*-2-methyl-1,3-dithiane 1-oxide (**22**).[1a] The



22 **23**

minor product, *cis*-2-phenyl-*trans*-2-methyl-1,3-dithiane 1-oxide (**23,** mp 89–90.5 °C), was isolated in 8% yield. In a separate methylation experiment, LC analysis of the crude reaction mixture gave a **22**:**23** ratio of 84:16. An almost identical **22**:**23** ratio of 86:14 was obtained on metalation–methylation of **4c,** but the conversion was low (41%).

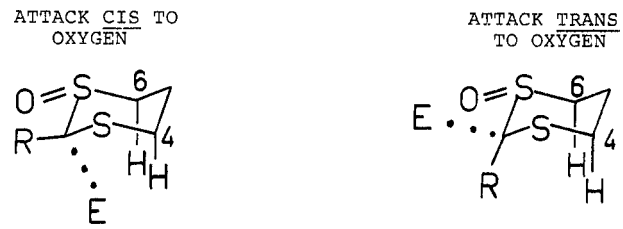


Figure 1. Representations of transition state geometries for electrophilic attack on anionic species derived from 1,3-dithiane 1-oxide.

The stereoselectivity of the metalation step was also considered. The kinetic preference for abstraction of the C(2) equatorial vs. C(2) axial proton in **1** can readily be determined through the use of the stereospecifically deuterated substrates **7a** and **7b.**[3,14] Metalation of **7a** and **7b,** in separate experiments, followed by reaction with methyl iodide and mass spectrometric analysis of the extent of deuterium retention in the methylated product, permits the selectivity factor (k_{eq}/k_{ax}) and the isotope effect (k_H/k_D) to be calculated[3] (see Experimental Section for details). The selectivity factor favoring equatorial proton abstraction was determined to be 2.7 and the isotope effect k_H/k_D to be 1.1.

Discussion

As measured by their relative ease of abstraction by lithium diisopropylamide, the diastereotopic protons at C(2) in **1** do not differ greatly in kinetic acidity. An apparent selectivity factor k_{eq}/k_{ax} = 2.7 was determined. This measurement is subject to the reservation that **1** exists as an 86:14 mixture of two conformations which may exhibit different selectivities for a pair of diastereotopic protons in two different environments. The low apparent selectivity may reflect a leveling effect associated with the enhanced acidity of this system relative to systems in which the anion is stabilized to a lesser degree, e.g., **13–17.**

The stereoselectivity of the reactions of lithiated 1,3-dithiane 1-oxides is dependent upon the attacking electrophile and the substituent already present at C(2). The reactions are not stereospecific. The same product mixtures are obtained irrespective of which diastereomer of a 2-substituted 1,3-dithiane 1-oxide is used. Reactive electrophiles (DCl, benzophenone) attack 2-lithio-1,3-dithiane 1-oxide (**12**) cis, in preference to trans, to the sulfoxide oxygen by a factor of 3–4:1. The preference for protonation (or deuteration) increases to 8–10:1 when a methyl group is present at C(2) as in the lithio derivatives of **3b** and **4b,** and to >20:1 in the lithio derivative of **3c.**

The ground-state geometry at C(2) in **12** and related lithio derivatives,[15] as well as the extent of ion pairing and aggregation, is not known. These factors clearly play a role in determining the intrinsic preference for attack cis to sulfoxide oxygen. A steric model such as outlined in Figure 1, however, suffices quite well to rationalize the observed *trends* in stereoselectivity. The geometry at C(2) in the transition state must be more congested than in the ground state, and so both the attacking electrophile and the substituent at C(2) will alter the "normal" preference for attack cis to oxygen. A C(2) substituent will increase the tendency toward attack cis to oxygen because the energy of the transition state for attack trans to oxygen is raised to the extent that the substituent approaches an axial orientation. The increased stereoselectivities observed when R = CH_3 and R = Ph are in accord with this analysis. When the electrophilic reagent is less reactive, such as methyl iodide, the transition state is reached later and requires a more highly developed covalent interaction between

C(2) and the electrophile. The interactions between an attacking methyl iodide molecule and the syn-axial hydrogens at C(4) and C(6) oppose the "normal" mode of attack and increase the fraction of product in which the incoming group (methyl) is trans to oxygen. When R = H, the ratio of cis/trans attack is 45:55 (vs. 4:1 for deuteration). When R = Ph, it is 84:16 (vs. >20:1 for protonation).

For simplicity, only the conformation of the lithio derivatives having the sulfoxide oxygen equatorial was considered in the preceding analysis and the transition state models represented in Figure 1. The alternative conformation of the lithio derivatives in which the sulfoxide oxygen is axial could be significant if (a) the conformational equilibrium between the lithio derivatives deviated significantly from that of the precursors, or (b) the sulfoxide oxygen-axial conformation is attacked by electrophilic reagents much faster than the sulfoxide oxygen-equatorial conformation. The internal consistency of the results indicates that neither of these possibilities is very likely. For example, if the "reacting conformation" had the sulfoxide oxygen axial (or approximately axial) it is difficult to understand why the tendency for methylation cis to oxygen would *increase* from 45% in **12** (R = H) to 84% in **20** (R = Ph) where a phenyl group moves toward an axial site in the transition state. Similarly, the fact that protonation of the lithio derivative **20** gives a **3c**:**4c** ratio significantly in excess of that at equilibrium (>20:1 vs. 89:11) argues against the importance of conformations of the lithio derivative in which the oxygen-axial:oxygen-equatorial energy relationship is reversed from that of **3c** itself.

In conclusion, the stereoselectivity of the reactions of 2-lithio-1,3-dithiane 1-oxide and its analogues with electrophilic reagents can be understood as a combination of an intrinsic preference for attack cis to the sulfoxide oxygen and steric effects of a conventional type. These include syn-axial repulsions between the C(2) substituent and the C(4) and C(6) axial protons in the transition state and van der Waals repulsions between the electrophile and the C(4) and C(6) axial protons. The intrinsic preference for attack cis to sulfoxide oxygen is not high and provides little in the way of an answer to the continuing question of the preferred geometry of sulfinyl carbanions.

Experimental Section

The general experimental information and listing of the instruments used is identical with that of the preceding paper. All reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran and diisopropylamine were distilled from calcium hydride. *n*-Butyllithium in *n*-hexane was purchased from Alfa Inorganics and its concentration determined by the double titration method of Gilman using 1,2-dibromoethane.[16] Deuterium oxide (99.7%) and 20% DCl in D_2O (99$^+$ atom % D) were purchased from Diaprep.

1,3-Dithiane 1-Oxide (1). The procedure of Carlson[2] involving sodium metaperiodate oxidation of 1,3-dithiane was followed to afford 1 in yields corresponding to those reported. For larger scale preparations it is more economical to use hydrogen peroxide in acetic anhydride. To 12.4 g (0.1 mol of 97% pure material) of 1,3-dithiane in 200 ml of acetic anhydride cooled to −15 °C was slowly added 8.6 ml (0.1 mol) of 30% hydrogen peroxide. The solution was stirred for 1 h at −15 °C, allowed to stand at room temperature for 36 h, and evaporated at 25 °C under vacuum, and the residue recrystallized from dichloromethane–cyclohexane to afford 8.3 g (61%) of **1**, mp 88–89.5 °C (reported[2] 87–88 °C). Mass spectrometric analysis indicated that no sulfone or disulfoxide was present.

General Procedure for Metalation of 1,3-Dithiane 1-Oxide (1). A. With *n*-Butyllithium. A solution of 1 in purified tetrahydrofuran (7 ml/mmol of 1) was cooled to −70 °C and a solution of *n*-butyllithium in *n*-hexane (1 equiv) added. The resulting yellow solution was stirred at −70 °C for 15 min to ensure complete metalation.

B. With Lithium Diisopropylamide. Lithium diisopropylamide was prepared by adding *n*-butyllithium (1.1 equiv) in *n*-hexane to a cooled (−30 to −40 °C) solution of diisopropylamine (1.5 equiv) in tetrahydrofuran (7 ml/mmol of 1). The reaction mixture was permitted to warm to ca. 0 °C, then cooled to −60 °C and a solution of 1 in tetrahydrofuran (5 ml/mmol) added rapidly. The pale yellow solution was stirred at −60 °C for 20 min to complete the metalation. This metalation procedure was found to be cleaner and more generally useful than that using *n*-butyllithium.[17]

Deuteration of 2-Lithio-1,3-dithiane 1-Oxide (12). The metalation of 136 mg (1 mmol) of 1,3-dithiane 1-oxide (1) was performed as described in A. The solution of the lithio derivative was then added, using a syringe, to a cooled (bath temperature −70 °C) mixture of 0.85 ml of 20% DCl in D_2O and 2–3 ml of tetrahydrofuran. After stirring for ca. 3 min, solid sodium carbonate was added and the mixture allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (30 ml), washed with water, brine, and dried with potassium carbonate. The residue after evaporation (74 mg, 54%) was purified by preparative TLC to afford 38 mg of 1,3-dithiane-1-oxide (mp 83–87 °C). Mass spectral analysis at 15 eV and an inlet temperature of 100 °C gave an isotopic composition of 3% d_0, 96% d_1, and 1% d_2. The stereoselectivity of deuteration was determined by NMR analysis at 100 MHz in $CDCl_3$ and found, from the 4:1 ratio of the integrated intensity of the equatorial proton at C-2 to the axial proton at C(2), to be 80% axial deuterium to 20% equatorial deuterium.

Hydrogen–Deuterium Exchange of 1 in CH_3OD. A solution of 50 mg (0.37 mmol) of 1 in 0.5 ml of methanol-*O*-*d* containing 2 mg (0.04 mmol) of sodium methoxide was allowed to stand at 25 °C for 47 h, then diluted with D_2O, brine added, and extracted with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated to leave 38 mg (76%) of white solid, mp 88.5–89.5 °C. NMR and mass spectral analysis established the composition as 26% **1**, 28% **7a**, 28% **7b**, and 18% **18**.

Methylation of 1. Metalation of 272 mg (2.0 mmol) of 1 was effected using procedure B. Iodomethane (0.65 ml, 10 mmol) was added, and the solution stirred for 20 min at −60 °C and allowed to warm to room temperature. Water was added and the tetrahydrofuran removed by evaporation. Brine was added to the residue, and the product extracted with chloroform (2 × 25 ml). The organic phase was dried and the solvent evaporated. The crude product (307 mg) was examined by liquid chromatography, using standard solutions of **4b**, **3b**, and **1** fo calibration. These materials had retention times of 9.8, 11.5, and 10.9 min, respectively. The product mixture was found to consist of 55% *trans*-2-methyl-1,3-dithiane 1-oxide (**3b**) and 45% *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). No starting material was detected.

In order to confirm the above analytical results, the components of the reaction mixture were isolated by preparative TLC on silica gel using carbon tetrachloride–2-propanol (3:1) as developing solvent. The higher R_f band afforded 149.2 mg (50%) of **3b**, mp 91–92.5 °C. Recrystallization from ether and a trace of dichloromethane gave fine white needles melting at 94–95 °C (lit.[2] mp 93–94 °C). From the lower R_f band was obtained 121.7 mg (40%) of crude **4b**, mp 41–51 °C. Recrystallization from ether and a trace of dichloromethane gave white crystals, mp 58–60.5 °C. The trans/cis ratio of isolated materials was 55:45, in excellent agreement with the analytical result.

Reaction of 2-Lithio-1,3-dithiane 1-Oxide with Benzophenone. Lithiation of 272 mg (2.0 mmol) of 1 was effected using procedure A. The solution of **12** was treated with 364 mg (2.0 mmol) of benzophenone and stirred at −70 °C for 0.5 h. A solution of hydrochloric acid (1 ml, 20%) in 2 ml of tetrahydrofuran was added. Solid sodium carbonate was then added and the solution allowed to warm to room temperature and worked up in the usual manner. The crude product was a white solid (668 mg), mp 154–164 °C, which appeared from its NMR spectrum to be a 3:1 mixture of *cis*-2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxide (**4d**) and *trans*-2-(diphenylhydroxmethyl)-1,3-dithiane 1-oxide (**3d**).

Recrystallization from dichloromethane–ether afforded 333 mg (54%) of **4d**, mp 155–157 °C dec (reported[2] mp 155–156 °C dec). The NMR and ir spectra were identical with those of the adduct of undefined stereochemistry reported previously.[2] Assay by NMR indicated that **4d** was the only isomer present.

Determination of Stereoselectivity of Metalation Step. The methylation of *trans*-2-deuterio- (**7a**) and *cis*-2-deuterio-1,3-dithiane 1-oxide (**7b**) was carried out on a 1.5-mmol scale using procedure B.[18] The mixture of **3b** and **4b** obtained was analyzed for deuterium content by mass spectrometry at 15 eV. The deuterium incorporation data are presented in Table I. The selectivity factor (k_{eq}/k_{ax}) and isotope effect (k_H/k_D) are related by the equations below.

For the product from **7b**

$$\frac{d_1}{d_0} = (k_{eq}/k_{ax})(k_H/k_D)$$

Table I. Deuterium Retention in Methylated Products Obtained from *cis*- and *trans*-2-Deuterio-1,3-dithiane 1-Oxides

Run	Starting material	Isotopic composition of product, %[a] d_0	d_1
1	Cis (**7b**)[b]	32.3	67.7
2	Cis (**7b**)[b]	17.6	82.4
	Av	25.0	75.0
3	Trans (**7a**)[c]	67.8	32.2
4	Trans (**7a**)[d]	74.4	25.6
	Av	71.1	28.9

[a] Corrected for d_0, d_1, d_2 composition of starting material. [b] 1.34% d_0, 98.3% d_1, 0.4% d_2. [c] 6.12% d_0, 93.4% d_1, 0.4% d_2. [d] 12.67% d_0, 87.33% d_1.

For the product from **7a**

$$\frac{d_1}{d_0} = \frac{(k_H/k_D)}{(k_{eq}/k_{ax})}$$

then

$$\frac{75.0}{25.0} = (k_{eq}/k_{ax})(k_H/k_D)$$

and

$$\frac{28.9}{71.1} = \frac{(k_H/k_D)}{(k_{eq}/k_{ax})}$$

which gives

$$k_{eq}/k_{ax} = 2.7$$

$$k_H/k_D = 1.1$$

In runs 2 and 4, the cis- and trans-methylated products **4b** and **3b** were separated and analyzed for deuterium content independently. For run 2, the **4b** obtained was 15.9% d_0, 84.1% d_1; the **3b** was 22.3% d_0 and 77.7% d_1. For run 4, the **4b** obtained was 71.9% d_0, 28.1% d_1; the **3b** was 72.1% d_0 and 27.9% d_1.

Generation and Protonation of 2-Lithio-2-methyl-1,3-dithiane 1-Oxide (19). The metalation was carried out as described in procedure B, the reaction mixture stirred at −45 to −65 °C for 7 h and quenched at −60 °C with 20% hydrochloric acid. After workup in the usual way, the reaction mixture was analyzed by liquid chromatography. The product from *trans*-2-methyl-1,3-dithiane 1-oxide (**3b**) was an 89:11 mixture of **3b** and *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). The product from **4b** was a 91:9 mixture of **3b** and **4b**.

Methylation of *trans*-2-Methyl-1,3-dithiane 1-Oxide (3b). Metalation of 1.00 g (6.67 mmol) of **3b** was carried out using procedure B and the resulting solution treated with 1.0 ml (16.1 mmol) of iodomethane at −55 °C. The solution was warmed to room temperature and quenched with water and the solvent removed by evaporation. The residue was partitioned between brine and chloroform, and the chloroform removed to leave a yellow oil which was then distilled. The 2,2-dimethyl-1,3-dithiane 1-oxide was collected as a colorless liquid (808 mg, 74%) at 90–91 °C (0.09 Torr) [lit.[10] bp 98–100 °C (0.15 Torr)]. The NMR spectrum corresponded to that reported,[10] with methyl signals at δ 1.62 and 1.56 ppm.

Equilibration of *trans*- (3c) and *cis*-2-Phenyl-1,3-dithiane 1-Oxide (4c). A methanol (25 ml) solution containing 99.6 mg (0.47 mmol) of **3c** and 0.106 mmol of sodium methoxide was stirred at room temperature for 21 h. No appreciable change had occurred; so an additional 0.104 mmol of sodium methoxide was added and the solution refluxed for 5 h. The reaction mixture was allowed to cool, methanol removed in vacuo, and the residue partitioned between 10 ml of saturated ammonium chloride and 10 ml of dichloromethane. Layers were separated and the aqueous layer extracted with a second 10-ml portion of dichloromethane. Combined dichloromethane solutions were dried over sodium sulfate. Removal of solvent gave 95.1 mg of white solid, mp 136.5–139.5 °C, which was analyzed by LC. The material was found to consist of 89.6% **3c** and 10.4% **4c**.

In a similar fashion, 57.5 mg (0.271 mmol) of **4c** was treated with sodium methoxide in methanol. The equilibrium mixture was determined to consist of 89.0% **3c** and 11.0% **4c**.

Metalation and Protonation of *trans*-2-Phenyl-*cis*-2-deuterio-1,3-dithiane 1-Oxide (21). Lithiation of 320 mg (1.5 mmol) of **21** was carried out according to procedure B. The reaction mixture was quenched with 20% hydrochloric acid, and after 5 min, solid sodium carbonate (398 mg) was added, and the mixture allowed to warm to room temperature. The reaction mixture was worked up as usual, and 319 mg of yellowish-white solid (mp 142–145 °C) was isolated. The NMR spectrum of this material confirmed a quantitative yield of **3c**.

Methylation of *trans*-2-Phenyl-1,3-dithiane 1-Oxide (3c). Lithiation of 637 mg (3.0 mmol) of **3c** by procedure B followed by treatment with 0.75 ml (12 mmol) of methyl iodide gave a solution which, after warming from −60 °C to room temperature, was quenched with 10 ml of water. The tetrahydrofuran was removed under vacuum. To the residue were added 50 ml of brine and 50 ml of chloroform. The layers were separated, and the aqueous layer extracted with an additional 50 ml of chloroform. The combined chloroform layers were dried over sodium sulfate. Evaporation of the solvent gave 672 mg of crude product. Recrystallization from 2-propanol and preparative TLC (silica gel; 20% 2-propanol/carbon tetrachloride) of material remaining in the mother liquor yielded 516.4 mg (76%) of *trans*-2-phenyl-*cis*-2-methyl-1,3-dithiane 1-oxide (**22**), mp 126.5–129 °C, and 53.4 mg (7.9%) of *cis*-2-phenyl-*trans*-2-methyl-1,3-dithiane 1-oxide (**23**), mp 86.5–88 °C. Recrystallization of crude **22** from dichloromethane–ether gave the analytical sample as long, white needles: mp 129–130 °C; NMR ($CDCl_3$) δ 1.87 (s, 3, CH_3), 2.0–2.9 (m, 6, dithiane ring protons), 7.2–7.45 (m, 3, meta and para aromatic protons), 7.45–7.7 (m, 2, ortho protons); mass spectrum *m/e* (rel intensity) 226 (27), 121 (100), 193 (65), 77 (73).

Anal. Calcd for $C_{11}H_{14}S_2O$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.31; H, 6.26; S, 28.22.

Recrystallization of crude **23** from cyclohexane gave the analytical sample: mp 89–90.5 °C; NMR ($CDCl_3$) δ 1.88 (s, 3, CH_3), 2.1–3.0 (m, 6, dithiane ring protons), 7.27 (apparent t, 3, meta and para aromatic protons), 7.87 (doublet of doublets, 2, ortho protons); mass spectrum *m/e* (rel intensity) 226 (20), 121 (100), 103 (64), 77 (80).

Anal. Calcd for $C_{11}H_{14}S_2O$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.23; H, 6.29; S, 28.28.

Following the same procedure, 202 mg (0.95 mmol) of **3c** was converted to 223 mg of crude product. Analysis by LC gave the composition as 84% **22** and 16% **23**. The retention times were 8.0 min for **22** and 5.7 min for **23**. Isolation of the products by preparative TLC on silica gel using 4:1 carbon tetrachloride/2-propanol gave 24 mg (11%) of **23**, mp 84–86 °C, and 138 mg (64%) of **22**, mp 129.5–130.5 °C.

Methylation of *cis*-2-Phenyl-1,3-dithiane 1-Oxide (4c). The procedure was identical with that of the above experiment and afforded, from 105 mg (0.5 mmol) of **4c**, 107 mg of whit solid. The NMR spectrum of this material indicated that the alkylation was only about 41% complete. The product was determined to consist of 86% **22** and 14% **23** (LC analysis).

Oxidation of 2-Phenyl-2-methyl-1,3-dithiane (24). The oxidation of **24**[18] (3.16 g, 15 mmol) with *m*-chloroperoxybenzoic acid was carried out as described in the accompanying paper.[1a] The crude product (3.40 g, 97%), mp 124–132 °C, had an NMR spectrum virtually identical with that of the product mixture obtained on methylation of **3c**. Analysis by liquid chromatography indicated a composition of 89% **22** and 11% **23**.

Attempted oxidation of **24** with sodium metaperiodate in aqueous methanol was accompanied by extensive hydrolysis to acetophenone as indicated by the NMR spectrum of the crude product.

Registry No.—**1**, 16487-10-8; **3b**, 60349-75-9; **3c**, 60349-76-0; **3d**, 60349-77-1; **4b**, 60349-78-2; **4c**, 60349-79-3; **4d**, 60349-80-6; **7a**, 60349-84-0; **7b**, 60349-85-1; **12**, 60349-88-4; **18**, 60349-89-5; **19**, 60349-90-8; **21**, 60349-91-9; **22**, 60349-92-0; **23**, 60349-93-1; **24**, 6331-22-2; butyllithium, 109-72-8; lithium diisopropylamide, 4111-54-0; benzophenone, 119-61-9; 2,2-dimethyl-1,3-dithiane 1-oxide, 41893-06-5.

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

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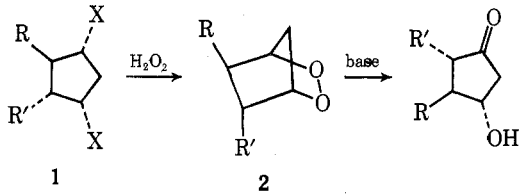
Mixed peroxides containing the *tert*-butyl group and secondary or primary alkyl groups are easily prepared under exceptionally mild conditions by reaction of primary or secondary trifluoromethanesulfonates with either potassium *tert*-butyl peroxide (method I) or with *tert*-butyl hydroperoxide in the 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



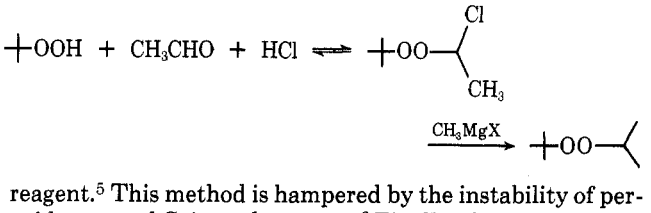
1 2

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