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Evidence from X-ray Crystallography for the Diequatorial Disposition of a Five-Membered Ring in a Sulfurane[1]

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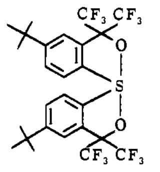
Abstract: The crystal and molecular structure of 1,1-bis[1,1,1,3,3,3-hexafluoro-2-phenyl-2-propanolato]-5-methyl-3,3-bis(trifluoromethyl)[3*H*-2,1-benzoxathiole], trialkoxysulfurane **8**, was solved by X-ray crystallographic techniques. The compound crystallizes in space group $P2_12_12_1$ of the orthorhombic system with four molecules in a cell of dimensions a = 19.74 (3), b = 14.20 (2), c = 10.74 (1) Å. The X-ray structure analysis (R = 0.099) reveals trigonal bipyramidal geometry around sulfur similar to structures previously determined for other sulfuranes. The five-membered ring including the sulfur atom is, however, clearly in the diequatorial orientation, **8**. The axial S–O bond lengths are 1.840 (10) and 1.829 (10) Å while the equatorial S–O and S–C bond lengths are 1.630 (9) and 1.777 (14) Å, respectively. The equatorial C–S–O angle is 95.0 (6)° while the O(apical)–S–O(apical) angle is 172.0 (4)° (bent away from the lone pair of electrons on sulfur). Observations are made concerning the relationship of structure with reactivity of **8**.

Introduction

The X-ray structures of a number of sulfuranes having two five-membered rings, compounds **1–5**, have been reported.[2-5] In all of these cases, approximate trigonal bipyramidal geometry is observed around the sulfur atom and the five-membered rings have always been observed to be in the axial–equatorial orientation. Arguments have been advanced from a nuclear magnetic resonance spectral study[6] of **6** and from an infrared study[7] of **7** which support the axial–equatorial orientation of the five-membered ring for these compounds. The proton ortho to sulfur in the fused-ring system linked by apical and equatorial bonds to sulfur in compounds such as **6** and **7** is held very near the apical S–X bond linking the monodentate apical ligand X to sulfur. Much evidence has accumulated to support the generalization that such protons are shifted to very low fields.[8]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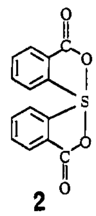
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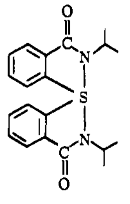
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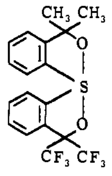
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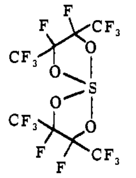
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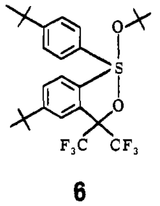
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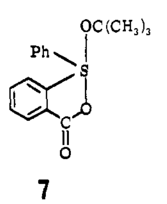
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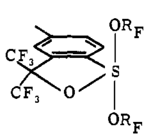
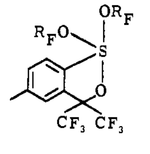
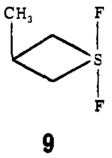
Astrologes and Martin have reported[8] the synthesis and reactions of trialkoxysulfurane **8**. A second covalent structure, **8a**, resembles structure **8** in that both satisfy both the electronegativity rules,[9,10] with apical fluoroalkoxy ligands, and the stricture against diapical linkage of five-membered rings. A nuclear magnetic resonance spectrum of the compound reveals an upfield shift of the proton ortho to the sulfur atom in the fused-ring system related to the ortho-proton resonances of other sulfuranes studied.[8,11] This has been interpreted[8] in terms of a preference for the geometry (**8**) with a diequatorial five-membered ring.


8, R_F = OC(CF$_3$)$_2$C$_6$H$_5$


8a

Denny has shown[12] from NMR evidence that difluorosulfurane **9** exists in a conformation with a diequatorial four-membered ring. In this case the preference for the geometry **9** with two apical fluorines over that (**10**) with one apical car-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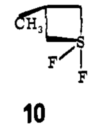
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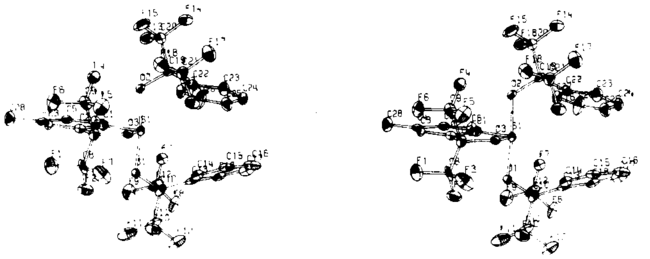


Figure 1. Stereoscopic view of a single molecule of **8**.

bon can be explained on grounds of the greater apicophilicity of fluorine. No such factor is operative in the choice between **8** and **8a** since both structures have two very similar fluoroalkoxy ligands. It was therefore considered important to get firmer evidence upon which to base a choice between conformations **8** and **8a**.

An X-ray structure determination was undertaken to help resolve this question, as well as to examine the geometry as a possible source of new insights into the bonding and reactivity patterns observed for such species.

Experimental Section

Sulfurane **8** was recrystallized from ether-pentane utilizing a previously described[13] glass apparatus. A single crystal of approximate dimensions 0.5 × 0.5 × 0.3 mm was selected and wedged in a 0.5-mm thin-walled glass capillary which was sealed under a dry nitrogen atmosphere. This precaution was necessary to protect the crystal from moisture.

Crystal Data for 8. $C_{28}H_{16}F_{18}O_3S$, mol wt = 774.48, orthorhombic, a = 19.74 (3) Å, b = 14.20 (2) Å, c = 10.74 (1) Å, V = 3010.5 Å, Z = 4, ρ_{calcd} = 1.71 g cm^{-3}, $F(000)$ = 1544, μ (Cu Kα) = 23.3 cm^{-1}, systematic absences for $h00$ when $h = 2n + 1$, for $0k0$ when $k = 2n + 1$, and for $00l$ when $l = 2n + 1$ establish the space group as $P2_12_12_1$. The cell dimensions were obtained by a least-squares fit to be automatically centered setting for 13 reflections on a Syntex P2$_1$ diffractometer equipped with a graphite monochromator: λ(Cu Kα_1) = 1.541 78 Å.

Solution and Refinement of the Structure of 8. Intensity data were collected using a 2θ scan mode with relatively fast variable scan speeds (5.0-15.0°/min) with the total background time/scan time set at 0.5. The fast 2θ scan mode was chosen to minimize crystal decomposition during data collection. Three standards from different parts of the reciprocal space were monitored every 50 reflections. By the end of the data collection, the standards had deviated from initial values from a 2% drop in intensity to a 6% increase in intensity. The hkl octant was collected out to 2θ = 130° ($\sin \theta/\lambda$ = 0.588). Out of the possible 2900 unique reflections collected, 1923 (66.3%) were observed using a 2σ criterion based on counting statistics. The data were corrected for Lorentz and polarization effects, but not for absorption.

A version of the direct methods program MULTAN[14] served to locate the sulfur atom and six other atoms in an E map. Sixteen successive Fourier maps revealed the remainder of the nonhydrogen atoms. Refinement was carried out using the Gauss-Seidel blocked-diagonal least-squares program supplied by Syntex.[15] Full-matrix least-squares refinement did not proceed normally, possibly owing to the large number of atoms involved. The hydrogens could not be reliably located from difference maps. Those on the benzene rings were calculated at the theoretical positions while none are given for the methyl group (C(28)). Blocked-diagonal least-squares refinement of the positional and anisotropic thermal parameters for the nonhydrogen atoms while holding the positions and isotropic thermal parameters of the hydrogen atoms constant converged with values for R and R_w of 0.099 and 0.102, respectively.[16] The weights were taken as $1/(\sigma(F_o)^2 + (0.02F_o)^2)$, where $\sigma(F_o)$ is the standard deviation based on counting statistics. The final value of $[\sum w(|F_o| - |F_c|)^2/(m - n)]^{1/2}$, where m is the number of observations and n is the number of variables, was 2.68. A final difference map showed peaks corresponding to 70% of the electron density observed for an average hydrogen atom between S(1) and O(3). The rest of the peaks were less than 50% of an average hydrogen. The scattering curves were taken from the analytical expression used in the "International Tables of X-ray Crystallography".[17] The final values of the atomic coordinates[18] are given in Table I in the microfilm edition (see paragraph at end of paper regarding supplementary material).

Table II. Selected Bond Lengths and Angles in **8** with Estimated Standard Deviations in Parentheses[a]

	Bond Lengths, Å		
S(1)-O(1)	1.840 (10)	O(1)-C(10)	1.427 (15)
S(1)-O(2)	1.829 (10)	C(10)-C(11)	1.510 (24)
S(1)-O(3)	1.630 (9)	C(8)-F(1)	1.330 (18)
S(1)-C(1)	1.777 (14)	O(2)-C(19)	1.451 (17)
O(3)-C(7)	1.430 (15)	C(19)-C(20)	1.519 (23)
C(7)-C(2)	1.484 (18)	C(19)-C(21)	1.522 (21)
C(1)-C(2)	1.469 (19)	C(19)-C(22)	1.597 (18)
C(2)-C(3)	1.429 (18)	C(8)-F(2)	1.299 (19)
C(3)-C(4)	1.321 (19)	C(8)-F(3)	1.360 (19)
C(4)-C(5)	1.475 (20)	C(9)-F(4)	1.217 (21)
C(5)-C(6)	1.325 (20)	C(9)-F(5)	1.371 (17)
C(1)-C(6)	1.342 (19)	C(9)-F(6)	1.319 (17)
C(4)-C(28)	1.555 (21)		
	Bond Angles, deg		
C(1)-S(1)-O(3)	95.0 (6)	C(8)-C(7)-C(9)	113.8 (12)
C(1)-S(1)-O(1)	89.3 (6)	C(8)-C(7)-O(3)	109.2 (11)
C(1)-S(1)-O(2)	82.8 (6)	C(9)-C(7)-O(3)	104.3 (10)
O(3)-S(1)-O(1)	89.2 (4)	F(1)-C(8)-C(7)	111.3 (13)
O(3)-S(1)-O(2)	92.8 (4)	F(2)-C(8)-C(7)	112.6 (13)
O(1)-S(1)-O(2)	172.0 (4)	F(3)-C(8)-C(7)	110.6 (13)
S(1)-O(1)-C(10)	118.9 (8)	F(1)-C(8)-F(2)	106.1 (13)
S(1)-O(2)-C(19)	120.0 (8)	F(1)-C(8)-F(3)	109.4 (13)
S(1)-O(3)-C(7)	116.3 (8)	F(2)-C(8)-F(3)	106.6 (13)
C(2)-C(7)-C(8)	113.2 (12)	F(4)-C(9)-C(7)	115.6 (13)
C(2)-C(7)-C(9)	107.8 (11)	F(5)-C(9)-C(7)	106.5 (12)
O(3)-C(7)-C(2)	108.0 (10)	F(6)-C(9)-C(7)	110.5 (12)
C(3)-C(2)-C(1)	116.0 (12)	F(4)-C(9)-F(5)	107.1 (13)
C(7)-C(2)-C(1)	113.6 (11)	F(4)-C(9)-F(6)	111.5 (14)
C(2)-C(1)-S(1)	106.9 (10)	F(5)-C(9)-F(6)	104.1 (12)

[a] Complete bond lengths and bond angles may be found in the pages following the text in the microfilm edition.

Results

The X-ray analysis establishes the diequatorial geometry, structure **8**, for the crystalline material, excluding structure **8a**. Some selected[18] bond lengths and bond angles are given in Table II. Figure 1 provides a stereoview of a single molecule and shows the numbering scheme. The root mean square deviation among the 18 C-C (aromatic) bond lengths is 0.021 Å, which is the same as the average standard deviation from least squares for these lengths; this agreement indicates that the effect of systematic errors in the data, such as absorption, is not very important. This observation is also supported among the 18 C-F bond lengths, where the root means square deviation and the average standard deviation from least squares are equal to 0.019 Å.

The configuration about the sulfur atom in trialkoxysulfurane **8** is an approximate trigonal bipyramid. The oxygen atom O(3) and the carbon atom C(1) of the five-membered ring occupy two of the equatorial positions with the C-S-O angle between them being 95.0 (6)°. The third equatorial position is considered to be occupied by the lone pair of electrons.[19,20] The apical positions are occupied by the R_FO ligands (where $R_F = OC(CF_3)_2C_6H_5$). The O_a-S-O_a angle is 172.0 (4)°, with the distortion from linearity in the general direction of the diequatorial five-membered ring and away from the lone pair of electrons. (We will use O_a to refer to an apical oxygen and O_e to refer to an equatorial oxygen.) The O_a-S-C_e angles are 82.8 (6) and 89.3 (6)°, while the O_a-S-O_e angles are 89.2 (4) and 92.8 (4)°.

The six carbon atoms making up each of the phenyl rings are coplanar within the accuracy of the analysis. The five-membered ring with the attached benzene ring and methyl

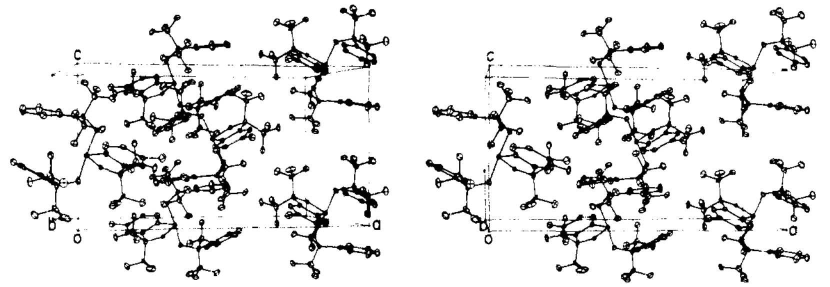


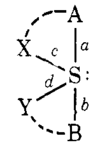
Figure 2. Stereoview of molecular packing for trialkoxysulfurane **8**.

Table III. Intermolecular Contacts <3.40 Å for Nonhydrogen Atoms[a]

F(2)···F(13$^{\mathrm{I}}$)	3.37	F(11)···F(16$^{\mathrm{II}}$)	2.77
F(10)···F(14$^{\mathrm{I}}$)	3.04	C(27)···F(17$^{\mathrm{III}}$)	3.16
F(8)···F(5$^{\mathrm{II}}$)	3.16	C(26)···F(17$^{\mathrm{III}}$)	3.38
F(9)···F(3$^{\mathrm{II}}$)	3.07	F(1)···F(4$^{\mathrm{IV}}$)	2.90
F(11)···F(18$^{\mathrm{II}}$)	3.30		

[a] The Roman numerals as superscripts refer to the equivalent positions, relative to the reference molecule at x, y, z: I = $x, y, -1+z$; II = $-x, -\frac{1}{2}+y, \frac{1}{2}-z$; III = $-x, -\frac{1}{2}+y, 1\frac{1}{2}-z$; IV = $\frac{1}{2}-x, -y, -\frac{1}{2}+z$.

Table IV. Bond Angles (deg) around Sulfur in Sulfuranes Studied by X-ray Diffraction[a]



compd	∠ab[b]	∠cd	ref
12	185.5	108.6	22
1	177.1	108.1	2
	178.2[c]	107.6[c]	
4	177.3	107.9	4b
2	178.5	107.8	3
3	179.8	104.8	4a
5	171.5	104.6	5
11	175.1	104.4	13
8	172.0	95.0	this work

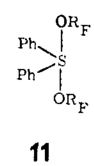
[a] Ligands A and B represent axial ligands while X and Y represent equatorial ligands. [b] The ∠ab is taken along the internal bisector of the X–S–Y plane. [c] These values are for a second independent molecule in the unit cell.

group (S(1), O(3), C(1)–C(6), C(7), and C(28)) forms a reasonably good plane; the atoms C(7) and C(1) are 0.05 Å above and below the plane, respectively, while the other atoms deviate less than 0.03 Å from the plane. The plane defined by the atoms S(1), O(1), and O(2) makes a dihedral angle of 91.0° with the plane defined by the atoms S(1), C(1), and O(3).

There are no short (<3.40 Å) intermolecular contact involving the sulfur atom (Table III). A number of fluorine-fluorine intermolecular contacts are observed, some of which are only slightly longer than the sum of the van der Waals radii (2.70 Å).[21] A stereoscopic view of the unit cell packing is shown in Figure 2.

Discussion

The geometry of trialkoxysulfurane **8** about sulfur may be described as a considerably distorted trigonal bipyramid with the lone pair of electrons "occupying" the third equatorial position.[19,20] The deviation from this ideal geometry as measured by the difference in the angle between the two equatorial bonds (95°) and the 120° of the ideal TBP structure is greater than that for any other sulfurane structure reported[2-5,13,22] (see Table IV). The fact that the two equatorial ligands are included in a five-membered ring must explain the greatly decreased equatorial angle observed for trialkoxysulfurane **8**. An additional consideration is the presence of the highly electronegative oxygen atom in the equatorial plane. The general trend of decreasing equatorial angle with increasing electronegativity of the apical ligands has been noted previously.[13] Chen and Hoffmann[23] have advanced a rationalization of this in terms of molecular orbital theory. The synthesis and characterization of acyclic trialkoxysulfuranes underway in this laboratory may help to resolve the question of the relative importance of the five-membered ring or of the electronegative equatorial atom as the determinant of the observed decrease of the equatorial angle of trialkoxysulfurane **8** relative to all other sulfuranes. The torsion angles as viewed along the axial S–O bonds are shown in Figure 3. The dihedral angle between the plane defined by S(1), O(2), and C(19) and the plane defined by S(1), O(1), and C(10) is 24.5°. The conformation which best avoids[23] interactions of the lone pair of electrons on sulfur with the lone pairs on the oxygen atoms of the OR_F groups is that shown in **13**, which is approximated in the structure of **8**. The preference for such a geometry might also be explained as resulting from a hyperconjugative electron delocalization involving the lone pair p orbital and a σ^*-type skeletal orbital in the equatorial plane. A similar geometry was also observed[13] for the OR_F ligands of acyclic sulfurane **11**.



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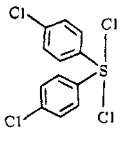

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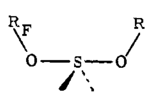
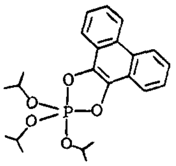


13

A strong preference for axial-equatorial five-membered rings is observed for phosphoranes. Trippett has reviewed[24] pentacovalent phosphoranes and lists free energies of activations (ΔG^*) in the range of 8.9–21.2 kcal for the axial-equatorial five-membered ring undergoing pseudorotation to the diequatorial position. Crystal structures of phosphoranes **14**[25] and **15**,[26] described as having a trigonal bipyramidal and a 15°-turnstile rotation configuration,[27] respectively, show a preference for an approximate axial-equatorial configuration of the five-membered rings.



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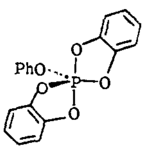


15

Cyclic five-membered-ring phosphate esters have been shown[28] to react 10^6–10^8 times faster than their acyclic

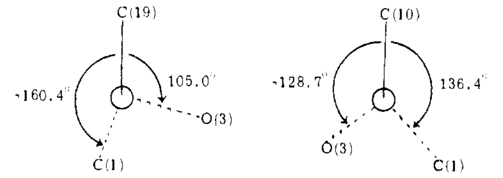
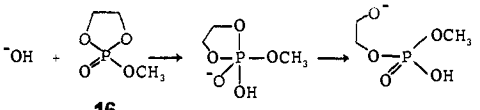


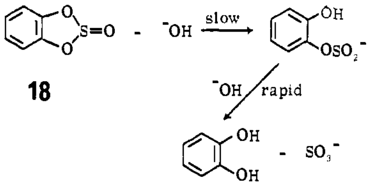
Figure 3. Torsion angles viewed along the axial S–O bonds. The sign of the torsion angle A–B–C–D is considered positive if, when looking along the BC bond, we must rotate atom A clockwise to eclipse atom D.

counterparts. For example, the base hydrolysis of methyl ethylene phosphate (**16**) proceeds 10^6 times faster than for trimethyl phosphate.[29] To explain this increase in rate it is postulated[28a,29,30] that ring strain is relieved in going from phosphate ester **16** to phosphorane **17**. Recently, Gorenstein et al. have reported[31] calculations which suggest that orbital stereoelectronic effects must be considered in addition to the above effect to account for the stabilization of the cyclic vs. the acyclic transition states.



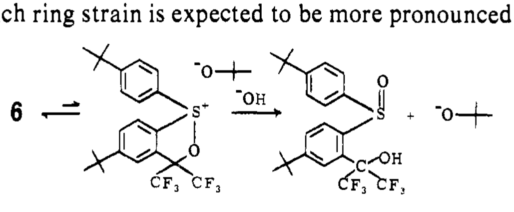
16 **17**

Sulfur-containing esters such as **18** are also observed[32] to react about 10^7 times faster than the corresponding acyclic analogues. Tillet et al.[32b] state, for the hydrolysis of the acyclic sulfites: "In the transition state for hydrolysis, the molecule takes up a more ordered structure and the molecular motion of the alkyl or aryl groups and the larger-ring sulphites are suppressed. This loss of entropy increases the free energy of activation. For the five-membered cyclic sulphites the molecule is already constrained and far less energy is required to reach the transition state, which results in a much lower free energy of activation."



18

For cyclic sulfurane **6**, the reaction with base may be considered[6] as the geometric inverse of the hydrolysis of sulfites or phosphate esters. The stabilization afforded by this "five-membered-ring effect" is a consequence of the preference of the cyclic sulfuranes over the cyclic sulfonium ions (e.g., **19**) in which ring strain is expected to be more pronounced.



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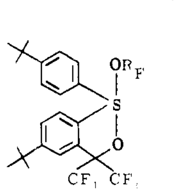
Although the base hydrolysis of trialkoxysulfurane **8** has not as yet been studied, the ligand exchange rates for **8** with R_FOH are reported[8] as roughly nine times slower than that of cyclic sulfurane **20** and five orders of magnitude slower than that of sulfurane **11**. This exchange may involve a dissociative mechanism like that proposed for **11**[33] or **20**.[6] The slowness of this exchange may result, in part, from the action of the substituent effect of the third alkoxy ligand in **8**. It almost certainly also results in part, from the geometrical constraints of the five-membered ring. The conformational choice between **8** and **8a** appears to be resolved in favor of **8**. It is therefore likely that the angle strain in the diequatorial ring, with an angle of 95° at S, is less than in the apical-equatorial ring, with its smaller angle at S. Even if other influences, such as the steric effects of the bulky apical ligands, help to determine the preference for **8** over **8a**, the angle strain in the diequatorial ring must not be much larger than that in the apical-equatorial ring of **8a**. Sulfuranes, unlike phosphoranes, have only two equatorial ligands and the angle between them in acyclic cases (see Table IV) is less than the 120° which is expected for the trigonally hybridized phosphorus of phosphoranes; thus the strain-free equatorial angle at S may be even nearer the ideal for incorporation in a five-membered ring than the 90° apical-equatorial angle.



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Supplementary Material Available: A listing of the final atomic coordinates for **8** (Table I), thermal parameters (Table V), complete bond lengths and angles (Tables VI and VII), and observed and calculated structure factors (Table VIII) (22 pages). Ordering information is given on any current masthead page.

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Desulfurization of Epidithiodioxopiperazines. A Mechanistic and Chiroptical Study

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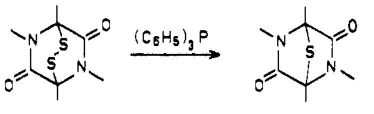
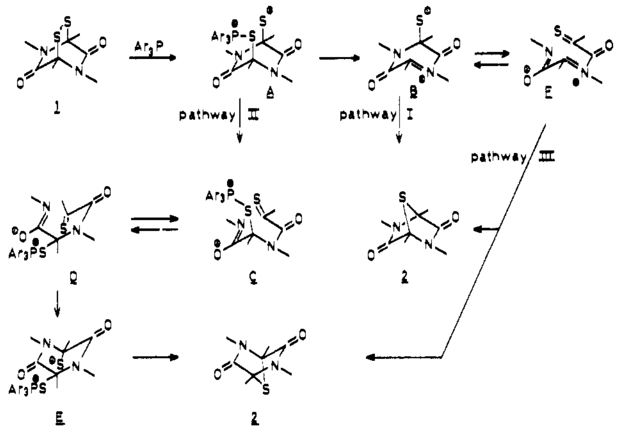
Abstract: The stereochemical course of the desulfurization reaction of the epidithiodioxopiperazine **6** with $(C_6H_5)_3P$ has been studied. The resulting monosulfide **7** has inverted chirality at the bridgehead carbon atoms, as has been established by X-ray analysis. In addition, a novel method is described for the determination of the stereochemistry of this reaction. It is based upon ^1H NMR spectroscopy in the presence of a chiral shift reagent. As the sign of the CD curves of **6** and **7** and the corresponding tri- and tetrasulfides **8** and **9** correlates with the configuration of the bridgehead carbon atoms, it is, at least for these epi(poly)thiodioxopiperazines, a good criterion for their absolute configuration. A mechanism for the desulfurization is proposed, in which the phosphine attacks regiospecifically sulfur atom β of compound **6**, followed by an epimerization of carbon atom C_{9a} through a thiocarbonyl intermediate (Scheme I, pathway II).

The 2,5-epidithiodioxopiperazine system **1** has been found in many natural products that have antiviral, antitumor, and antimicrobial properties as well as high mammalian toxicity.[3] Recently, several syntheses of derivatives of **1** have appeared.[4,5] The desulfurization of **1** into the corresponding monosulfide **2** with $(C_6H_5)_3P$ is a known reaction.[6,7] However, the mechanism of this conversion is not clear, as the stereochemical course is unknown up to now. For a complete description of the reaction at least the relative configurations of the starting material **1** and the reaction product **2** have to be known. On the basis of CD studies, Safe and Taylor[7] proposed that the desulfurization of dehydrogliotoxin, a natural product containing moiety **1**, to the corresponding monosulfide proceeds with inversion of configuration at both the bridgehead carbon atoms of the dioxopiperazine ring. This was suggested because the CD curves of the two compounds showed opposite signs. However, Sammes[8] regarded this as "mechanistically unfeasible", and argued that the CD curves are not comparable. In addition, Sato and Hino[9] treated another derivative of **1** with $(C_6H_5)_3P$ and found a dimeric product. They proposed that an intermediate monosulfide **2** is formed in this reaction with retention of configuration by a S_N1-type mechanism (Scheme I, pathway I). However, this is in contrast with the mechanism which Harpp and Gleason[10] proposed for the conversion of 1,2-dithianes **3** with aminophosphines to the corresponding thiolanes **5** (Scheme II). They found that inversion of configuration occurs at one of the carbon atoms. This was explained by a mechanism in which decomposition of an intermediate phosphonium salt **4** takes place in a S_N2-type manner.



Scheme I



Recently,[11,12] we have developed a method for the resolution of compounds containing moiety **1**, and determined the absolute configurations of the enantiomers of the disulfide **6**, obtained in this way, from their CD spectra. The enantiomer having *R*,*R* chirality has now been used for an investigation of the stereochemical course of the conversion into the corresponding monosulfide.

Absolute Configuration of 7

When **6** was allowed to react with $(C_6H_5)_3P$ in dioxane, the monosulfide **7** was obtained in 93% yield. The CD measure-

Scheme II