Conformational Equilibria in Cyclic Sulfites and Sulfates. The Configurations and Conformations of the Two Isomeric Thiodans[1]

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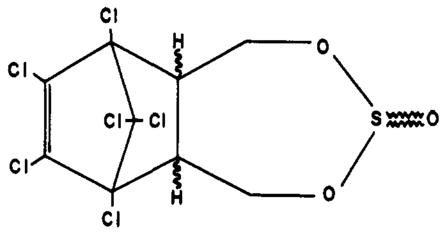
Received July 22, 1964

The configurations and conformations of the lower melting (α) and the higher melting (β) isomers of the commercial insecticide, Thiodan (I), a seven-membered cyclic sulfite attached to a perchlorocyclopentene residue, are found to be XA and XIB, respectively. These assignments are based on a qualitative interpretation of the infrared and nuclear magnetic resonance spectra, followed by a theoretical analysis of the n.m.r. spectra. Our conclusions are contrary to those proposed by previous workers on the basis of dipole moment calculations. Oxidation of either Thiodan isomer with permanganate yields the same cyclic sulfate (V), which is shown to be conformationally mobile.

Although several examples of isomerism in cyclic sulfites arising from the stable pyramidal configuration of sulfite groupings are known,[3] it has often proved difficult to assign a particular configuration and conformation to any one compound. Probably the most complex example studied so far is the commercial insecticide, Thiodan[4] (I), 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,-9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin 3-oxide (for brevity we shall use the trivial name ordinarily found in the literature[3-10]) for which it is possible to draw 24 configurational and conformational isomers.



I

In spite of this complexity, Riemschneider[5-9] has assigned configurations and conformations to the two known stereoisomers of Thiodan (α, m.p. 108–110°; β, m.p. 208–210°). His conclusions are derived from a consideration of the results of a number of degradative experiments which eliminate several of the possible stereoisomers. A comparison of the calculated dipole moments of the remaining isomers with the experimentally determined values led him to propose structure XIB for the lower melting or α-isomer and structure XA for the higher melting or β-isomer. We have recently concluded a reinvestigation of this problem and our experimental results do not agree with Riemschneider's structural assignments.

The mixture of isomeric Thiodans can be prepared by the Diels–Alder addition of hexachlorocyclopentadiene and *cis*-butene-1,4-diol followed by treatment of the product diol with thionyl chloride.[9] The synthetic method and other chemical and analytical data unambiguously establish the formulation I for the isomeric Thiodans.

The stereochemistry at the ring junction has also been established conclusively. Three alternatives are possible; the *cis–exo* structure II, the *cis–endo* structure III, and the *trans* structure IV. Both known Thiodan isomers yield the same cyclic sulfate V on oxidation with permanganate. This sulfate was first isolated by Cassil[10] from plant spray residues obtained after application of Thiodan to crops. Work on the chemical identification and interest in the biological activity of the sulfate led to this study of conformational equilibria in cyclic sulfites and sulfates. More will be said about the sulfate later. Both isomers also yield the same diol (VI) on hydrolysis[11] or on reduction with lithium aluminum hydride[5] and the same ether (VII) by loss of SO_2 on heating at 235°,[12] and by autoradiolysis.[13] These results prove that both α and β have the same configuration at the junction of the sulfite ring and the bicycloheptene system.

Structures of the *trans* series IV can be excluded by the n.m.r. spectra which show the presence of only three different kinds of protons for each isomer, *vide infra*, while IV requires six different kinds of protons. Positive evidence that the two known Thiodan isomers exist in the *endo* configuration III has been obtained by Riemschneider[6] who showed that the diol VI obtained on reduction of Thiodan was identical with the diol obtained on hydride reduction of the known *endo* adduct of hexachlorocyclopentadiene and maleic anhydride (VIII) (see p. 170, col. 1).

These results eliminate 16 of the possible configurations and conformations for the two known Thiodans and only the stereochemistry about the sulfite grouping and the conformation of each isomer remain undetermined. The four possible conformations (IX–XII) of each of the two possible configurations (A and B) of the *endo* adduct III are illustrated in the accompanying

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(1) Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) (a) FMC Corp.; (b) Harvard University. Work was done at both places.

(3) H. F. van Woerden, *Chem. Rev.*, **63**, 557 (1963).

(4) H. Frensch and H. Goebel, German Patent 1,015,797 (Feb. 20, 1958).

(5) R. Riemschneider and J. C. Hilscher, *Z. Naturforsch.*, **15b**, 809 (1960).

(6) R. Riemschneider, *ibid.*, **17b**, 723 (1962).

(7) (a) R. Riemschneider and V. Wuscherpfennig, *ibid.*, **17b**, 585 (1962). (b) In "Abb. 3" of this reference, the printer has evidently reversed the figures from the way that the authors intended; elsewhere in this reference, in R. Riemschneider and V. Wuscherpfennig, *Naturwissenschaften*, **48**, 130 (1961), and in ref. 8 and 9, the representations of the Thiodan isomers do not agree with "Abb. 3."

(8) R. Riemschneider and V. Wuscherpfennig, *Z. Chem.*, **37**, 387 (1963).

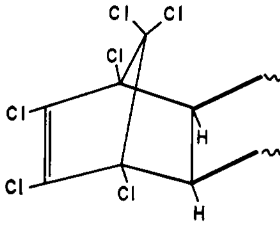
(9) R. Riemschneider, *World Rev. Pest Control*, **2**, (4), 29 (1963).

(10) C. C. Cassil, Niagara Chemical Division, FMC Corp., Richmond, Calif., private communication.

(11) D. A. Lindquist and P. A. Dahm, *J. Econ. Entomol.*, **50**, 483 (1957).

(12) This reaction is not very common though a few examples are known: L. Denivelle, *Compt. rend.*, **208**, 1024 (1939); S. Wawzonek and J. T. Loft, *J. Org. Chem.*, **24**, 641 (1959).

(13) S. E. Forman and J. R. Graham, *ibid.*, **29**, 233 (1964).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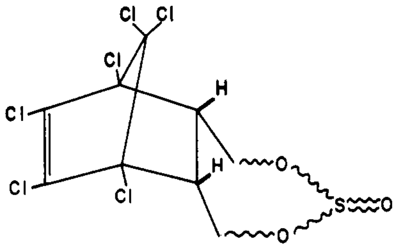
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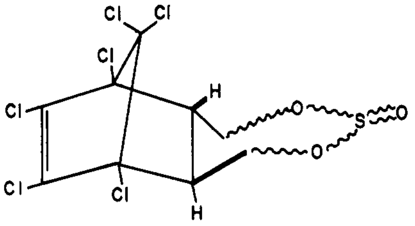
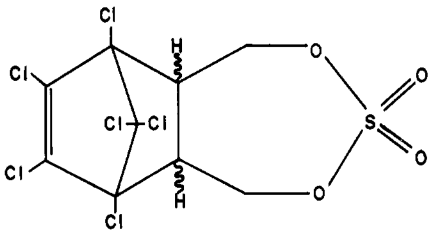

IV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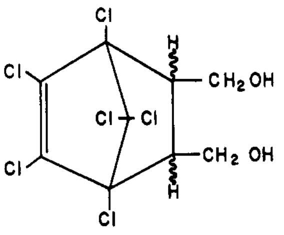
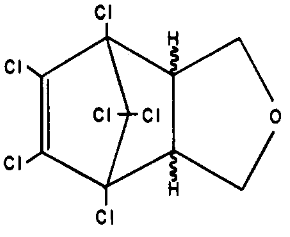
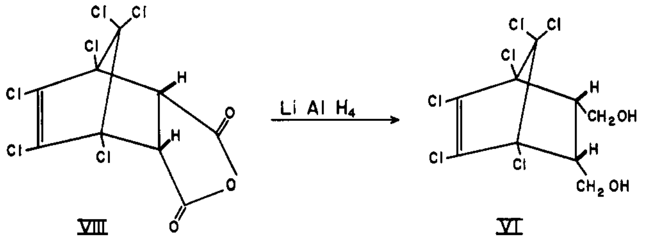

VI


VII



VIII VI

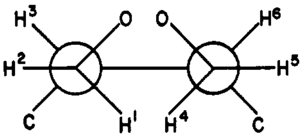
Chart I. It should be noted that for each of the two configurational isomers (A and B) there are two different chair (X and XI) and two different boat (IX and XII) conformations of the seven-membered sulfite ring.[14] In four of the structures, IXA, XB, XIA, and XIIB, the S=O group is equatorial and in the other four, IXB, XA, XIB, and XIIA, it is axial. Finally as all of the structures have the same plane of symmetry each has only three different kinds of hydrogen. Although there seem to be steric problems associated with XIIA, we shall not find it necessary to eliminate this structure on steric grounds alone. The important features of each structure are summarized in Table I.

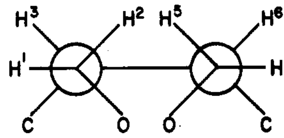
The n.m.r. spectra of the lower melting isomer (α) and the higher melting isomer (β) of Thiodan are reproduced in Figures 1 and 2. These spectra do not change significantly between −35 and +150°. This suggests that each compound is conformationally stable, especially in view of the complexity of the spectra.

After a cursory examination of these n.m.r. spectra, we concluded that very probably there were only three different kinds of protons represented in each spectrum. Further, a simple application of the Karplus relation[15] which correlates the coupling constant of two vicinal protons with the dihedral angle between them (the coupling constant is large when the dihedral angle is 0 or 180° and falls to zero when the dihedral angle approaches 90°) suggested that the exact geometry of Thiodan-α (Figure 1) corresponded to partial structure XIII and the geometry of Thiodan-β (Figure 2) to partial structure XIV (Newman projections).

Table I

Compd.	Configuration A	Compd.	Configuration B
IX	Boat S=O equatorial H^1–H^3 *trans* H^2–H^3 skew	IX	Boat S=O axial (opposite side *vs.* H^1) H^1–H^3 *trans* H^2–H^3 skew
X	Chair S=O axial (same side as H^1) H^1–H^3 *trans* H^2–H^3 skew	X	Chair S=O equatorial H^1–H^3 *trans* H^2–H^3 skew
XI	Chair S=O equatorial H^1–H^3 skew H^2–H^3 skew	XI	Chair S=O axial (same side as H^1) H^1–H^3 skew H^2–H^3 skew
XII	Boat S=O axial (opposite side *vs.* H^1) H^1–H^3 skew H^2–H^3 skew	XII	Boat S=O equatorial H^1–H^3 skew H^2–H^3 skew


XIII


XIV

For example it can be seen in Figure 2 that the two low-field protons represented in structure XIV by H^1 and H^2 or H^4 and H^5 are strongly coupled as expected for geminal protons, while the coupling of H^1 and H^2 to the high-field methine proton, H^3, is small as would be expected if both H^1 and H^2 were skew to H^3. In Figure 1, as represented by structure XIII, it seems that the least shielded proton is strongly coupled to both H^2 and H^3. According to the Karplus relation, H^1 is then *trans* to H^3 (since none of the structures in Chart I have two nonequivalent vicinal protons at a dihedral angle of 0°). H^2, on the other hand, while strongly coupled to H^1 is only weakly coupled to H^3; therefore H^2 is probably skew to H^3, and Thiodan-α is best represented by structure XIII.

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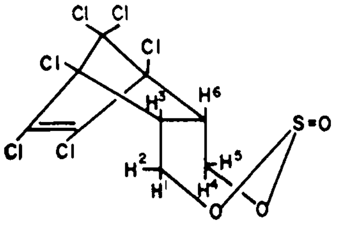
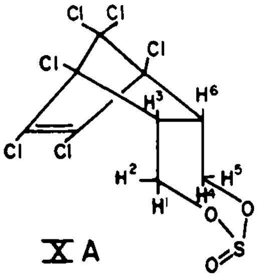
(14) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 253.

(15) M. Karplus, *cf.* H. Conroy in "Advances in Organic Chemistry: Methods and Results," Vol. II, R. A. Raphel, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 308–311.

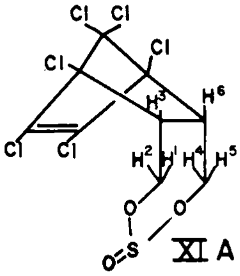
CHART I
POSSIBLE THIODAN STRUCTURES



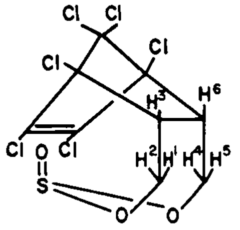
IX A



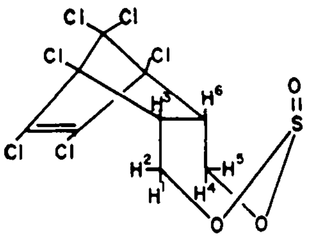
X A



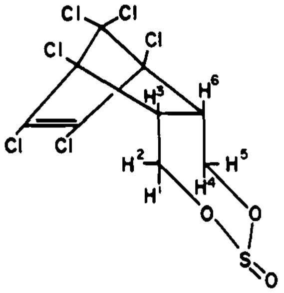
XI A



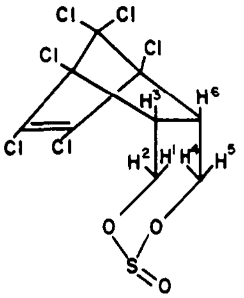
XII A



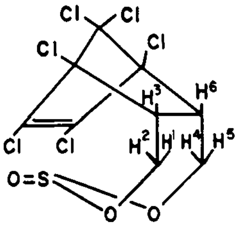
IX B



X B



XI B



XII B

Since the spectrum of the lower melting Thiodan isomer is quite complex, we decided to confirm our qualitative interpretation with a complete theoretical calculation of its spectrum and that of its isomer. The results of our calculations are reproduced in Figures 1 and 2 and the actual calculated data are found in Table II.

TABLE II
CALCULATED N.M.R. SPECTRA

Chemical shift[b]	J, c.p.s.
Thiodan-α (XIII)[a]	
$H^1 = H^4 = -285.1$	$J_{12} = J_{45} = -12.8$
$H^2 = H^5 = -235.7$	$J_{13} = J_{46} = +12.1$
$H^3 = H^6 = -205.6$	$J_{23} = J_{56} = +3.4$
	$J_{36} = +8.7$
	All other J's = 0
Thiodan-β (XIV)[c]	
$H^1 = H^4 = -302.8$	$J_{12} = J_{45} = -13.9$
$H^2 = H^5 = -246.9$	$J_{13} = J_{46} = +2.5$
$H^3 = H^6 = -190.5$	$J_{23} = J_{56} = +2.5$
	$J_{36} = +8.5$
	All other J's = 0

[a] See Figure 1. [b] Chemical shifts are expressed in cycles per second relative to tetramethylsilane at 60 Mc. The negative direction is downfield. [c] See Figure 2.

The spectra were calculated using IBM 7094 Fortran computer programs which required chemical shifts and coupling constants as input data.[16] These parameters were then adjusted both crudely, by varying the input data, and exactly, by using the LAOCOON computer program of Bothner-by[17] (a least-squares approximation which minimizes the differences between the experimental and calculated values), until the calculated spectra approximated the experimental ones. The calculated spectra were plotted using a program written by Hopkins[18] for the IBM 1620 connected to a Calcomp 565 plotter.

In the calculations, the coupling constants for the geminal protons were taken to be negative, and the coupling constants for the vicinal protons were taken to be positive in accordance with recent evidence.[19-21] The magnitude of J_{36} can be evaluated here because "virtual coupling"[22] is observed. A value for this parameter, J_{36}, was initially taken from ref. 16 and later adjusted.

Of the four conformational isomers pictured on Chart I, only IX and X have H^1 and H^3 in a *trans* relationship and H^2 and H^3 in a skew relationship as shown in partial structure XIII. The n.m.r. spectrum of Thiodan-α is then in agreement only with structures IXA, IXB, XA, and XB and cannot be reconciled with the other four structures. Conformations XI and XII have H^1 and H^2 both skew to H^3 in agreement with partial structure XIV and therefore also in agreement with the n.m.r. spectrum of Thiodan-β. These results show conclusively that the structural assignments of Riemschneider[6-9] (α = XIB, β = XA) cannot be correct.

In the n.m.r. spectrum of Thiodan-α, the resonance for protons H^1 and H^4 is at lowest field and these protons are therefore the least shielded. In the possible structures, IXA, IXB, XA, and XB, H^1 and H^4 are always axial protons. Ordinarily in cyclic systems the peaks of axial protons are at higher field than those of equatorial protons because of shielding by adjacent axial hydrogens.[23] This suggests that we should consider some special factor in this system.

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(16) B. D. Nageswara Rao and J. D. Baldeschwieler, *J. Mol. Spectr.*, **11**, 440 (1963).

(17) A. A. Bothner-by, private communication.

(18) R. C. Hopkins, private communication.

(19) M. Karplus, *J. Am. Chem. Soc.*, **84**, 2458 (1962).

(20) P. C. Lauterbur and R. J. Kurland, *ibid.*, **84**, 3405 (1962).

(21) F. Anet, *ibid.*, **84**, 3767 (1962).

(22) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(23) A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962).

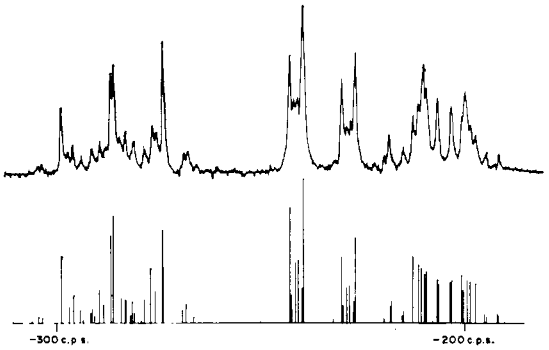


Figure 1.—Thiodan (lower melting isomer).

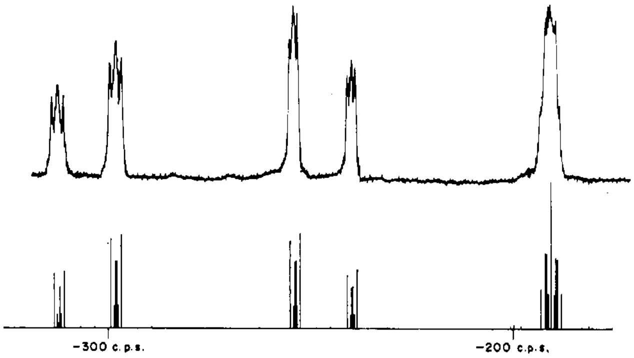
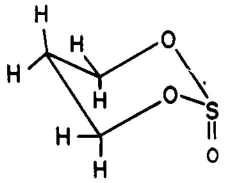


Figure 2.—Thiodan (higher melting isomer).

Last year Hellier and co-workers[24] showed that trimethylene sulfite exists in the rigid chair conformation (XV) with the S=O group axial. Their conclusions are based on a study of the infrared and n.m.r. spectra of this and a number of model compounds. In trimethylene sulfite the axial protons are also less shielded than the equatorial protons. From a study of model compounds (including those of Lauterbur[25]) Hellier, *et al.*, concluded that the stretching frequency of an axial S=O in a cyclic sulfite occurs at 1190 ± 5 cm.$^{-1}$ and is independent of solvent or structural changes. Similarly an equatorial S=O in a cyclic sulfite gives rise to a peak at 1230 cm.$^{-1}$.[25a]



XV

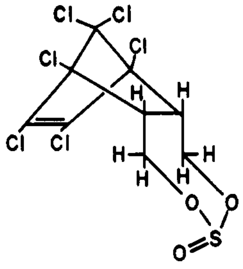
Thiodan-α shows a peak in the infrared at 1195 cm.$^{-1}$ (CS_2). Of the four possible structures for Thiodan-α, only two, IXB and XA, have an axial S=O. IXB is in the boat conformation while XA is in the more stable chair conformation. This suggests that the lower melting Thiodan isomer (α) is XA.

A more compelling argument that the Thiodan-α is XA and not IXB is the following. Only structure XA has a axial S=O group capable of a magnetic interaction with adjacent axial protons, an interaction which explains why the axial protons are less shielded than the equatorial protons in this system.

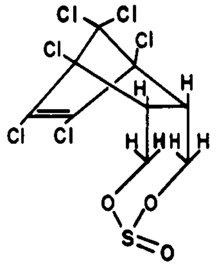
In the higher melting Thiodan isomer (β) we cannot tell whether the equatorial or axial methylene proton is the H^1 whose position we have computed since both $J_{\mathrm{H^1-H^3}}$ and $J_{\mathrm{H^2-H^3}}$ are about the same. Other arguments must be used to choose between XIA, XIB, XIIA, and XIIB, the possible structures for Thiodan-β. As this compound also has an S=O stretching band in the infrared at 1195 cm.$^{-1}$ (CS_2), the S=O group is axial and Thiodan-β must be XIB or XIIA. Two independent arguments lead to the choice of XIB over XIIA.

First, it should be noted that the synthesis of Thiodan from the diol VI and thionyl chloride would not be expected to be completely stereospecific and therefore the isomers should have different configurations. We have shown that Thiodan-α has structure XA. Since both Thiodans are thermally stable, it would be almost impossible for them to be just conformational isomers; they must differ in configuration about the sulfite group. As Thiodan-α has configuration A, Thiodan-β must have configuration B and must therefore be XIB and not XIIA. Second, XIB has a chair conformation while XIIA seems to be the least stable of all the boat conformations pictured in Chart I.

We therefore conclude that the lower melting Thiodan isomer (α) has structure XA and that the higher melting Thiodan isomer (β) has structure XIB.



X A
M.p. 108–110°



XI B
M.p. 208–210°

Since these assignments are just the reverse of those proposed by Riemschneider,[5-9] we carried out an independent set of dipole moment measurements. Our results were 1.02 D. for the lower melting isomer and 3.18 D. for the higher melting isomer compared with Riemschneider's values of 1.63 D. and 2.31 D. The dipole moments determined by us do not agree with any of the values calculated by Riemschneider for the possible *endo* isomers, although they could correspond to values calculated for the *exo* isomers; this agreement is only

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(24) D. G. Hellier, J. G. Tillet, H. F. van Woerden, and R. F. M. White, *Chem. Ind.* (London), 1956 (1963).

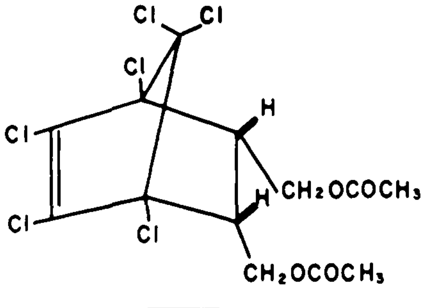
(25) P. C. Lauterbur, J. G. Pritchard, and R. L. Vollmer, *J. Chem. Soc.*, 5307 (1963).

(25a) NOTE ADDED IN PROOF.—B. A. Arbuzov, Y. Y. Samitov, and R. M. Mamina [*Proc. Acad. Sci. USSR*, **143**, 186 (1962)] have calculated the effect of the electric field of the sulfite group on the various proton chemical shifts in the cyclic sulfite derived from 2,2-dimethyl-1,3-propanediol assuming that the S=O group is in an equatorial conformation. Using these calculations, E. J. Grubbs and D. J. Lee [*J. Org. Chem.*, **29**, 3105 (1964)] have recently argued that, in another cyclic sulfite, the S=O group is in an equatorial conformation even though this compound also exhibits a strong band in its infrared spectrum at 1190 cm.$^{-1}$. Arbuzov's calculations lead to the conclusion that axial α-protons are more shielded than equatorial α-protons. Our results prove this is not the case in Thiodan-α (*vide supra*). In the experimental spectra of both Arbuzov and Grubbs the symmetry of the compounds is such that it is impossible to distinguish axial from equatorial protons. Further, calculations assuming an axial S=O group would not be in disagreement with these experimental spectra. Hellier's infrared criterion for an axial S=O group is confirmed by our n.m.r. studies on Thiodan-α and we would suggest that the cyclic sulfites of Arbuzov and Grubbs, therefore, also must have axial S=O groups.

fortuitous, since convincing evidence has been presented, *vide supra*, that α and β are in the *endo* series. Hellier and co-workers[24] have also found that dipole moment studies are not a good criterion for distinguishing between conformers in cyclic sulfites. Distortions in these molecules are probably responsible for anomalies in the calculated dipole moment values.

We shall next consider the cyclic sulfate (V), 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin 3,3-dioxide, which we will refer to by the trivial name of Thiodan sulfate. This compound was first isolated by chromatographic methods by Cassil[10] from plant spray residues obtained after application of Thiodan to leafy vegetables. Cassil prepared a small amount of V in variable yield by oxidation of the commercial Thiodan mixture with hydrogen peroxide in glacial acetic acid at elevated temperature. He established that the oxidation product had the same retention time on a gas chromatographic column, and that it had the same chlorine-sulfur ratio as the material isolated from plant spray residues. Drummond[26] further established the identity of the two samples by elemental analysis and infrared spectroscopy. The bands at 1400 and 1190 cm.$^{-1}$ were particularly informative.[27]

Since further studies of V were desired with regard to chemical characterization and biological activity, we undertook the preparation of this compound. Oxidation of Thiodan-α to the sulfate was achieved in chloroform-acetic acid at 4-6° with aqueous calcium permanganate with a yield of 46% based on the amount of sulfite consumed. Another major product was the diacetate (XVI). Oxidation of Thiodan-β with barium permanganate gave similar results. Analogous oxidations of cyclic sulfites have already been accomplished by Lichtenberg and Hincky[28] and by Kaiser.[29] The sulfate samples obtained from both Thiodan isomers were identical as indicated by melting point behavior, v.p.c., infrared and n.m.r. spectra, dipole moments, and X-ray diffraction patterns. The presence of the sulfate group was verified chemically by saponification under nitrogen to ionic sulfate which was characterized by precipitation as barium sulfate.



XVI

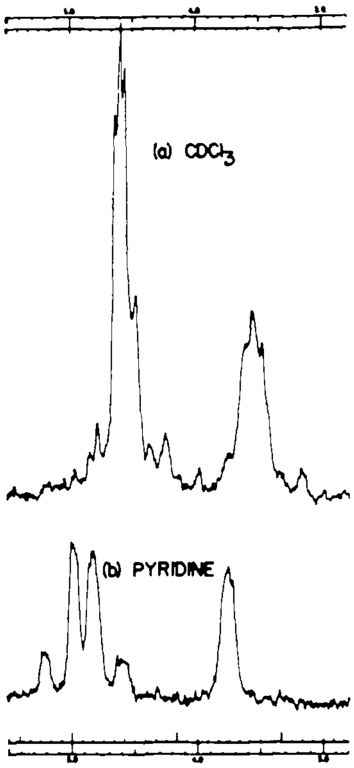
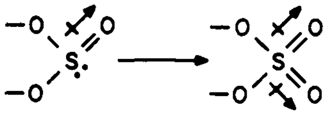


Figure 3.—Thiodan sulfate.

Thiodan sulfate must be in the *endo* series, has no asymmetry at the sulfur, and could exist in any of four conformations, two boat forms and two chair forms. The n.m.r. spectrum of V in deuteriochloroform (Figure 3a) shows only two broad peaks at −275 and −211 c.p.s. in the ratio of 2:1 and with unresolved coupling. The lack of resolution of the methylene region of the spectrum indicates that V exists as rapidly interconverting conformers. An n.m.r. spectrum of Thiodan sulfate in pyridine (Figure 3b) shows three different kinds of nonaromatic hydrogen. This result suggests that the pyridine is complexing with the sulfate group and that the complex interferes with the interconversion of the conformers. The n.m.r. spectrum of V in pyridine has a marked similarity to the spectrum of Thiodan-β taken in deuterochloroform. We conclude that the conformation in this case approaches that of Thiodan-β. The spectrum of Thiodan sulfate in pyridine does not change between room temperature and 80°; at higher temperature, decomposition occurs. The n.m.r. spectra of the two Thiodans in pyridine differ in only minor respects from the spectra in deuteriochloroform.

As melting point studies show that Thiodan sulfate and Thiodan-β are isomorphic, in the solid state, the conformation probably corresponds to XI.

The fact that the Thiodan isomers are conformationally stable while Thiodan sulfate is in mobile equilibrium suggests that there may be an attractive interaction between the axial hydrogens and the lone pairs of electrons on an S=O oxygen. This interaction is weaker in the sulfate than in the sulfites because the nucleophilicity of one oxygen is decreased by the addition of a second oxygen (XVII → XVIII).



XVII XVIII

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(26) P. E. Drummond, private communication.

(27) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 364.

(28) J. Lichtenberg and J. Hincky, *Bull. soc. chim. France*, 1495 (1961).

(29) E. T. Kaiser, Thesis, Harvard University, 1959.

Experimental

Purification of Thiodan-α.—Technical Thiodan-α (200 g.) was recrystallized from 500 ml. of hexane. The purified material 171 g., m.p. 106.5–109°, was 98.0% pure and contained 0.2% of Thiodan-β as determined by v.p.c.

Purification of Thiodan-β.—Technical Thiodan-β (400 g.) was recrystallized first from a mixture of 800 ml. of hexane and 300 ml. of benzene and then from 1350 ml. of cyclohexane. The purified material, 206 g., m.p. 210–211.5°, was 98.8% pure and contained 0.5% Thiodan-α as determined by v.p.c.

Preparation of Thiodan Sulfate. A.—Purified Thiodan-α, 102 g. (0.25 mole), dissolved in a mixture of 250 ml. of chloroform and 500 ml. of acetic acid was stirred, and 125 ml. of an aqueous solution containing 0.15 mole of calcium permanganate was added dropwise over 2.5 hr. while the reaction temperature was held at 5°. The conversion was severely limited by the rapidity of the spontaneous autocatalytic decomposition of the permanganate. After another hour at 5°, a solution of 50 g. of sodium metabisulfite in 300 ml. of water was added slowly while the temperature was permitted to rise to 25°. The hydrated calcium sulfate was filtered from the reaction mixture, and the chloroform layer in the filtrate was separated from the aqueous layer. The solids and the aqueous phase were extracted separately with chloroform. Analysis of the aqueous layer by v.p.c. indicated the presence of the diacetate (XVI) as the only organic solid.

The combined chloroform layers were concentrated until the pot temperature reached 85° at 20 mm. The residue, 68 g., which crystallized on cooling, consisted of 45.6% Thiodan sulfate with the rest being substantially Thiodan-α as indicated by v.p.c. The solids were extracted with one 110-ml. and two 50-ml. portions of hot hexane and the undissolved material was recrystallized successively from 300-ml. and 200-ml. portions of cyclohexane, yielding 17 g. of V; this was augmented by another 7 g., m.p. 179.5–181°, by reworking the mother liquors. The conversion of Thiodan-α to V was 29% while the yield of V based on consumption of α was 46%. Analysis of V by v.p.c. indicated the presence of 98.9% Thiodan sulfate, 0.3% α-isomer, and 0.3% β-isomer.

Anal. Calcd. for $C_9H_6Cl_6O_4S$: C, 25.6; H, 1.43; Cl, 50.3; S, 7.6; SO_4, 22.7; SO_2, 0.0. Found: C, 25.5; H, 1.38; Cl, 50.3; S (Schöniger combustion), 7.7; SO_4 (saponification in an inert atmosphere, precipitation as $BaSO_4$), 20.1; SO_2 (saponification in inert atmosphere and titration of acidified solution with iodine), 0.0.

B.—Purified Thiodan-β (102 g., 0.25 mole) dissolved in a mixture of 1 l. of chloroform and 1 l. of acetic acid was stirred, and a solution of 0.165 mole of barium permanganate in 125 ml. of water was added over 1.3 hr. while the temperature was maintained at 5°. After another hour, a solution of 50 g. of sodium metabisulfite in 800 ml. of water was added without further cooling, and the chloroform layer was separated from the aqueous layer which had the barium sulfate suspended in it. The barium sulfate was removed by filtration and the filtrate was extracted with chloroform. V.p.c. showed that the aqueous layer contained XVI. Evaporation of the combined chloroform extracts yielded 77 g. of crystalline material which consisted of 35.5% Thiodan sulfate, 59% Thiodan-β, and 5.5% XVI by v.p.c. Recrystallization from 200 ml. of carbon tetrachloride gave a first fraction which was largely Thiodan-β while the sulfate was concentrated in the subsequent fractions obtained by evaporation of the mother liquor. These concentrates of V were recrystallized several times from cyclohexane and were more effectively purified by a number of recrystallizations from methanol to yield pure V. Carbon disulfide was also an especially effective solvent for crystallization. The conversion of Thiodan-β to the sulfate was 26% while the yield of the sulfate based on consumption of Thiodan-β was 46%. About half the product was isolated as pure sulfate. Analysis of the purified sulfate by v.p.c. indicated it was 98.6% pure and contained 1.3% of Thiodan-β. The melting point of this sulfate sample was 181–182°; mixture melting point on admixture of product from procedure A was 180–182°. The infrared and n.m.r. spectra and the X-ray diffraction patterns were identical for the two samples.

Anal. Calcd. for $C_9H_6Cl_6O_4S$: C, 25.6; H, 1.43; Cl, 50.3; S, 7.6; SO_4, 22.7; SO_2, 0.0. Found: C, 25.9; H, 1.48; Cl, 51.8; S, 7.8; SO_4, 21.2; SO_2, 0.61.

C.—Other attempts to prepare the sulfate gave the following conversions as determined by v.p.c.: Thiodan-α and $KMnO_4$ in acetic acid, 5%; Thiodan-α and $Ba(MnO_4)_2$ in acetone at 25°, <1%; Thiodan-α and $Ca(MnO_4)_2$ in acetone at 25°, 12%; Thiodan-α and H_2O_2 in aqueous ethanol with tungstic acid catalyst at 60°, 6%; Thiodan-α and SO_3 in dioxane at 60°, 13%; Thiodan-α or Thiodan-β and peracetic acid in acetic acid at 60°, 5%; Thiodan-α and oleum gave the ether (VII); thiodan-α and oxygen at 180–250° (liquid phase) gave Thiodan-β and the sulfate; neither Thiodan-α nor XVI and dimethyl sulfate at 150° yielded the sulfate (V).

4,5,6,7,8,8-Hexachloro-1,3,3a,4,7,7a-hexahydro-4,7-methanoisobenzofuran (VII).—Thiodan-α (0.276 g.) was placed in a 100 × 15 mm., cork-stoppered test tube and put in an oil bath preheated to a constant temperature of 235°. The solid melted and the resulting melt rapidly discolored. After 4.5 hr. no liquid remained in the test tube and an off-white solid coated the walls. SO_2 fumes were detected when the test tube was unstoppered. The solid was recovered to give 0.231 g. (99%) of product. Recrystallization from absolute ethanol and Norit treatment gave a white solid (m.p. 196–203° with decomposition) identified as VII by comparison with an authentic sample.[13]

Thiodan-β gave the same product in 89% yield using the above procedure.

Dipole Moment Data.—The solutions used to determine the data were prepared by weighing both solute and solvent. All measurements were made with benzene solutions thermostated at 25°. The specific volumes were determined by means of a pycnometer with calibrated capillary arms[30] and the weighings were corrected for air bouyancy. Refractive indices were determined with an Abbé-type refractometer.

Dielectric measurements were made with a General Radio Company capacitance measuring assembly, Type No. 1610 A, in which the null detector was replaced with a Dumont oscilloscope, Type 403B, for greater precision and sensitivity in the determination of the null balance. Measurements were made in conjunction with a 200-μμf. standard air capacitor at 0.03 v. a.c. with a frequency of 1000 c.p.s. The liquid measuring cell, constructed by Balsbaugh Laboratories, had completely glass-enclosed, polished nickel concentric cylindrical electrodes. The leads from the cell were kept as short as possible, and care was taken always to arrange the leads in the same manner, so that the lead capacitance would remain constant. The same volume (30.0 ml.) for each solution was used for the measurements. Calibrations of the apparatus were done with air and benzene before each series of determinations, and all values were obtained in units of μμf.

The experimental data (Table III) was subjected to the treatment suggested by Halverstadt and Kumler.[31] The distortion

TABLE III

DIPOLE MOMENT DATA

Sample	$f_2 \times 10^3$	$n^{25.0}_D$	$V^{25.0}$	ϵ	μ
Air				1.0006^a	
Benzene		1.4973^b	1.1450	2.273^a	
α	4.032	1.4983	1.1329	2.326	
α	4.252	1.4984	1.1322	2.330	
α	8.259	1.4990	1.1223	2.338	
α	16.61^b	1.5004^b	1.0988^b	2.346	1.02
β	3.979	1.4984	1.1329	2.303	
β	8.006^b	1.4992^b	1.1212^b	2.370	
β	16.19	1.5010	1.0987	2.482	3.18
V^c	0.9984	1.4973	1.1418	2.314	
V^c	4.001	1.4983	1.1322	2.394	
V^c	8.024^b	1.4988^b	1.1199^b	2.469	
V^c	16.28	1.5001	1.0964	2.680	4.08
V^d	1.978	1.4978	1.1387	2.320	
V^d	4.926	1.4983	1.1290	2.374	
V^d	5.824	1.4984	1.1268	2.408	
V^d	7.942^b	1.4990^b	1.1204^b	2.464	4.12

[a] Values used to calibrate apparatus; see ref. 32. [b] Values used to calculate P_D values. [c] Prepared from Thiodan-α. [d] Prepared from Thiodan-β.

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(30) M. R. Lipkin, J. A. Davison, W. T. Harvey, and S. S. Kurtz, Jr., *Ind. Eng. Chem., Anal. Ed.*, **16**, 55 (1944).

(31) J. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

polarization, P_D, was calculated from the solution data[32] and the values were checked by calculation from the bond refractivities.[33]

Vapor Phase Chromatography.—The chromatograms were run with a Hi Fi chromatograph manufactured by Wilkins Instrument and Research, Inc., with a flame ionization detector. A 1.5-m. tube, 2 mm. in diameter, was packed with 60–80-mesh hexamethylene–disilazane-treated Chromasorb W with 2.5% Epon 1001. The column was maintained at 200° and the nitrogen flow-rate was 30 ml./min. Peaks appeared in the following order (minutes after injection): VII, 1.5; Thiodan-α, 5.0; XVI, 9.5; Thiodan-β, 13.5; and V, 23.0. The column factors for multiplication of the peak areas for the quantitative estimations are Thiodan-α, 1.00; Thiodan-β, 1.00; and V, 1.29.

Infrared Spectra.—The spectra were obtained with a Baird Model 4–55 apparatus, with samples incorporated in potassium bromide pellets, and in CS_2 on a Perkin-Elmer model 237 grating spectrophotometer.

X-Ray Diffraction.—The data was obtained with a Norelco Diffractometer equipped with a Geiger tube detector. Cu Kα radiation was used with a nickel filter at 35 kv. and 20 mamp. on a flat mounted sample in a nitrogen atmosphere. Slit adjustments were divergence, 1°; receiving, 0.003 in.; and scatter, 1°. There were no differences noted in the diffraction patterns obtained from V prepared from Thiodan-α or Thiodan-β.

N.m.r. Spectra.—These were obtained on a Varian A 60 apparatus equipped with a temperature probe with tetramethylsilane as the standard. The spectra were calibrated with the side bands from an audiooscillator.

Acknowledgment.—We are grateful to Professor Paul von Raugé Schleyer and Professor John D. Baldeschwieler for aid in the interpretation of the n.m.r. spectra, to Dr. Charles F. Ferraro for advice in the dipole moment studies, and to Dr. Robert C. Hopkins and Miss Yvonne DeWolf for help in programming.

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(32) R. J. W. LeFevre, "Dipole Moments," Methuen and Co., Ltd., London, 1948, p. 19.

(33) A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1957, p. 1036.

Organic Disulfides and Related Substances. XII. (2-Aminoethyldithio)benzoic Acids and Derivatives[1a,b]

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Received July 23, 1964

Syntheses and structural evidence are reported for the *ortho, meta,* and *para* isomers of (2-aminoethyldithio)-benzoic acid and for various derivatives. The *ortho* isomer was protective against lethal effects of ionizing radiation, but related substances were not. The *ortho* isomer exists in two isomorphic forms. Efforts to cyclize the *ortho* isomer to the eight-membered lactam gave polymeric products, susceptible to further polymerization, suggesting that the lactam readily breaks at the disulfide bond and subsequently polymerizes. Relative resistance of the various unsymmetrical disulfides toward disproportionation into symmetrical disulfides was examined, and correlations are suggested between the degree of resistance and structural features. Preparation of aromatic thiolsulfonates using the chlorinolysis procedure developed by Douglass and Farah for aliphatic disulfides usually was quite effective.

In a continuing study of disulfides and thiolsulfonates,[1b] *o*-(2-aminoethyldithio)benzoic acid (**1**) and related compounds became of interest for several reasons (most of these compounds are shown in Charts I and II). (1) Unsymmetrical disulfides undergo disproportionation according to the following general equation.[2] Information about the disproportionation

$$2RSSR' \rightleftarrows RSSR + R'SSR'$$

of disulfides here reported should lead to better understanding of factors which play a role in the stability of unsymmetrical disulfides. (2) The acid **1** and its congeners offered promise of worthwhile protection against lethal effects of ionizing radiation, owing to presence in an unusual environment of the 2-aminoethylthio moiety, which frequently confers protective activity.[3] (3) Several considerations led to interest in conversion of the acid **1** to its lactam **2**. First, 1,2-dithiacyclooctane polymerizes readily in what amounts to a disproportionation,[4,5] and it was worthwhile to learn whether incorporation of an aromatic disulfide and an electron-withdrawing amide moiety would stabilize or destabilize such a system. Secondly, the less polar lactam (**2**) should traverse membrane barriers better than the zwitterionic acid **1** and thus might be more protective against radiation. Finally, models show that the lactam **2** should be dissymmetric; resolution of **2** or a suitable derivative thus would provide the first chemical evidence of optical activity dependent on a sulfur–sulfur bond.

The acid **1** was synthesized by thioalkylation of *o*-mercaptobenzoic acid by a 2-aminoethyl thiolsulfonate (**3**), as shown in Chart I. The acid **1** proved to be "good" in protective capability,[6a] thus lending early encouragement to an extensive study of related disulfides.

Initial work in the synthesis of the acid **1** was quite puzzling, because two products resulted (**1A** and **1B**). They differed in melting point and infrared spectra. Compound **1A**, obtained first, changed during recrystallization to **1B**, which had an infrared spectrum like that of **1A** except for three new bands and for loss

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(1) (a) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., Nov. 1962. This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (b) Paper XI: L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964). (c) Texaco Fellow in Chemistry, 1961–1962; abstracted from a portion of the Ph.D. Dissertation of R. R. C., Vanderbilt University, 1963. (d) To whom correspondence should be addressed.

(2) For discussion see L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

(3) *Cf.* J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962.

(4) J. G. Affleck and G. Dougherty, *J. Org. Chem.*, **15**, 865 (1950).

(5) A. Schöberl and H. Gräfje, *Ann.*, **614**, 66 (1958).

(6) (a) Protective activities against ionizing radiation were provided through the kindness of Drs. T. R. Sweeney and D. P. Jacobus of the Walter Reed Army Institute of Research, Washington, D. C. General procedures and the meaning of activity ratings have been described earlier.[6b] (b) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).