2-Halogeno-3-morpholinothietan 1,1-Dioxides. Syntheses, Configurations, and Conformations

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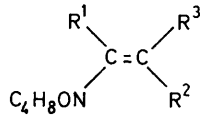
Several *cis*- and *trans*-2-halogeno-3-morpholinothietan 1,1-dioxides have been synthesized. Their configurations and conformations have been assigned from ^{1}H n.m.r. data, including lanthanide-induced shifts. The stereochemical assignments agree with predicted relative thermodynamic stabilities based upon inspection of molecular models.

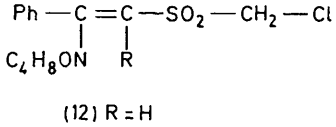
THE reaction between α-chloromethanesulphonyl chloride and some morpholino-enamines in the presence of triethylamine is known to give (*via* α-chlorosulphen, $ClCH{=}SO_2$) the corresponding 2-chloro-3-aminothietan 1,1-dioxide derivatives.[1-3] This particular class of four-membered ring α-halogeno-sulphones attracted our attention in connection with our interest in the chemical behaviour of 2-functionalized thietan 1,1-dioxides.[4] The stereochemistry and ring-substitution of this class of compounds could be expected to be important in controlling their chemical behaviour.

We now report the synthesis and stereochemistry of a selected [5] series of 2-halogeno-3-aminothietan 1,1-dioxides.

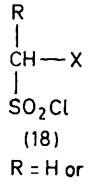
Synthesis.—Treatment of the morpholinoethylenes



(15) R^1 = H, R^2 = R^3 = Me
(16) R^1 = Ph, R^3 = Me, R^2 = H
(17) R^1 = Ph, R^2 = R^3 H



(12) R = H
(13) R = Me
C_4H_8ON = Morpholino



(18)
R = H or Me, X = Cl, Br, or I

(15)—(17) with α-halogenomethanesulphonyl chlorides of general formula (18) in the presence of triethylamine led to a mixture of diastereomeric four-membered ring sulphones (1)—(11), along with, in two cases, the open chain enamino-sulphones (12) and (13). The latter product was a mixture of two isomers.† Also the 1,2-cycloaddition reaction between α-chlorosulphen and (*E*)-α-morpholino-β-methylstyrene (16) [6] afforded only two (and not four) diastereoisomers because of its stereospecificity.[7]

Open chain β-enamino-sulphones were formed only when at least one hydrogen atom was present in the β-position of the enamine. Products (12) and (13) must have arisen from an independent acylation of the enamines, since their isomeric cyclic derivatives (5), (10), and (11) were stable in benzene solution and in the presence of triethylamine at room temperature.[8]

Physical, analytical, and spectroscopic data of compounds (1)—(14) are in Tables 1 and 2.

^{1}H N.m.r. data were valuable in distinguishing between the open-chain and cyclic isomers. Signals at τ 4·77 (=CH–SO_2) and 5·96 (SO_2–CH_2Cl) in the spectrum of (12), and at 7·8 and 8·22 (Me–C–SO_2) and 5·85 and 5·23 (SO_2–CH_2Cl) in the spectrum of the mixture (13) support the structures of the open-chain sulphones. Hydrolysis to the corresponding ketones [5] also confirmed these structures.

Configurations.—Configurations could be assigned to the cyclic diastereomers (1)—(10): (i) by ^{1}H n.m.r. correlations ‡ with compounds of known configuration [(4) and (9) §]; (ii) on the basis of the relative thermodynamic stabilities of each pair of isomers; and (iii)

† The possibility of separating the isomers and assigning their stereochemistry is still under study.

‡ The Karplus relationship [9] is not useful in assigning configurations to our products, even qualitatively, because of the small differences between the J_{cis} and J_{trans} values and because of the presence of electron-withdrawing substituents on the thietan ring. Unfortunately we were not able to obtain enough data to fit the Barfield–Karplus [10] equation.

§ Molecular parameters of (9) were determined by *X*-ray analysis.[11a] It is assumed that no variation occurs in passing from the solid to the solution phase.

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[3] C. T. Goralski and T. E. Evans, *J. Org. Chem.*, 1972, **13**, 2080.
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[6] P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, 1970, **92**, 4261; D. Pocar and R. Stradi, personal communication.
[7] L. A. Paquette, J. P. Freeman, and S. Maiorana, *Tetrahedron*, 1971, **27**, 2599; G. Opitz, *Angew. Chem. Internat. Edn.*, 1968, **7**, 646.
[8] For analogous cases see ref. **4** and references therein.
[9] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; *J. Amer. Chem. Soc.*, 1963, **85**, 2871.
[10] Ref. 11 *d* and ref. 19 therein.
[11] For the evidence in support of a puckered conformation for the thietan dioxide ring system and for leading references see: (*a*) G. D. Andreetti, L. Cavalca, and P. Sgarabotto, *Gazzetta*, 1971, **101**, 440; (*b*) G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Cryst. Struct. Comm.*, 1972, **1**, 423; (*c*) L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, 1971, **93**, 944; (*d*) R. M. Dodson, E. H. Jancis, and G. K. Lose, *J. Org. Chem.*, 1970, **35**, 2520.

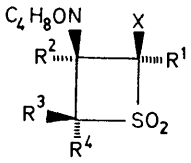
from inspection of molecular models and ^{1}H n.m.r. Eu(fod)$_3$-induced shifts.

X-Ray analysis showed the ring of (9) to be puckered,[11] the angle between planes CCC and CSC being 154·9° *

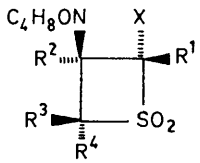
related to the protons α to the nitrogen atom in the morpholine ring appeared as an $A_2A_2'X_2X_2'$ system, whereas in the *cis*-isomer they were strongly modified and should be regarded as an A_2B_2 part of an $A_2B_2X_2X_2'$

TABLE 1

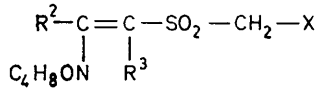
Physical and analytical data of compounds (1)—(14)



cis [a] (1)—(5)



trans (6)—(10)



(12)—(13)

C_4H_8ON = Morpholino

Compd.	R^1	R^2	R^3	R^4	X	Yield (%) [g]	M.p. (°C) [c]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(1)	H	H	Me	Me	Cl	52·0	128	42·8	6·5	5·6	$C_9H_{16}ClNO_3S$	42·6	6·4	5·5
(2)	H	H	Me	Me	Br	67·5	152	36·4	5·1	4·8	$C_9H_{16}BrNO_3S$	36·25	5·4	4·9
(3)	H	H	Me	Me	I	86·4	156	31·6	4·8	4·0	$C_9H_{16}INO_3S$	31·3	4·7	4·1
(4) [e]	Me	H	Me	Me	Cl	27·0	140—150	44·6	6·5	5·7	$C_{10}H_{18}ClNO_3S$	44·85	6·7	5·2
(5)	H	Ph	H	Me	Cl	38·4	168	53·0	5·6	4·3	$C_{14}H_{18}ClNO_3S$	53·3	5·7	4·4
(6)	H	H	Me	Me	Cl	10·5	157	42·5	6·9	5·6	$C_9H_{16}ClNO_3S$	42·7	6·3	5·5
(7) [b]	H	H	Me	Me	Br	29·0	139	36·2	5·6	4·5	$C_9H_{16}BrNO_3S$	36·25	5·4	4·9
(8) [b]	H	H	Me	Me	I	6·8	148	31·6	4·8	4·0	$C_9H_{16}INO_3S$	31·3	4·7	4·1
(9) [f]	Me	H	Me	Me	Cl	6·8	186	44·8	6·65	5·2	$C_{10}H_{18}ClNO_3S$	44·85	6·7	5·2
(10)	H	Ph	H	Me	Cl	9·6	131	52·7	5·65	4·3	$C_{14}H_{18}ClNO_3S$	53·25	5·7	4·4
(11) [d]	H	Ph	H	H	Cl	70·0	145	51·7	5·2	4·8	$C_{13}H_{16}ClNO_3S$	51·7	5·3	4·6
(12)		Ph	H		Cl	8·0	118	51·5	5·4	4·5	$C_{13}H_{16}ClNO_3S$	51·7	5·3	4·6
(13)		Ph	Me		Cl	23·0	110 [f]	53·4	5·9	4·6	$C_{14}H_{18}ClNO_3S$	53·25	5·7	4·4
(14)	H	H	Me	Me	H	75·0	91	49·7	7·9	6·4	$C_9H_{17}NO_3S$	49·3	7·8	6·4

[a] *cis*-Isomers were usually found to be less soluble in ether than *trans*-isomers. [b] Obtained in a pure form by isomerization of (2) and (3). [c] From ethanol. [d] See note *d*, Table 2. [e] Analytical data refer to the *cis–trans* isomer mixture. [f] This is the highest m.p. we obtained. [g] Yields show that the cycloaddition between the α-halogenosulphens and enamines is under kinetic control.

TABLE 2

^{1}H N.m.r. data [a] of compounds (1)—(14)

Compound	R^1	R^2	R^3	R^4	$-CH_2\cdot X$	Morpholine protons	$\lvert J\rvert_{R^1R^2}$	$\lvert J\rvert_{R^1R^3}$	$\lvert J\rvert_{R^3R^4}$
(1)	4·63(d)	6·90(d)	8·25(s)	8·43(s)		6·21, 7·53(m) [f]	6·98		
(2)	4·56(d)	7·06(d)	8·21(s)	8·44(s)		6·22, 7·52(m) [f]	7·05		
(3)	4·35(d)	*b*	8·14(s)	8·46(s)		6·23, 7·53(m) [f]	7·45		
(4) [e]	8·03(s)	7·28(s)	8·26(s)	8·44(s)		6·22, 7·50(m)			
(5)	3·79(d)	2·67(m)	5·22(dq)	8·73(d)		6·30, 7·30(m) [f]		0·86	7·41
(6)	4·72(d)	7·22(d)	8·39(s)	8·42(s)		6·28, 7·52(m)	8·23		
(7)	4·69(d)	7·09(d)	8·38(s)	8·41(s)		6·29, 7·51(m)	8·55		
(8)	4·53(d)	6·97(d)	8·38(s)	8·42(s)		6·26, 7·55(m)	8·84		
(9)	7·93(s)	6·98(s)	8·35(s)	8·38(s)		6·21, 7·46(m)			
(10)	4·02(d)	2·41(m)	5·18(dq)	8·96(d)		6·21, 7·25(m)		1·88	7·28
(11) [d]	4·02(m)	2·60(m)	5·42(m)			6·25, 7·55(m)			
(12)		2·61(m)	4·77(s)		5·97(s)	6·32, 6·84(m)			
(13)		2·56(m)	7·79(s)		5 86(s)	6·29, 6·82(m)			
			8·22(s)		5·23(s)				
(14)	*e*	7·19(t)	8·43(s)	8·44(s)		6·23, 7·63(m)			

[a] τ Values relative to Me_4Si in $CDCl_3$ on a Varian A-60A spectrometer, *J* values in Hz. Assignment of the chemical shifts to R^3 and R^4 is conventional and has no stereochemical implication. [b] The absorption lies under the signal of the protons α to the nitrogen atom of the morpholine. [c] Data were inferred from the spectrum of the *cis–trans* mixture, subtracting peaks due to the latter. [d] We presume (11) is the mixture of the expected diastereoisomers; however the separation of the isomers and their stereochemical study were not pursued since the reactivity was found to be independent of the stereochemistry.[5] [e] In this case (X = H), assignment of the protons R^1 and X is not possible because of the signals of the protons α to the oxygen atom of the morpholine. [f] Higher field multiplet appears as an A_2B_2 part of an $A_2B_2X_2X_2'$ system.

whereas chlorine and morpholine were in a *trans*-pseudoequatorial position. The ^{1}H n.m.r. spectrum of (9) and of the corresponding *cis*-isomer (4) showed that (i) the 4-methyl groups were magnetically less different in the *trans*- than in the *cis*-isomer and (ii) the peaks

* The extent of puckering in thietan rings strongly depends upon ring substitution.[11b]

system. An analogous trend was observed with the other pairs of isomers (Table 2, note *g*).

These recurrent ^{1}H n.m.r. features of the thietans (1)—(10) seem to be directly related to the stereochemical relationships of the halogen atom, the morpholine ring, and the methyl groups, the halogen atom seeming to play the decisive role. In fact the ^{1}H n.m.r. spectrum

of 2,2-dimethyl-3-morpholinothietan 1,1-dioxide (14) shows the usual pattern for protons α to the nitrogen atom of the morpholine ring and the 2-methyl groups are magnetically almost equivalent (Δτ 0·01 p.p.m.).*

Moreover the isomers which were expected to be *trans* on the basis of the above considerations were actually thermodynamically more stable than the *cis*-isomers, as seen previously.[12] In fact compounds (1)—(3), and (5) were readily epimerized to the corresponding *trans*-isomers in mild basic medium (NaOH in pyridine or acetonitrile solution).

Inspection of Dreiding models appears to support the above arguments, showing that the least interaction between the halogen atom and the other substituents occurs when the morpholine group and the chlorine are in a *trans*-relationship.

Further support to the preceding stereochemical assignments arises from consideration of the ^{1}H n.m.r. shifts induced upon treatment of the thietans (5) and (10) with Eu(fod)$_3$. An examination of Dreiding models shows that with a primary site for complex formation near the morpholine oxygen,† the hydrogens in positions 2 and 4 of the *trans*-isomer (10) are symmetrically disposed with respect to this site. However, this is not so with the *cis*-isomer (5). When equal amounts of Eu(fod)^3 were added to the $CDCl_3$ solution of (5) and (10) the difference in chemical shifts between the 2- and 4-protons remained almost constant (70 to 71·5 Hz) in the *trans*-isomer (10) whereas it was found to decrease sharply (86 to 69 Hz) in the *cis*-isomer (5).

Conformations.—trans-4,4-*Dimethyl derivatives* (6)—(8). ^{1}H N.m.r. data allow some conclusions to be drawn concerning the stable conformations of the thietan 1,1-dioxide derivatives (6)—(8), which should exist largely in a preferred puckered conformation.

In compounds (6)—(8), $^3J_{R^1R^2}$ has values (8·23—8·84 Hz) near those predictable [11d,12] for axial–axial coupling (9—10 Hz) and this confirms that the *trans*-pseudo-equatorial disposition of morpholine and chlorine is highly preferred [this is in accord with data from *X*-ray analysis of *r*-2-chloro-2,4,4-trimethyl-*t*-3-morpholinothietan 1,1-dioxide (9)].[11]

cis-4,4-*Dimethyl derivatives* (1)—(3). The literature data concerning the stable conformations for a number of substituted thietan dioxides [11d,12,13] and the above considerations on the existence of a preferred ring conformation in the *trans*-2-halogeno-3-morpholino-4,4-dimethylthietan 1,1-dioxides suggest that the *cis*-isomers (1)—(3) also exist largely in a preferred puckered conformation ($^3J_{R^1R^2}$ values give no useful information in these cases).

Comparing (14) with the *cis*-isomers (1)—(3) (see Table 2) it can be seen that: (i) asymmetry induced by halogen substitution on the thietan ring causes a downfield shift of one of the methyl groups in the *cis*-isomers, and the effect increases in the series (Cl < Br < I); and (ii) in the *trans*-isomers (6)—(8) the deshielding of both the methyl groups is very small and almost independent of the nature of the halogen atom.

A direct non-bonding interaction is clearly occurring in the *cis*-isomers, presumably because of a preferred pseudoaxial orientation of the halogen atom. The dependence of the methyl group shift on the nature of the halogen atom in the observed cases is reasonably explained by van der Waals interaction.‡

cis- *and* trans-4-*Methyl derivatives* (5) *and* (10). The existence of a preferred puckered conformation is also supported in these cases by the fact that variable temperature ^{1}H n.m.r. experiments on (5) and (10) did not show any significant change in coupling constants between +60 and −50°.§

In both *cis*- and *trans*-isomers (5) and (10), because of the shielding effects of the phenyl group, the signal of the methyl group (which lies on the same side as the phenyl group) [6,7] is observed at higher field than in the 4,4-dimethyl isomers (1)—(3) and (6)—(8).

The highest methyl group shift is observed in the *trans*-isomer and no non-bonding influence is observed for the methyl group in passing from a chlorine to a bromine substituent.[15] These considerations are in accord with a pseudoequatorial chlorine conformation and, also, the value of ^4J (1·88 Hz), whose sign is unknown, seems to be better related to an axial–axial long-range coupling than to a positive W coupling through four planar σ-bonds.[13] Based upon these conclusions the lower field shift of the methyl group in the *cis*-isomer (5) can be explained by a smaller shielding effect by the phenyl group in a pseudo-equatorial position. In consequence, morpholine would be pseudoaxial and chlorine pseudoequatorial. Finally it is observed that in the series of cyclic sulphones (1)—(3) and (6)—(8) axial protons always appear at higher field than the equatorial protons.

EXPERIMENTAL

α-*Halogenoalkanesulphonyl Chlorides.*—Bromomethanesulphonyl chloride [16] and α-chloroethanesulphonyl chloride,[17]

* Presumably further halogen substitution on the thietan ring of compound (14) sterically influences ring inversion and inversion at the nitrogen atom of the morpholine in *cis*-isomers. However, we have not performed variable temperature ^{1}H n.m.r. studies. van der Waals interactions seem to be most important with methyl groups, but additional effects associated with the dipole moment and anisotropy of the substituent might be operative.

† A very large shift of the protons α to the oxygen atom of the morpholine can be observed.

‡ Analogous deshielding effects have been reported for conformationally rigid steroid rings.[14]

§ Solubility problems did not allow us to reach lower temperatures and at higher temperatures rearrangements occurred.[15]

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were prepared as in the literature. Chloromethanesulphonyl chloride [18] was obtained in highest yield (64%) by adding, with vigorous stirring, PCl_5 to the sodium salt of chloromethanesulphonic acid and heating for 8 h at 110°. Iodomethanesulphonyl chloride [19] was obtained by slowly adding PCl_5 to a slurry of an equimolar amount of the sodium salt of iodomethanesulphonic acid [20] in chloroform with stirring and cooling at 10° until the reaction subsided. The temperature was then kept at 60° for 4 h. The cooled mixture was extracted into chloroform and the sulphonyl chloride was isolated by distillation; b.p. 70—75° at 0·2 mmHg (lit.,[19] 105—110° at 12 mmHg).

Enamines.—1-Morpholino-2-methylpropene and α-morpholinostyrene were prepared as in the literature.[21] α-Morpholino-β-methylstyrene was prepared as described for α-morpholinostyrene. The product (64·5% yield) had b.p. 105° at 0·2 mmHg.

Reaction of α-Halogenoalkanesulphonyl Chlorides with Morpholinoethylenes.—Alkanesulphonyl chloride (0·06 mol) in anhydrous ether (20 ml) was added dropwise to a stirred and cooled (−2° to 0°) solution of the appropriate enamine (0·6 mol) and triethylamine (0·07 mol) in anhydrous ether (150 ml). After 2 h at room temperature the solid was collected, washed with water (*ca.* 10 ml), and crystallized from ethanol to give pure compounds (1)—(3), (10), and (14), and the mixtures (4) + (9) and (11). From the ethanolic mother liquors, variable amounts of the *cis*-isomers [particularly (5)] could be recovered. The ethereal mother liquors were washed with water, dried, and evaporated to leave a residue which was worked up in various ways: (i) direct crystallization gave (12); (ii) washing several times with petroleum (b.p. 30—40°), adding a small amount of absolute ethanol, and leaving the mixture overnight gave a crop of crystals from which (5) and (13) were separated by fractional crystallization from ethanol (prolonged heating resulted in rearrangement) [15]; (iii) following the isomerization procedure (see below) pure (6)—(8) were obtained; (iv) treatment with 10% H_2SO_4 solution (15 ml) for 2 h at room temperature, extraction with ether, and basification of the aqueous layer gave more of the mixture (4) + (9); and (v) direct crystallization gave more of (14).

Isomerization.—cis-Isomers (2·77 mmol) were dissolved with stirring in a mixture of pyridine (8·5 ml) and aqueous 2% sodium hydroxide solution (3·5 ml). After 3 h water was added (60 ml) and the solid was collected and crystallized.

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