2-Halogeno-3-morpholinothietan 1,1-Dioxides. Reactivity in Base Promoted Elimination and Ring Cleavage

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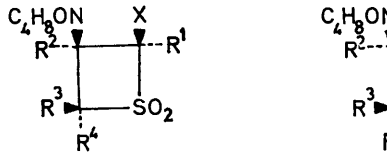
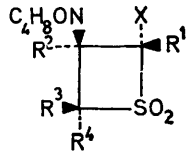
The behaviour of some 2-halogeno-3-morpholinothietan derivatives towards basic reagents has been studied. The pattern of ring substitution and the stereochemical relationships between the substituent groups partly determine the reaction paths. The 4,4-dimethyl derivatives undergo hydrogen halide elimination. The 4-unsubstituted or 4-methyl derivatives are structurally prevented from undergoing hydrogen halide elimination when they bear a 3-phenyl group and ring cleavage is then the preferred reaction. Further transformations of these primary products in the reaction medium are described.

RECENTLY, we have reported the synthesis and the stereochemical features of a number of 2-halogeno-3-morpholinothietan 1,1-dioxide derivatives.[1] Those reported in the Table were selected in order to study their chemical behaviour towards basic reagents according to their stereochemical relationships and ring substitution. In particular, ring substitution was expected to play a role in controlling all the reactions that could occur in the presence of basic reagents: (i) ring cleavage through deprotonation in position α or α′ to the sulphonyl group; (ii) Ramberg–Bäcklund reaction; and (iii) hydrogen halide elimination from the positions α and β to the sulphonyl group.† The stereochemical relationships between the substituent groups were expected to control the possible elimination reactions.



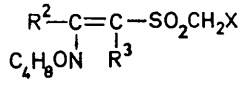
cis (1)-(5)



trans[a] (6)-(10)

Compd.	R^1	R^2	R^3	R^4	X
(1)	H	H	Me	Me	Cl
(2)	H	H	Me	Me	Br
(3)	H	H	Me	Me	I
(4)	Me	H	Me	Me	Cl
(5)	H	Ph	H	Me	Cl

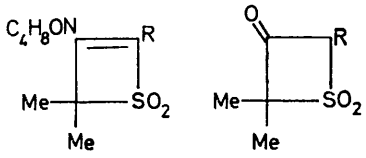
Compd.	R^1	R^2	R^3	R^4	X
(6)	H	H	Me	Me	Cl
(7)	H	H	Me	Me	Br
(8)	H	H	Me	Me	I
(9)	Me	H	Me	Me	Cl
(10)	H	Ph	H	Me	Cl
(11)[c]	H	Ph	H	H	Cl



(12) R^2 = Ph, R^3 = H, X = Cl
(13)[b] R^2 = Ph, R^3 = Me, X = Cl
C_4H_8ON = morpholino

[a] For brevity's sake we use the notations *cis* and *trans* instead then those based on I.U.P.A.C. rules.[2] [b] See the note * in ref. 1. [c] See note *d*, Table 2 in ref. 1.

Reactions with Bases of the 2-Halogeno-3-morpholino-4,4-disubstituted-thietan Dioxide Derivatives.—Treatment of the mixed or pure *cis*- and *trans*-isomers (1)—(3) and (6)—(8) with boiling *ca.* 2N-aqueous alcoholic sodium hydroxide solution both led to the same cyclic β-sulphonylenamine (14) through hydrogen halide elimination. Hydrolysis of (14) gave the corresponding cyclic β-ketosulphone derivative (15). When the mixture of the diastereoisomeric 2,4,4′-trimethyl-substituted halogeno-thietan dioxides (4) + (9), was refluxed in a *ca.* 1N-aqueous alcoholic sodium hydroxide solution, after acidic hydrolysis the unchanged *trans*-isomer (9) was isolated along with the β-ketosulphone derivative (17) [which arises from hydrolysis of the corresponding unisolated intermediate cyclic sulphonylenamine (16)].



(14) R = H (15) R = H (18) R = H
(16) R = Me (17) R = Me (19) R = Me

Reactions with Bases of the 2-Halogeno-3-morpholino-4-monosubstituted- or -unsubstituted-thietan Dioxide Derivatives.—Reflux in the presence of triethylamine of a water–dioxan solution of (11) led to 5-phenyl-2*H*-1,3-oxathiole 3,3-dioxide (20) together with sodium 2-benzoylethanesulphonate (24). Under analogous conditions, the pure single isomers (5) and (10) or their diastereomeric mixture gave a mixture of products from which 4-methyl-5-phenyl-1,3-oxathiole 3,3-dioxide (21), isopropenyl phenyl ketone (25), and propiophenone (26) were identified ‡ (see Scheme).

The presence of formaldehyde was also proved through the preparation of its dimedone derivative. A probable reaction path has been elucidated by stepwise isolation of some intermediates. The open chain sulphone (12) was obtained independently, by refluxing the corresponding cyclic sulphone (11) in an anhydrous solution of triethylamine in dioxan; § an independent

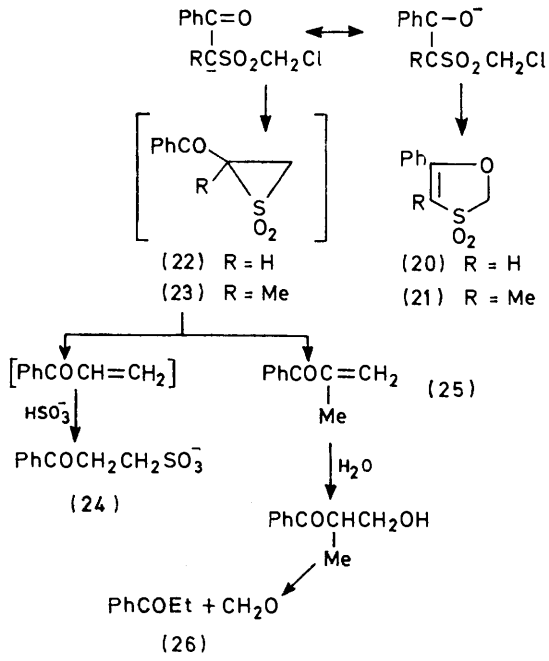
† The possibility of elimination of morpholine might also be considered *a priori* as a possibility, particularly when the derivatives (5) and (10) are concerned, as they are structurally prevented from giving hydrogen halide elimination. Moreover we have found that in the case of the 2-chloro-3-morpholino-3-phenyl-4,4′-dimethylthietan 1,1-dioxide, this reaction takes place in basic medium.[3]

‡ Another product of empirical formula $C_{14}H_{18}ClNO_2S$ was isolated in 16% yield; its formation is related to some rearrangement reactions which are under study.

§ Refluxing (5) or (10) in anhydrous solvent led to some rearrangement reactions which are under study. However ^{1}H n.m.r. spectra analysis gives evidence that open chain sulphones (13) are intermediates.

[1] P. Del Buttero and S. Maiorana, *J.C.S. Perkin I*, 1973, 2540.
[2] I.U.P.A.C. Tentative Rules for the Nomenclature of Organic Chemistry, *J. Org. Chem.*, 1970, **35**, 2849.
[3] P. Del Buttero and S. Maiorana, unpublished results.

hydrolysis of the open chain sulphones (12) and (13) gave the chloromethyl phenacyl sulphones (18) and (19). Starting from both the open chain sulphones (12) and (13) or the ketones (18) and (19) we have



SCHEME

isolated the same final products obtained from the cyclic isomers (11), (5), and (10) under analogous reaction conditions.

The foregoing experimental results support the hypothesis that cleavage of the ring of the cyclic sulphones (11), (5), and (10) is mainly followed by hydrolysis of the resulting sulphonylenamines (12) and (13) to give the ketones (18) and (19). The corresponding ambident anions undergo intramolecular chlorine ion displacement leading both to the oxathiole dioxide derivatives (20) and (21) and to the unisolated intermediate episulphone derivatives (22) and (23). Further transformation of these two last compounds affords the identified reaction products (24),* (25), and (26) as represented in the Scheme.† The sulphonic acid (24) has also been obtained independently adding hydrogen sulphite ion to the propiophenone Mannich base. Addition of water to the vinyl ketone (25) followed by retro-aldol condensation seems the simpler explanation for the formation of propiophenone and formaldehyde, in the case in which R = Me: in any case, we cannot completely rule out the hypothesis of C–C or C–S bond breaking [4] in the intermediate acyl-episulphone (23) ‡ followed by elimination of SO_2 and retro-aldol condensation of the resulting 2-benzoylpropan-1-ol.

In conclusion, in the case of 2,4,4′-trimethyl derivatives, the stereospecific *trans* hydrogen halide elimination is the preferred reaction and *cis*-elimination does not occur under the described conditions. The *cis*-isomers (1)—(3) are less thermodynamically stable than the *trans*-isomers and can epimerize in basic solution easily.[1] However, it seems reasonable that under the described conditions the *cis*-isomers (1)—(3) are more prone to eliminate hydrogen halide by an antiperiplanar mode than are the *trans*-isomers, and pre-isomerization of the *trans*-isomers gives elimination.

The β-hydrogen halide elimination is prevented in the case of the 3-phenyl-4-unsubstituted or 4-monomethyl derivatives (11), (5), and (10): ring cleavage is the preferred reaction and takes place exclusively through C(2)–C(3) bond cleavage to give the open chain β-sulphonylenamines (12) and (13) that undergo the described transformations in the reaction medium.

EXPERIMENTAL §

Reaction with Bases of the 2-Halogeno-3-morpholino-4,4-dimethyl-isomers.—The pure 2-halogenothietan derivatives (1)—(3) and (6)—(8) or their isomeric mixtures were refluxed in absolute ethanol for 4 h in the presence of an equimolar amount of sodium ethoxide. Ethanol was evaporated off under reduced pressure, the residue taken up in water (a few ml), and the resulting *2,2-dimethyl-3-morpholinothiet 1,1-dioxide* (14) isolated by filtration. Yields were 75% from (1) and (6), 85 from (2) and (7), and 83 from (3) and (8), m.p. 173° (from ethanol) (Found: C, 49·8; H, 6·9; N, 6·3. $C_9H_{15}NO_3S$ requires C, 49·8; H, 6·9; N, 6·5%), τ ($CDCl_3$) 5·18 (1H, s, =CH), 7·79 and 6·79 (8H, m, morpholine), and 8·3 (6H, s, Me). Substantially analogous results were obtained using as basic reagent a *ca.* 2N-NaOH solution in ethanol and water (3 : 2).

The diastereoisomeric mixture of the trimethyl-halogenothietans (4) + (9) (1·56 g) was heated at reflux for 24 h with a solution of NaOH (0·75 g) in ethanol (7·5 ml) and water (8 ml). After concentration, the mixture of (16) and (9) was filtered off (1·2 g), m.p. 158—172° (from ethanol–water). This mixture was treated with aqueous 30% sulphuric acid (4 ml) and ethanol (2 ml) for 30 min and extracted with ether. Subsequent evaporation of the ethereal layer gave *2,2,4-trimethylthietan-3-one 1,1-dioxide* (17) (0·36 g, 38%), m.p. 104—105° (from benzene) (Found: C, 44·3; H, 6·2. $C_6H_{10}O_3S$ requires C, 44·4; H, 6·2%), τ ($CDCl_3$) 4·88 (1H, q, *J* 7·5 Hz, C*H*Me), 8·3—8·43 (6H, s, Me_2C), and 8·44 (3H, d, *J* 7·5 Hz, *Me*CH). Basification of the aqueous layer and subsequent filtration gave unchanged *trans*-isomer (9), 0·22 g (14%).

2,2-Dimethylthietan-3-one 1,1-Dioxide (15).—Compound (14) (0·4 g) was treated with a solution of concentrated hydrochloric acid (1·4 ml) and water (2·5 ml) at room temperature for 16 h. Extraction with chloroform gave

* When R = Me we did not isolate the corresponding product although we had some ^1H n.m.r. indication of its presence in the mother liquors of the reaction as its triethylamine salt.

† We have not carried out a complete study of the solvent dependence of these reactions; however, as expected, starting from the keto-sulphone derivative (19) and carrying out independently the reaction with triethylamine in dimethyl sulphoxide solution only the oxathiole derivative (21) in 90% yield was obtained.

‡ Our and other authors' [5] attempts to prepare such derivatives for independent evaluation of their behaviour failed.

§ Preparation of compounds (1)—(13) together with their yields and evidence for their purity were reported previously,[1] the products being numbered in the same way.

[4] S. Matsumura, T. Nagai, and N. Tokura, *Bull. Chem. Soc. Japan*, 1968, **41**, 2672.

[5] L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, 1970, **93**, 944.

the ketone (15) (0·15 g, 55%), m.p. 108—109° (from ethanol) (lit.,[6] 108—110°).

Reaction with Bases of the 2-Chloro-3-morpholino-3-phenyl-4-unsubstituted- or -4-methyl-isomers (11), (5), *and* (10).—The pure cyclic isomers (5) or (10) or their isomeric mixture (3·65 g) were refluxed for 8 h in 20 ml of a solution of dioxan (17·5 ml), water (5 ml), and triethylamine (8·75 ml). Water (70 ml) was then added and the mixture extracted with ether (3 × 50 ml). Evaporation of the solvent at room temperature under reduced pressure gave an oil which was washed with light petroleum (b.p. 30—60°) and taken up in a little ethanol or ether to give a product of general formula $C_{14}H_{18}ClNO_2S$ (0·6 g, 16·4%), m.p. 101° (from ethanol). The oil recovered from the ethanol mother liquors (1·64 g) was a mixture of: (i) propiophenone (64·8%) (identified by comparison with an authentic sample); (ii) *isopropenyl phenyl ketone* (25) (18·3%), τ ($CDCl_3$) 2·55 (5H, m, Ph), 3·68 (2H, m, $=CH_2$), and 7·7 (3H, s, Me) (Found: C, 82·5; H, 6·55. $C_{10}H_{10}O$ requires C, 82·15; H, 6·9%); and (iii) *4-methyl-5-phenyl-2H-oxathiole 3,3-dioxide* (21) (16·9%), m.p. 100°, τ ($CDCl_3$) 2·84 (5H, m, Ph), 5·02 (2H, s, CH_2), and 7·85 (3H, s, Me) (Found: C, 57·15; H, 4·85. $C_{10}H_{10}O_3S$ requires C, 57·15; H, 4·8%). These three compounds have been separated by g.l.c. on a Carlo Erba gas chromatograph model C equipped with a 2 m stainless steel column (i.d. 4 mm), packed with 3% SE 30 on 60—80 mesh Chromosorb W. Temperatures employed were: injection 190°, column 175°, nitrogen pressure 1 kg cm^{-2}. Retention times were respectively 4·25, 5·6, and 10·06 in, with a chart speed of 30 in h^{-1}. Alternatively, distillation of the crude oil gave a mixture of the ketones (25) and (26) (b.p. 70—150° at 0·2 mmHg) which was separated by g.l.c. as described, and the oxathiole (21), which could be distilled, b.p. 180° at 0·2 mmHg, m.p. 100°.

Formaldehyde was identified (as its dimedone derivative) in the starting dioxan–water mother liquors.

Compound (11) (4 g) was treated under the above reaction conditions and the resulting solution was evaporated to half volume at reduced pressure. 5-Phenyl-2*H*-oxathiole 3,3-dioxide (20) (1 g, 38·4%) was isolated by filtration after cooling, m.p. 165° (lit.,[7] 160—165°). Further evaporation of the mother liquors gave a viscous residue from which *sodium 2-benzoylethanesulphonate* (24) (9·5%) was isolated by filtration after treatment with 20% sodium hydroxide solution, m.p. 219° (from ethanol) (Found: C, 45·6; H, 3·9. $C_9H_9NaO_4S$ requires C, 45·75; H, 3·85%). The salt (24) was also compared (i.r. and ^1H n.m.r.) with an authentic sample prepared by reaction of β-dimethylaminopropiophenone hydrochloride [8] (0·02 mol) with an equimolar amount of sodium sulphite dissolved in the minimum of water. After 30 h stirring at room temperature the precipitated sodium 2-benzoylethanesulphonate was filtered off and purified as before (50%).

No formaldehyde or acetophenone could be detected among the reaction products from compound (11).

The same compounds in analogous yields have been isolated by treating, under the foregoing reaction conditions, the open chain enamino-sulphones (12) and (13) or the corresponding chloromethyl keto-sulphones (18) and (19).

The Keto-sulphones (18) *and* (19).—The open chain enamino-sulphones (12) and (13) (0·1 mmol) were stirred in 10% sulphuric acid solution (5 ml) for 4 h (eventually adding a little methanol). Dilution with water and extraction with chloroform afford the ketones; *chloromethyl α-methylphenacyl sulphone* (19) (72% yield), b.p. 130° at 0·01 mmHg (Found: C, 49·05; H, 4·7. $C_{10}H_{11}ClO_3S$ requires C, 48·7; H, 4·5%), τ ($CDCl_3$) 4·67 (1H, q, *J* 7 Hz, CH), 5·29 (2H, AB q, *J* 12 Hz, CH_2), and 8·22 (3H, d, *J* 7 Hz, Me); chloromethyl phenacyl sulphone (18) was obtained in 70% yield, m.p. 80—81° (lit.,[6] 80—82°).

Chloromethyl β-Morpholinostyryl Sulphone (12).—An anhydrous ethanol or dioxan solution of compound (11) (1 g in 20 ml) was heated at reflux for 2·5—3 h in the presence of triethylamine (12 ml). After evaporation of the solvent the residue was crystallized from ethanol (70% yield), m.p. 118° (lit.,[1] 118°).

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[7] K. Dickore, *Annalen*, 1964, **671**, 135.

[8] C. E. Maxwell, *Org. Synth.*, Coll. Vol. III, 1955, p. 305.