Reactions of 3-Alkoxy- and 3-Alkylthio-benzo[*b*]thiophen 1,1-Dioxides with Morpholine, Piperidine, and Pyrrolidine

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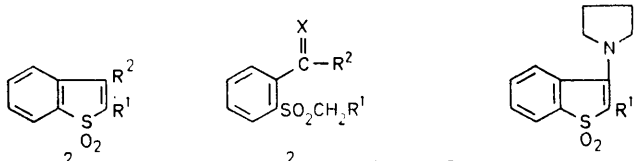
2-Phenyl- (1a) and 2-methyl-3-methoxybenzo[*b*]thiophen 1,1-dioxide (1b) undergo ring opening to form amides on treatment with morpholine and with piperidine, but react with pyrrolidine to yield enamines; the 2-unsubstituted analogue (1c) undergoes ring-cleavage to amides with all three amines. 3-Benzyloxy- 6(a) and 3-benzylthio-2-phenylbenzo[*b*]thiophen 1,1-dioxide (8a) also yield the corresponding amide or thioamide with morpholine and piperidine but the enamine with pyrrolidine.

CLEAVAGE of β-oxo-sulphones by amines with formation of amides is well known.[1] The reaction of benzo[*b*]-thiophen-3(2*H*)-one 1,1-dioxide with pyrrolidine has been reported [2] to give both the enamine and amide while the 2-phenyl derivative with morpholine yielded only the amide.[3] We describe here the behaviour of some enol ethers of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxides and their thio-analogues with morpholine, piperidine, and pyrrolidine.

RESULTS AND DISCUSSION

The methyl enol ethers (1a—c) reacted with morpholine and with piperidine to yield the *o*-(methylsulphonyl)benzoylmorpholine derivatives (2a—c) and the *o*-(methylsulphonyl)benzoylpiperidine derivatives (3a—c). In contrast, the substituted methyl ethers (1a, b) on treatment with pyrrolidine afforded the enamines (4a, b) while the unsubstituted ether (1c) gave the amide (5c). For comparison we prepared the amide (5a) by the reaction of 2-phenylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide with pyrrolidine. The results of the reaction with the methyl ethers for which the amine was used as



solvent are shown in Table 1. When the reactions were carried out by using only 3 equiv. of the amine in benzene solution the same products were formed, as shown by

[1] J. J. Looker, *J. Org. Chem.*, 1966, **31**, 2714.
[2] J. G. Lombardino, *J. Org. Chem.*, 1968, **33**, 3938.
[3] N. D. Ryan, Ph.D. Thesis, National University of Ireland, 1972, p. 90.

t.l.c., but much more slowly. *N*-Methylmorpholine was detected in the reaction mixture obtained by heating the ether (1a) in the minimum amount of morpholine.

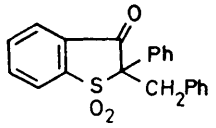
TABLE 1

Reactions of 3-methoxy-, 3-benzyloxy-, and 3-benzylthiobenzo[*b*]thiophen 1,1-dioxide with morpholine (morph), piperidine (pip), and pyrrolidine (pyrr)

Compound	Base	Reaction time [a]/h	% Product	
			Amide	Enamine
(1a)	morph	6	86 (2a)	
(1a)	pip	4	97 (3a)	
(1a)	pyrr	24 [b]		84 (4a)
(1b)	morph	4	98 (2b)	
(1b)	pip	3	99 (3b)	
(1b)	pyrr	2		73 (4b)
(1c)	morph	3	64 (2c)	
(1c)	pip	2	64 (3c)	
(1c)	pyrr	1	51 (5c)	
(6a)	morph	120 [b]	91 (2a)	
(6a)	pip	1	88 (3a)	
(6a)	pyrr	48 [b]		85 (4a)
(8a)	morph	28	95 (10a) [c]	
(8a)	pip	3	25 (11a) [d]	
(8a)	pyrr	14 [b]		75 (4a) [e]

[a] Reflux temperature unless otherwise stated. [b] Room temperature. [c] And PhCHO (67%). [d] And PhCHO (37%), (12) (28%), and (13) (30%). [e] And PhCHO (60%).

The reaction of 3-benzyloxy-2-phenylbenzo[*b*]thiophen 1,1-dioxide (6a) with the three amines was examined next. The benzyl ether (6a) was prepared by the reaction in base of benzyl alcohol with 3-chloro-2-phenylbenzo[*b*]thiophen 1,1-dioxide. The alternative reaction between benzyl chloride and 2-phenylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide yields the *C*-alkyl product (7) and not the ether (6a) as previously described.[4]

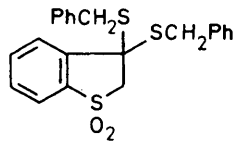


(7)

The benzyl ether (6a), as expected, reacted with morpholine and piperidine to yield the amides (2a) and (3a) and with pyrrolidine to give the enamine (4a) (see Table 1). In each of the reactions of the benzyl ether (6a) with morpholine and piperidine the *N*-benzyl base was isolated and identified by g.l.c. The reaction of (6a) with piperidine, when carried out at room temperature, afforded a further minor product. The n.m.r. spectrum of this suggested that it was a mixture of the *Z*- and *E*-isomers of the adduct 3-benzyloxy-2-phenyl-3-piperidino-2,3-dihydrobenzo[*b*]thiophen 1,1-dioxide, but consistent analytical figures were not obtained.

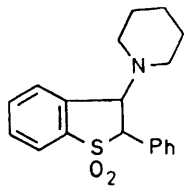
The results obtained with the enol ethers prompted us to examine the reactions of the sulphides (8a,[3] c) with the amines. Reaction of phenylmethanethiol with benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide afforded a mixture of the sulphide (8c) and the dithioacetal (9). The latter was converted into the former by treatment with triethylamine.

The reactions of the sulphide (8a) with morpholine and piperidine paralleled those of the benzyl ether (6a).



(9)

Treatment of the sulphide (8a) with morpholine afforded the thioamide (10a), identical with a sample prepared by treating the amide (2a) with phosphorus pentasulphide. The other products isolated were *N*-benzylmorpholine and benzaldehyde. Reaction of the sulphide (8a) with pyrrolidine gave the enamine (4a) and benzaldehyde. The reaction of (8a) with piperidine was more complex, affording, in addition to benzaldehyde and *N*-benzylpiperidine, three other products, the relative yields of which varied with the conditions. One of these products was the expected thioamide (11a), which was also synthesised from the amide (3a). The second was identified spectroscopically as 2,3-dihydro-2-phenyl-3-piperidinobenzo[*b*]thiophen 1,1-dioxide (12). This assignment was



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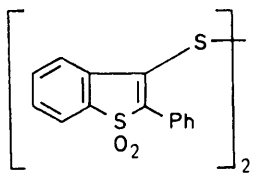


(13)

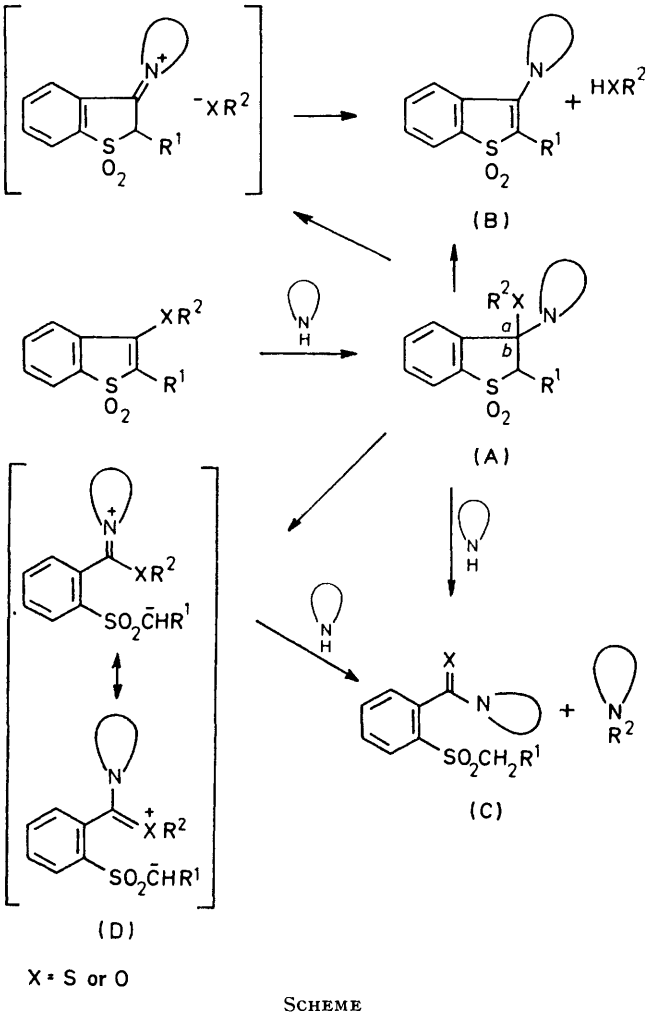
confirmed by comparison with a sample obtained by treating 2-phenylbenzo[*b*]thiophen 1,1-dioxide with piperidine.[5] The third and most insoluble product proved to be the disulphide (13), identical with a sample obtained by oxidation of the sodium salt of 3-mercapto-2-phenylbenzo[*b*]thiophen 1,1-dioxide with iodine.[6] The disulphide (13) was reduced with sodium dithionite and the resulting sodium thiolate was treated with benzyl chloride to yield the sulphide (8a).

Isolation of the disulphide (13) from the reaction with piperidine indicates the intermediacy of 3-mercapto-2-phenylbenzo[*b*]thiophen 1,1-dioxide. The disulphide may undergo further reaction in the presence of piperidine and eliminate sulphur (*cf.* ref. 7) to give 2-phenylbenzo[*b*]thiophen 1,1-dioxide, which then forms (12). The mechanism for the formation of benzaldehyde as well as the *N*-benzylamine from the reactions of the sulphide (8a) is not clear; the fact that it is not obtained from the benzyl ether (6a) indicates that the benzaldehyde may arise from thiobenzaldehyde, formed in a side reaction of the type found in Willgerodt–Kindler

[4] A. Cohen and S. Smiles, *J. Chem. Soc.*, 1930, 406.
[5] Centre d'Etudes pour l'Industries Pharmaceutique, Ger. Offen. 2,341,894 (*Chem. Abs.*, 1974, **80**, 146007f).
[6] K. Buggle and P. McManus, unpublished data.
[7] Ya. S. Tsetlin, V. A. Usov, and M. G. Voronkov, *Zhur. org. Khim.*, 1975, **11**, 1945.

reactions.[8,9] Treatment of the sulphide (8c) with morpholine or with pyrrolidine led to decomposition.

Presumably the intermediate in the formation of the amides and enamines from the enol ethers and the corresponding sulphides is the adduct (A) (Scheme) in



SCHEME

which elimination by cleavage of bond *a* gives the enamine (B) while cleavage of bond *b* by dealkylation with a second molecule of amine, possibly *via* an imidate ester (D), affords the amide (C) and *N*-alkyl base. An alternative pathway may involve initial dealkylation of the ether or sulphide by the amine with formation of the *N*-alkylamine and β-oxo- or β-thioxo-sulphone; the latter could then react further with the amine, resulting in ring-opening and formation of the amide as previously described.[1-3] Differences between pyrrolidine and piperidine in rates of formation of enamines from ketones and in product composition have been attributed [10] to the fact that a double bond exocyclic to a five-membered ring is more favoured than a double bond exocyclic to a six-membered ring. This may also be a determining factor in the formation of enamines rather than amides in the reaction of the enol ethers (1a, b), (6a), and (8a) with pyrrolidine.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R12 60 MHz spectrometer for solutions in $CDCl_3$ with tetramethylsilane as internal standard. I.r. spectra were obtained for potassium bromide discs with a Perkin-Elmer 700 spectrometer. G.l.c. was performed on a Perkin-Elmer F30 gas chromatograph. Silica gel for t.l.c. was Merck Kieselgel 60 PF 242 + 366. Analytical and spectroscopic data are given in Table 2.

3-Methoxy-2-methylbenzo[b]*thiophen 1,1-Dioxide* (1b).—2-methylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide (2.1 g) suspended in ether (100 ml) was treated with a three-fold excess of ethereal diazomethane. Removal of the solvent and recrystallisation of the residual oily material from benzene gave the ether (1b) (1.61 g, 70%).

3-Benzyloxy-2-phenylbenzo[b]*thiophen 1,1-Dioxide* (6a).—(*cf.* ref.11) A mixture of 3-chloro-2-phenylbenzo[*b*]thiophen 1,1-dioxide (1.0 g), potassium hydroxide (0.24 g), and benzyl alcohol (25 ml) was heated at 110 °C with stirring for 30 min. The cooled mixture was diluted with water and shaken with $CHCl_3$. Evaporation of the $CHCl_3$ and benzyl alcohol and recrystallisation of the residue from $CHCl_3$–light petroleum(b.p. 40—60 °C) gave the benzyl ether as needles (0.9 g, 72%).

2-Benzyl-2-phenylbenzo[*b*]*thiophen-3*(2H)*-one 1,1-Dioxide* (7).—A mixture of 2-phenylbenzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide (2.0 g), potassium carbonate (2.1 g), and benzyl chloride (4.06 g) in DMF (50 ml) was heated at 100 °C for 2.5 h. The solvent was removed and the oily residue was triturated with cold light petroleum (b.p. 40—60 °C). The resulting solid was recrystallised from $CHCl_3$ to give compound (7) (2.05 g, 76%).

Reaction of Ethers (1a—c) *and* (6a) *and Sulphides* (8a, c) *with Morpholine, Piperidine, and Pyrrolidine.*—A solution of the ether or sulphide (300 mg) in the amine (4 ml) was stirred at room temperature or heated under reflux until the starting material could no longer be detected by t.l.c. The amine was evaporated off *in vacuo* and the residue was separated by t.l.c. Reaction conditions and products are given in Table 1.

N-Methylmorpholine was detected by g.l.c. (stationary phase Porapak Q; carrier N_2) of the mixture obtained by heating the ether (1a) in the minimum amount of morpholine; morpholine was retained in the column. The *N*-benzylamines were isolated by t.l.c. and identified by comparison with authentic samples (n.m.r. and g.l.c.). The column packings employed were Apiezon L on Chromosorb W-AW (80—100 mesh) and SE30 on Chromosorb-AW (80—100 mesh).

Reaction of 2-Phenylbenzo[b]*thiophen-3*(2H)*-one 1,1-Dioxide with Pyrrolidine.*—A solution of the oxo-sulphone (515 mg) in pyrrolidine (4 ml) was heated under reflux for 10 min; the base was removed *in vacuo* and the residue purified by t.l.c. ($CHCl_3$) to give the amide (5a) (345 mg, 52.5%).

Reaction of Benzo[b]*thiophen-3*(2H)*-one 1,1-Dioxide with*

[8] F. H. McMillan and J. A. King, *J. Amer. Chem. Soc.*, 1948, **70**, 4143.
[9] F. Asinger, W. Schafer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem. Internat. Edn.*, 1964, **3**, 19.
[10] S. K. Malhotra in 'Enamines: Synthesis, Structure, and Reactions,' ed. A. G. Cook, Dekker, New York, 1969, pp. 32 and 8.
[11] A. H. Lamberton and J. E. Thorpe, *J. Chem. Soc.* (*C*), 1967, 2573.

Phenylmethanethiol.—A solution of phenylmethanethiol (0.7 g) in benzene (50 ml) was added during 14 h to a hot solution of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide (1.564 g) in benzene (180 ml) containing boron trifluoride–ether complex (*ca.* 20 ml). The mixture was washed with water, dilute aqueous NaOH (5%), and brine, dried, evaporated, and the residue purified by p.l.c. to afford the *benzyl sulphide* (8c) (0.392 g) and the *thioacetal* (9) (0.481 g).

in pyridine (4 ml). The mixture was refluxed for 40 min, cooled, and poured into water. T.l.c. of the resulting precipitate gave starting material ($CHCl_3$) (758 mg, 67.6%) and the thioamide (174 mg, 14·9%) (methanol–chloroform). In a similar experiment the amide (3a) with phosphorus pentasulphide gave the thioamide (11a) (17.8%).

Reduction of Bis-(2-phenyl-1,1-dioxobenzo[b]thiophen-3-yl) Disulphide.—A mixture of the disulphide (13) (300 mg),

TABLE 2

Analytical, i.r., and ^1H n.m.r. data

Compound	M.p. (°C)	Found (%) C	H	N	S	Formula	Required (%) C	H	N	S	$\nu_{max.}$/cm^{-1}	τ($CDCl_3$) (excluding aromatic protons)
(1a)	171—172 [a]											
(1b)	155—156.5	57.1	4.8		15.2	$C_{10}H_{10}O_3S$	57.1	4.8		15.2	1 630 (C=C)	7.65 (3 H s,) 5.78 (3 H, s)
(1c)	215 [b]										1 620 (C=C)	5.98 (3 H, s), 4.12 (1 H, t)
(2a)	145—146 [c]										1 630 (C=O)	6.68 (2 H, m), 6.15 (6 H, m), 5.26 (2 H, AB quartet)
(2b)	141—142	54.9	5.9	5.0	11.3	$C_{13}H_{17}NO_4S$	55.1	6.05	4.95	11.3	1 630 (C=O)	8.70 (3 H, t), 6.31 (10 H, m)
(2c)	114—116	53.2	5.5	5.5	12.3	$C_{12}H_{15}NO_4S$	53.5	5.6	5.2	11.9	1 610 (C=O)	6.69 (3 H, s), 6.40 (8 H, m)
(3a)	130	66.0	5.9	4.0	9.3	$C_{19}H_{21}NO_3S$	66.5	6.2	4.1	9.3	1 620 (C=O)	8.35 (6 H, m), 6.80 (2 H, m), 6.21 (2 H, m), 5.25 (2 H, AB quartet)
(3b)	94—95	59.7	7.0	4.85	11.0	$C_{14}H_{19}NO_3S$	59.8	6.8	5.0	11.4	1 640 (C=O)	8.70 (3 H, t), 8.30 (6 H, m), 6.45 (6 H, m)
(3c)	73	58.5	6.6	5.5	12.45	$C_{13}H_{17}NO_3S$	58.4	6.4	5.2	12.0	1 620 (C=O)	8.30 (4 H, m), 6.68 (3 H, m), 6.77 (2 H, m), 6.22 (2 H, m)
(4a)	210—212 [d]	69.5	5.8	4.3	10.0	$C_{18}H_{17}NO_2S$	69.4	5.5	4.5	10.3		
(4b)	185—186.5	62.3	6.3	5.55	12.9	$C_{13}H_{15}NO_2S$	62.6	6.1	5.6	12.8	1 590 (C=C)	8.10 (4 H, m), 7.69 (3 H, s), 6.15 (4 H, m)
(5a)	92	65.6	5.9	4.3	10.1	$C_{18}H_{19}NO_3S$	65.6	5.8	4.25	9.7	1 625 (C=O)	8.03 (4 H, m), 6.75 (2 H, m), 6.22 (2 H, m), 5.22 (2 H, s)
(5c)	117 [e]											
(6a)	182—183	71.9	4.6		9.4	$C_{21}H_{16}O_3S$	72.4	4.6		9.2	1 640 (C=C)	5.03 (2 H, s)
(7)	152—153 [f]	72.5	4.65		9.2	$C_{21}H_{16}O_3S$	72.4	4.6		9.2	1 720 (C=O)	6.03 (2 H, s)
(8a)	124—125 [g]											6.18 (2 H, s)
(8c)	144.5—146	62.5	4.3		21.9	$C_{15}H_{12}O_2S_2$	62.5	4.2		22.2		5.7 (2 H, s), 3.57 (1 H, s)
(9)	107.5—108.5	63.8	4.8		23.6	$C_{22}H_{20}O_2S_3$	64.1	4.9		23.3		6.18 (2 H, s), 6.09 (4 H, s)
(10a)	203—204	59.9	5.4	3.9	17.8	$C_{18}H_{19}NO_3S$	59.8	5.3	3.9	17.7		6.32 (4 H, m), 5.51 (4 H, m), 5.15 (2 H, q, *J* 13.2 Hz)
(11a)	174—176	64.0	6.0	3.8	17.5	$C_{19}H_{21}NO_2S_2$	63.5	5.9	3.9	17.8		8.30 (6 H, m), 6.54 (4 H, m), 5.11 (2 H, q)
(12)	187	69.6	6.6	4.15	9.9	$C_{19}H_{21}NO_2S$	69.7	6.5	4.3	9.8		8.56 (6 H, m), 7.56 (4 H, m), 5.02 (1 H, d), 5.18 (1 H, d)

[a] Lit., 171—172 °C (K. Buggle and D. O'Sullivan, *Chem. and Ind.*, 1974, 343). [b] Lit., 215 °C (F. Arndt and C. Martius, *Annalen*, 1932, **499**, 228). [c] Lit.,[3] 144—145 °C. [d] Lit., 215—217 °C (F. Sauter and U. Jordis, *Monatsh.*, 1974, **105**, 1252). [e] Lit.,[2] 113—115 °C. [f] Lit.,[4] 146 °C. [g] Lit.,[3] 124—125 °C.

Acidification of the alkaline washings yielded starting material.

A solution of the thioacetal (9) in EtOH–$CHCl_3$ (10 : 1; 15 ml) containing triethylamine was refluxed for 72 h. The solution was evaporated and the mixture of unchanged thioacetal (9) and sulphide (8c) separated by t.l.c.

N-[o-(*Benzylsulphonyl*)*thiobenzoyl*]*morpholine* (10a).—Phosphorus pentasulphide (0.8 g) was added to a solution of *N*-[*o*-(benzylsulphonyl)benzoyl]morpholine (2a) (1.12 g)

sodium dithionite (915 mg), and sodium hydroxide (185 mg) in aqueous ethanol (1 : 5; 50 ml) was heated under reflux for 1.5 h. Benzyl chloride (200 mg) was then added and heating was continued for 30 min. The mixture was cooled, diluted with water, and shaken with chloroform. The chloroform solution yielded 3-benzylthio-2-phenylbenzo[*b*]-thiophen 1,1-dioxide, m.p. 118—120 °C (from benzene–light petroleum), identical with an authentic sample.

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