Fused 1,2-Dithioles. IV. Synthesis and Reactions of 1,2-Dithiole *S*-Oxides

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1,2-Dithiolopyrrolones and their heterologues of type **1** are resonance stabilized systems displaying a high dipole moment. Upon oxidation with organic peracids compounds **2**, **5**, **15a**, **16a**, **20a** and **25a** gave the corresponding *S*(2)-oxides and, depending on substituents, in some cases the *S*(2)- and *S*(1)-dioxides. The *S*(2)-monoxides showed a proclivity to disproportionation and were easily reduced to dithioles with symmetrical dimethylhydrazine. From *S*(2)-oxides and several primary amines bicyclic isothiazole-*S*-oxides were obtained (*S/N*-exchange reaction). From the *N*-unsubstituted isothiazole *S*-oxide **10e** the *N*-hydroxyisothiazole **9d** was synthesized by an aza-Pummerer-type rearrangement. The assumption is made that *S*(2)-oxides may be biologically important as active metabolites of pyrrothines and analogues of type **1** in their action as antibacterials and antimycobacterials.

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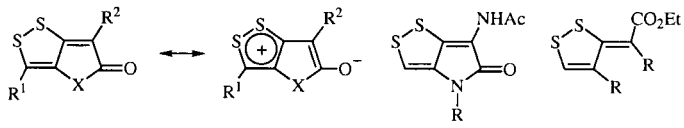
Introduction.

In the preceeding papers of this series [1-3] we have reported on the synthesis of a number of distinctly substituted 1,2-dithiolopyrroles, 1,2-dithiolofurans and 1,2-dithiolothiophenes of the general formula **1** (Scheme 1). These compounds are structurally related to naturally occuring 1,2-dithiolopyrroles, commonly named pyrrothines, the longest known representatives of which are thiolutin **2** and holomycin **3** [4-7]. Most of the synthetic analogues possess antituberculotic activity and some of them proved to be even more active than their lead compounds [8]. Noteworthy is the observed high potency against *Mycobacterium kansasii* and *M. avium*.

Scheme 1



1 (X = NH, NMe, O, S) **1a** **2**, R = Me; **3**, R = H **4**

Only vague hypotheses have been advanced on the mechanism of the pharmacological activity. Earlier reports suggested that **2** could act as an acylating agent toward bionucleophiles bearing formal resemblance to the β-lactams [9]. This, however, can be ruled out experimentally, since thiolutin is left unchanged even after prolonged exposure to ethanolic methylamine at ambient temperature. Beyond that, the amide carbonyl band in the ir spectra of β-lactams is found at 1770 cm^{-1} whereas thiolutin displays the highest band in the carbonyl region at 1675 cm^{-1}. This is due to the resonance stabilization of the dithiolopyrolone system as depicted in zwitterionic formula **1a**. The polar character of these compounds expresses itself in a high dipole moment which we have determined as 4.30 D for compound **5a** and as 3.60 D (±5%) for **16a** [10]. From some compounds of type **1** stable but readily hydrolizing perchlorates have been obtained [11].

From these facts we concluded that the pharmacophore of **2** and its mimics of type **1** might be the alkylidene dithiole system [12]. This notion was later substantiated by the fact that differently substituted 5-alkylidene 1,2-dithioles of general formula **4** indeed displayed notable antituberculotic activity [8]. But nevertheless a precise understanding of their mode of action is still missing. Therefore we assumed that the pyrrothines act as prodrugs which require activation by metabolic *S*-oxidation [13] thus diminishing the importance of the resonance stabilization of the alkylidene dithiole partial structure and hence enhancing the reactivity of the disulphide moiety against bionucleophiles [14,15]. 1,2-Dithiole-*S*-oxides are formally esters of thiosulphinic acids. The chemistry of thiosulphinates has in the past attracted considerable attention in the "Allium chemistry" [16,17]. Recently, the 1,2-dithiole-*S*-oxide moiety was found elsewhere in nature [18,19], which thereupon prompted the synthesis of mimics like benzodithiolanone *S*-oxide [20].

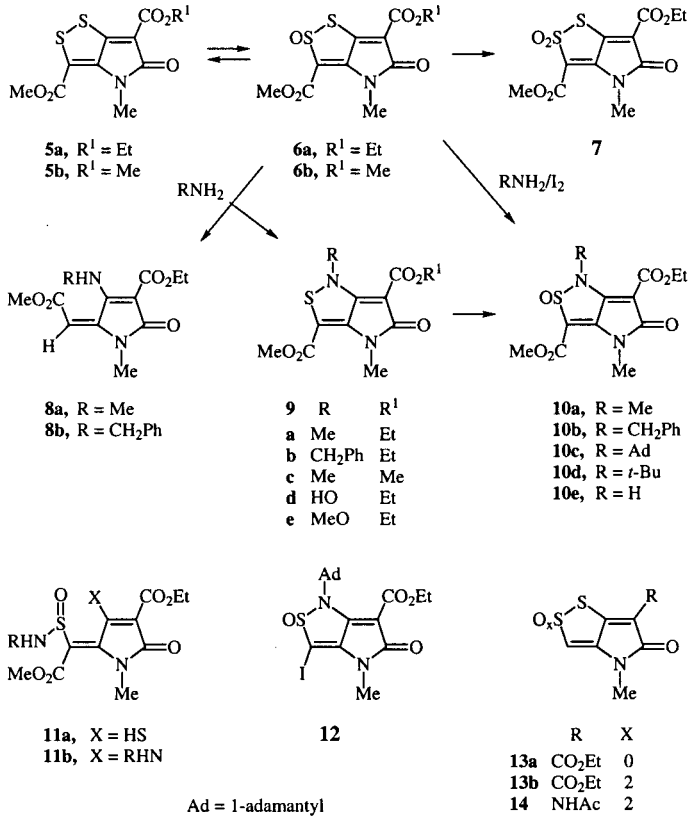
In this context we aimed at the synthesis of some fused 1,2-dithiole-*S*-oxides and the examination of their reactivity against amines, seen as prototypes of possible *in vivo* targets of pyrrothines and related compounds.

Chemistry.

The diester **5a** reacted with equimolar amounts of *m*-chloroperbenzoic acid [21] to give the dithiole monoxide **6a** as the main product (Scheme 2).

As suggested by computer-assisted calculations [22] S(2) as the more electron-rich sulphur atom in the dithiole ring was attacked by the peracid [23]. For the purpose of unambigous

Scheme 2



structure determination, however, **6a** was subjected to X-ray diffraction analysis (Figure 1) [24].

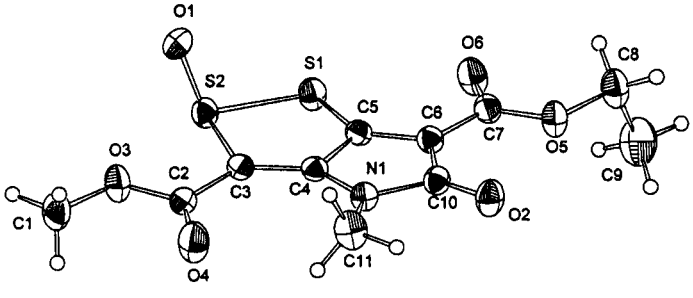


Figure 1. ORTEP plot of thiosulphinate **6a**.

Due to the chirality of the thiosulphinate group about one tenth of the investigated crystals was orientally disordered, *i.e.* the predominantly found *S*-enantiomer was accompanied by 10% of its mirror image isomer. Nevertheless the following conclusions can be made. The bond lengths of C(10)-O(2) and C(10)-N(1) provide little evidence for amide resonance stabilization as to be assumed in the starting dithiole **5a**. Noteworthy, however, are the short distances between C(4) and C(5) and between C(4) and N(1) as well as the relatively long C(3)-*S*(2) bond of 1.802 Å, a phenomenon

Table 1a

Single Crystal X-Ray Crystallographic Analysis of **6a**.

A. Crystal Parameters	
Formula	$C_{11}H_{11}NO_6S_2$ (317.33)
Crystal size, mm	0.57 x 0.47 x 0.17
Temperature	293(2) K
Wavelength	0.71069 Å
Space group	$P2_1/c$
Cell dimensions	a = 11.315(2) Å
	b = 16.144(2)Å
	c = 7.412(3) Å
	α = 90.00(2)°
	β = 99.23(2)°
	γ = 90.00(2)°
Volume	1336.4(6) Å^3
Z	4
Density calcd., Mg/m^3	1.577
Absorption coefficient, mm^{-1}	0.423
F(000)	656
Theta range for data collection	3.06 to 24.97°
Index ranges	-13≤h≤13, -19≤k≤0, -8≤l≤0
B. Refinement Parameters	
Reflections collected	2544
Independent reflections	2348 [R(int) = 0.0120]
non-zero reflections (I>2σI)	1973
Absorption correction	psi-scans
Max. and min. transmission	0.9996 and 0.9704
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2348 / 2 / 195
Goodness-of-fit on F^2	1.081
Final R indices [I>2σ(I)]	R1 = 0.0446, wR2 = 0.1137
R indices (all data)	R1 = 0.0562, wR2 = 0.1230
Largest diff. peak and hole	0.302 and -0.261 e.Å^{-3}
Used program	SHELXL-93

Table 1b

Bond Lengths (Å) and Bond Angles (°) for **6a**

S(1)-C(5)	1.706(3)	N(1)-C(4)	1.365(4)
S(1)-S(2)	2.1542(13)	N(1)-C(10)	1.416(4)
S(2)-O(1A)	1.41(2)	N(1)-C(11)	1.468(4)
S(2)-O(1)	1.468(3)	C(2)-C(3)	1.473(4)
S(2)-C(3)	1.802(3)	C(3)-C(4)	1.349(4)
O(2)-C(10)	1.196(4)	C(4)-C(5)	1.474(4)
O(3)-C(2)	1.318(4)	C(5)-C(6)	1.340(4)
O(3)-C(1)	1.443(4)	C(6)-C(7)	1.465(4)
O(4)-C(2)	1.185(4)	C(6)-C(10)	1.482(4)
O(5)-C(7)	1.321(4)	C(8)-C(9)	1.484(6)
O(5)-C(8)	1.464(4)	O(6)-C(7)	1.207(4)
C(5)-S(1)-S(2)	93.94(11)	C(2)-C(3)-S(2)	114.1(2)
O(1A)-S(2)-O(1)	124.3(7)	C(3)-C(4)-N(1)	136.5(3)
O(1A)-S(2)-C(3)	110.5(7)	C(3)-C(4)-C(5)	117.4(3)
O(1)-S(2)-C(3)	107.6(2)	N(1)-C(4)-C(5)	106.1(2)
O(1A)-S(2)-S(1)	107.5(6)	C(6)-C(5)-C(4)	110.3(3)
O(1)-S(2)-S(1)	108.72(12)	C(6)-C(5)-S(1)	131.9(2)
C(3)-S(2)-S(1)	94.07(10)	C(4)-C(5)-S(1)	117.8(2)
C(2)-O(3)-C(1)	117.5(3)	C(5)-C(6)-C(7)	123.3(3)
C(7)-O(5)-C(8)	116.6(3)	C(5)-C(6)-C(10)	107.0(3)
C(4)-N(1)-C(10)	110.4(2)	C(7)-C(6)-C(10)	129.6(3)
C(4)-N(1)-C(11)	129.1(3)	O(6)-C(7)-O(5)	125.3(3)
C(10)-N(1)-C(11)	119.9(2)	O(6)-C(7)-C(6)	120.8(3)
O(4)-C(2)-O(3)	123.2(3)	O(5)-C(7)-C(6)	113.8(3)
O(4)-C(2)-C(3)	125.5(3)	O(5)-C(8)-C(9)	109.7(3)
O(3)-C(2)-C(3)	111.2(3)	O(2)-C(10)-N(1)	123.7(3)
C(4)-C(3)-C(2)	129.8(3)	O(2)-C(10)-C(6)	130.1(3)
C(4)-C(3)-S(2)	116.0(2)	N(1)-C(10)-C(6)	106.2(2)

Table 1c

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement parameters ($Å^2$ x 10^3) for **6a**

	x	y	z	U(eq)
S(1)	4887(1)	1900(1)	2870(1)	54(1)
S(2)	6478(1)	1723(1)	1663(1)	49(1)
O(1)	6838(2)	2524(2)	986(4)	60(1)
O(1A)	7249(11)	1195(11)	2832(22)	39(6)
O(2)	1525(2)	825(2)	-1990(3)	62(1)
O(3)	7639(2)	987(2)	-850(3)	63(1)
O(4)	6211(2)	355(2)	-2717(5)	88(1)
O(5)	811(2)	1643(2)	1222(3)	57(1)
O(6)	2352(2)	2074(2)	3307(4)	69(1)
N(1)	3585(2)	842(2)	-1699(3)	44(1)
C(1)	8526(3)	700(3)	-1903(6)	73(1)
C(2)	6512(3)	796(2)	-1449(4)	47(1)
C(3)	5713(3)	1153(2)	-269(4)	43(1)
C(4)	4508(3)	1132(2)	-445(4)	40(1)
C(5)	3956(3)	1503(2)	1035(4)	41(1)
C(6)	2763(3)	1428(2)	670(4)	43(1)
C(7)	1958(3)	1747(2)	1871(5)	49(1)
C(8)	-43(3)	1956(3)	2349(5)	68(1)
C(9)	-270(4)	1313(4)	3681(6)	96(2)
C(10)	2474(3)	1007(2)	-1123(4)	45(1)
C(11)	3610(3)	507(3)	-3533(4)	65(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

commonly observed with push-pull alkenes such as β-enaminones [25]. In contrast, the C(5)-*S*(1) bond is nearly 0.1 Å shorter. The measured S-S distance of 2.154 Å is in accordance with bond lengths reported for other thiosulphinate esters [21]. The sulphinyl group is twisted out of the otherwise flat ring framework by 8.12°.

More than two dozens of alternative oxidants were tested on **5a**, but interestingly not one electrophilic, nucleophilic or radical oxidant other than *m*-chloroperbenzoic acid [26-31] was effective with the sole exception of the strongly electrophilic peroxytrifluoroacetic acid [32]. Prolonged exposure of dithiole **5a** or monoxide **6a** to a large excess of either reagent cleanly gave rise to dioxide **7**, albeit in moderate yield. Since oxidations of thiosulphinates were reported to proceed through an intermediate α,α'-disulphoxide [33] often a mixture of isomeric thiosulphonate esters is obtained [29,34]. Hence the structure of the sole oxidation product **7** had to be undoubtedly clarified by X-ray diffraction analysis (Figure 2).

The unit cell of the thiosulphonate ester **7** displays great similarity to the one observed with monoxide **6a**. Also the measured bond lengths are essentially the same as in **6a**, perhaps with the exception of the 0.02 Å shorter C(3)-*S*(2) and S(1)-S(2) linkages. The sulphonyl group is twisted out of the otherwise plane γ-alkylidenepyrrolidinone backbone by 8.66°.

The oxidation of **5a** to the oxides **6a** and **7** led to a shift of the ir lactam and ester carbonyl stretching bands thus indicating the lessened resonance participation of the carbonyl groups. With respect to the uv absorption the oxidation is

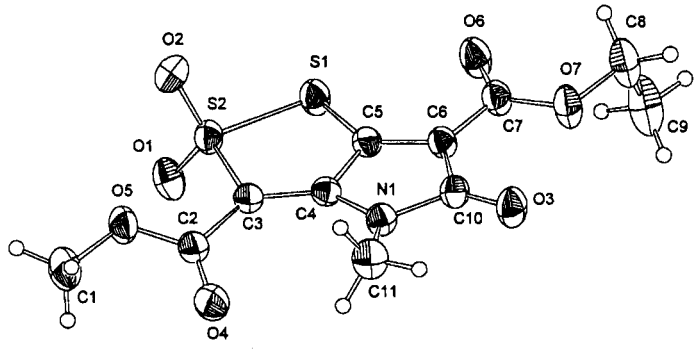


Figure 2. ORTEP plot of thiosulphonate **7**.

accompanied by a hypsochromic shift of the highest maximum of 100 nm.

The monoxide **6a** may be reduced to **5a** by a series of reagents, *e.g.* 1-phenyl-1*H*-tetrazole-5-thiol [35] or triphenyl phosphane. As we found out, this deoxygenation is best performed using either excess 1,2-dimethylhydrazine [36] or thiophenol [37,38]. To the best of our knowledge this is the first application of symmetrical dimethylhydrazine as a reducing agent for thiosulphinates. The reddening of **6a** in substance and the disintegration of concentrated solutions especially upon exposure to bright daylight result from the proneness to disproportionation.

Table 2a

Single Crystal X-Ray Crystallographic Analysis of **7**

A. Crystal Parameters	
Formula	$C_{11}H_{11}NO_7S_2$ (333.33)
Crystal size, mm	0.53.x 0.40 x 0.27
Temperature	293(2)K
Wavelength	0.71073 Å
Spacegroup	$P2_1/c$
Cell dimensions	a = 11.455(3) Å
	b = 16.258(5) Å
	c = 7.647(2) Å
	α = 90.00(2)°
	β = 99.76 (2)°
	γ = 90.00 (2)°
Volume	1403.5(7) $Å^3$
Z	4
Density calcd, Mg/m^3	1.578
Absorption coefficient, mm^{-1}	0.412
F(000)	688
Theta range for data collection	2.51 to 24.97°
Index ranges	-13≤h≤13,-19≤k≤3,-9≤l≤3
B. Refinement Parameters	
Reflections collected	3750
Independent reflections	2468 [R(int) = 0.0173]
Observed reflections (I>2σI)	2085
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2468/0/193
Goodness-of-fit on F^2	1.089
Final R indices [I>2σ(I)]	R1 = 0.0385,wR2 = 0.0992
R indices (all data)	R1 = 0.0474,wR2 = 0.1057
Largest diff. peak and hole	0.199 and -0.234e. $Å^{-3}$
Program used	SHELXL-93

Table 2b

Bond Lengths (Å) and Bond Angles (°) for **7**

S(1)-C(5)	1.710(2)	N(1)-C(4)	1.359(3)
S(1)-S(2)	2.1355(10)	N(1)-C(10)	1.419(3)
S(2)-O(1)	1.419(2)	N(1)-C(11)	1.472(3)
S(2)-O(2)	1.424(2)	C(2)-C(3)	1.479(3)
S(2)-C(3)	1.783(2)	C(3)-C(4)	1.349(3)
O(3)-C(10)	1.198(3)	C(4)-C(5)	1.481(3)
O(4)-C(2)	1.193(3)	C(5)-C(6)	1.341(3)
O(5)-C(2)	1.319(3)	C(6)-C(7)	1.469(3)
O(5)-C(1)	1.440(3)	C(6)-C(10)	1.482(3)
O(6)-C(7)	1.208(3)	C(8)-C(9)	1.478(5)
O(7)-C(7)	1.323(3)	O(7)-C(8)	1.472(3)
C(5)-S(1)-S(2)	91.02(8)	C(2)-C(3)-S(2)	116.5(2)
O(1)-S(2)-O(2)	119.05(12)	C(3)-C(4)-N(1)	135.7(2)
O(1)-S(2)-C(3)	110.91(12)	C(3)-C(4)-C(5)	117.9(2)
O(2)-S(2)-C(3)	110.11(12)	N(1)-C(4)-C(5)	106.4(2)
O(1)-S(2)-S(1)	108.46(9)	C(6)-C(5)-C(4)	109.8(2)
O(2)-S(2)-S(1)	108.13(9)	C(6)-C(5)-S(1)	130.8(2)
C(3)-S(2)-S(1)	98.05(8)	C(4)-C(5)-S(1)	119.4(2)
C(2)-O(5)-C(1)	116.9(2)	C(5)-C(6)-C(7)	122.2(2)
C(7)-O(7)-C(8)	115.8(2)	C(5)-C(6)-C(10)	107.3(2)
C(4)-N(1)-C(10)	110.4(2)	C(7)-C(6)-C(10)	130.6(2)
C(4)-N(1)-C(11)	127.9(2)	O(6)-C(7)-O(7)	125.4(2)
C(10)-N(1)-C(11)	120.5(2)	O(6)-C(7)-C(6)	120.9(2)
O(4)-C(2)-O(5)	124.8(2)	O(7)-C(7)-C(6)	113.7(2)
O(4)-C(2)-C(3)	123.9(2)	O(7)-C(8)-C(9)	109.5(3)
O(5)-C(2)-C(3)	111.3(2)	O(3)-C(10)-N(1)	123.9(2)
C(4)-C(3)-C(2)	130.7(2)	O(3)-C(10)-C(6)	130.0(2)
C(4)-C(3)-S(2)	112.8(2)	N(1)-C(10)-C(6)	106.1(2)

Table 2c

Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement parameters ($Å^2x10^3$) for **7**

	x	y	z	U(eq)
S(1)	94(1)	1902(1)	2302(1)	63(1)
S(2)	-1430(1)	1710(1)	3518(1)	57(1)
O(1)	-2237(2)	1201(1)	2390(3)	76(1)
O(2)	-1822(2)	2490(1)	4037(3)	77(1)
O(3)	3420(2)	864(1)	7101(3)	73(1)
O(4)	-1224(2)	244(1)	7584(3)	85(1)
O(5)	-2599(2)	1086(1)	6163(3)	70(1)
O(6)	2541(2)	2090(1)	1918(3)	79(1)
O(7)	4091(2)	1612(1)	3858(2)	74(1)
N(1)	1377(2)	873(1)	6807(3)	53(1)
C(1)	-3464(3)	765(2)	7147(5)	96(1)
C(2)	-1518(2)	782(2)	6542(4)	58(1)
C(3)	-729(2)	1155(1)	5418(3)	51(1)
C(4)	462(2)	1144(1)	5575(3)	48(1)
C(5)	996(2)	1507(1)	4118(3)	50(1)
C(6)	2179(2)	1439(1)	4491(3)	51(1)
C(7)	2951(2)	1748(2)	3287(3)	60(1)
C(8)	4903(3)	1911(2)	2701(4)	89(1)
C(9)	4984(3)	1295(3)	1305(5)	118(2)
C(10)	2474(2)	1034(2)	6247(3)	54(1)
C(11)	1346(3)	612(2)	8642(3)	73(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

In contrast to either **5a** or **7** the thiosulphinate **6a** reacted rapidly with methylamine even at dry ice temperature. From the host of compounds to be observed by tlc we isolated the sulphur-free lactam **8a** as the major component besides the fluorescent bicyclic isothiazole **9a** [39]. The (*E*)-configuration of **8a** was confirmed by homonuclear NOE difference spectroscopy. The structure of **9a** was assigned with reference to the analog synthesis of the corresponding dimethyl ester **9c** from dithiole **5b** via the *S*-oxide **6b**. Isothiazole **9c** in turn has recently been synthesized by us using an independent route [40]. Analogously, exposure of thiosulphinate **6a** to benzylamine gave rise to both the lactam **8b** and the fluorescent isothiazole **9b**.

From these results no unambiguous deductions concerning the reaction mechanism of **6a** with amines can been drawn. But, most likely, the amine attacks the thiosulphinate group forming an aminosulphinyl-substituted thiotetramic acid **11a** or its salt. Thereupon by an intramolecular addition reaction of the sulphinamide moiety followed by elimination of hydrogen sulphide, isothiazole oxides should be formed. The same outcome is to be expected by an addition-elimination reaction of **11a** and amines leading to intermediates **11b** and final cyclization involving an intramolecular transamidation. The evolved hydrogen sulfide may act as an reductant against the isothiazole oxides as well as the reaction intermediates and especially *vs.* the starting thiosulphinates. This would bring the reaction to an end and account for the low yields of the isothiazoles obtained. On the other hand amino-substituted lactams **8** may be formed from **10b** by loss of the corresponding thionylimine accompanied by prior or subsequent change of stereochemistry.

Based upon these observations we assumed that by adding iodine as a competitive scavenger of hydrogen sulfide the aminolysis of *S*-oxide **6a** would run in favour of the formation of the isothiazole oxides. This is indeed the case. Now from the reaction of thiosulphinate **6a** with methyl- or benzylamine the non-fluorescent isothiazole *S*-oxides **10a/b** were isolated as the main products. Hence formal *S/N*-exchange has taken place in this reaction. The analogous *S/N*-exchange does not occur with the dioxide **7**. Only reduced dithiole **5a** was obtained besides sulphur-free products which were not further investigated. The isothiazole oxides **10a/b** can be reduced to the isothiazoles **9a/b** by means of 1,2-dimethylhydrazine in excellent yields. To the best of our knowledge this is the first application of dimethylhdrazine as a reducing agent for sulphinamides [41].

The *S/N*-exchange with **6a** even proceeded well with the sterically highly demanding 1-adamantylamine to give the expected isothiazole oxide **10c** in addition to the bislactam **12**. Here obviously the oxidative recyclization of the intermediate thiosulphinate competed with its iodinative degradation, which then was followed by (*E/Z*)-isomerization and lactam ring closure. A slightly different course took the *S/N*-exchange using *tert*-butylamine. Besides the expected isothiazole oxide **10d** considerable amounts of thiosulphonate ester **7** were isolated. Obviously due to steric hindrance the *S/N*-exchange reaction is slowed down

allowing the partial disproportionation of the thiosulphinate **6a** to occur [42-46]. Compound **5a** as the corresponding reduction product could clearly be detected by tlc and hplc of the crude reaction mixture. In principle, disproportionation of thiosulphinate esters is known from acyclic representatives [45].

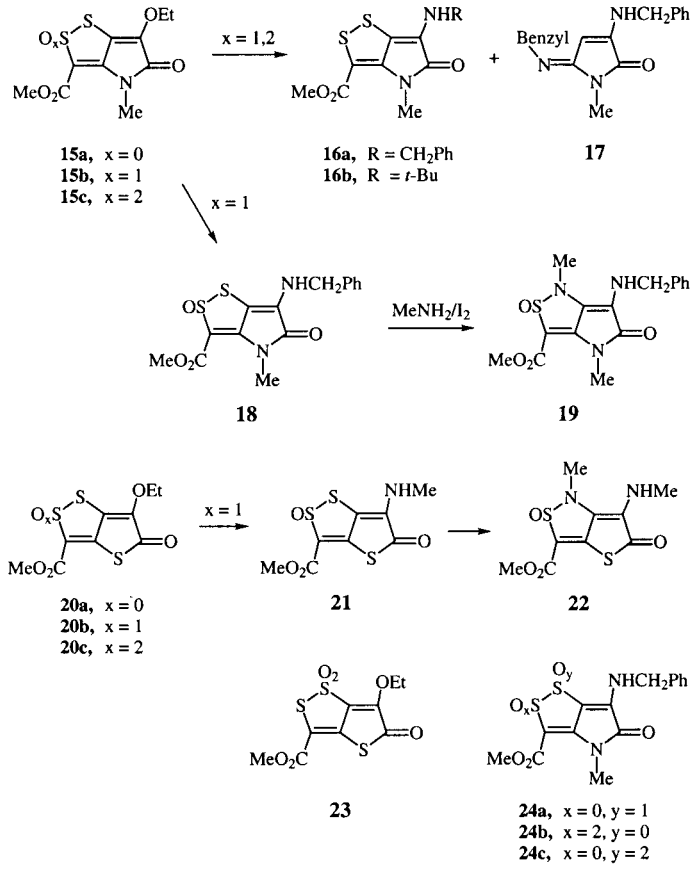
It is noteworthy that the *S/N*-exchange reaction could even be performed with poorly nucleophilic ammonia giving rise to isothiazole oxide **10e**. Much to our surprise **10e** could not be obtained alternatively by debutylation of **10d** with trifluoroacetic acid. Instead a structural isomer of **10e**, the *N*-hydroxyisothiazole **9d** was isolated in high yield. Obviously this is the result of a Pummerer-type rearrangement of the intermediate **10e** with trifluoroacetic acid. This notion was substantiated by conversion of pure **10e** into **9d** with trifluoroacetic acid. As a structural proof the *N*-hydroxyisothiazole **9d** was treated with diazomethane to produce the *N*-methoxyisothiazole **9e**. To the best of our knowledge this is the first aza-Pummerer-like rearrangement of a sulphinamide leading to the *N*-hydroxysulphenamide [47-50].

In the oxidation of other pyrrothines, different behaviour was observed depending upon the substitution pattern. The 3-unsubstituted dithiolopyrroles **2** and **13a** reacted only sluggishly with either *m*-chloroperbenzoic acid or peroxytrifluoroacetic acid to give the dioxides **14** and **13b**, respectively, as the sole products in poor yield. The donor-substituted pyrrothine **15a** on the other hand was rapidly oxidized with *m*-chloroperbenzoic acid giving rise to the corresponding monoxide **15b** accompanied by only minor amounts of the dioxide **15c** (Scheme 3). In this case alternative oxidants such as potassium peroxodisulphate [51] or sodium periodate/iodine [27] proved equally effective in the preparation of the thiosulphinate **15b**.

In this *S*-oxide the reactivity of the vinylogous carbonic ester partial structure apparently is enhanced since treatment of **15b** with benzylamine at room temperature gave the amino-substituted thiosulphinate **18**. Only under more severe conditions *S*-oxide **15b** reacted further with benzylamine *via* ring opening to furnish the sulphur-free lactam **17** along with a considerable amount of dithiole **16a**. The structure of **17** was established by analysis and *NO*-experiments indicating the steric proximity of the vinylic hydrogen to both benzylic groups. In the reaction of dioxide **15c** with *tert*-butylamine this deoxygenation became the predominant pathway and the dithiole **16b** was exclusively formed [52] though no corresponding oxidation product could be found. The *S/N*-exchange reaction of thiosulphinate **18** with methylamine, however, proceeded in the usual way to give the isothiazole oxide **19** in moderate yield.

Oxidation of the donor-substituted dithiolothiophene **20a** with equimolar amounts of *m*-chloroperbenzoic acid gave the thiosulphinate **20b** as the main product. Interestingly, monoxide **20b** could cleanly be reduced to

Scheme 3



dithiole **20a** by refluxing with excess isonicotinic acid hydrazide in ethanol [53]. Further oxidation of *S*-oxide **20b** with an excess of peracid, however, led to the formation of the two regioisomeric thiosulphonates **20c** and **23** in a ratio of 6:1 as evidenced by hplc analysis of the crude reaction mixture. For the sake of a doubtless structure assignment the minor product **23** was subjected to X-ray diffraction analysis (Figure 3) indicating the anticipated dioxygenation at S(1).

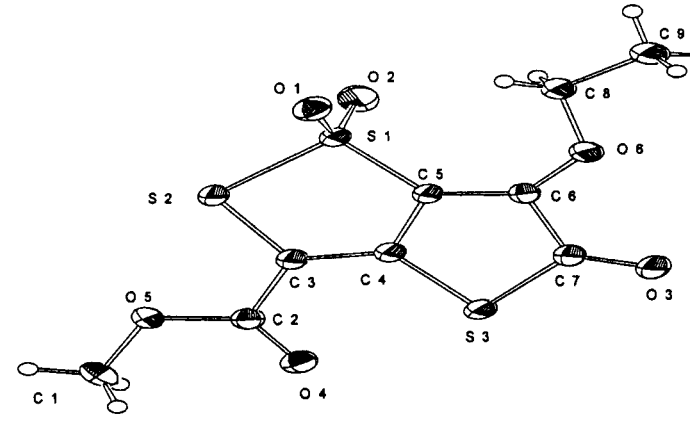


Figure 3. ORTEP plot of thiosulphonate **23**.

Table 3a

Single Crystal X-Ray Crystallographic Analysis of **23**

A. Crystal Parameters	
Formula	$C_9H_8O_6S_3$ (308.33)
Crystal size, mm	0.53 x 0.43 x 0.37
Temperature	293(2) K
Wavelength	0.71073 Å
Spacegroup	P-1 (no. 2)
Cell dimensions	a = 6.4619(10) Å
	b = 6.4284(11) Å
	c = 14.851(3) Å
	α = 91.252(14)°
	β = 96.680(14)°
	γ = 100.514(13)°
Volume	601.8(2) Å^3
Z	2
Density calcd, Mg/m^3	1.701
Absorption coefficient, mm^{-1}	0.631
F(000)	316
Theta range for data collection	2.76 to 24.97°
Index ranges	0≤h≤7,-7≤k≤7,-17≤l≤17
B. Refinement Parameters	
Reflections collected	2326
Independent reflections	2119 [R(int) = 0.0127]
Observed reflections [I>2(σI)]	1954
Absorption correction	Semi-empirical from ψ-scans
Max. and min. transmission	0.9993 and 0.9417
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2119/0/165
Goodness-of-fit on F^2	1.069
Final R indices [I>2σ(I)]	R1 = 0.0340, wR2 = 0.0893
R indices (all data)	R1 = 0.0369, wR2 = 0.0925
Largest diff. peak and hole	0.340 and -0.315 e. Å^{-3}
Program used	SHELXL-93

Table 3b

Bond Lengths (Å) and Bond Angles (°) for **23**

S(1)-O(2)	1.422(2)	O(5)-C(2)	1.331(3)
S(1)-O(1)	1.422(2)	O(5)-C(1)	1.450(3)
S(1)-C(5)	1.763(2)	O(6)-C(6)	1.306(3)
S(1)-S(2)	2.1103(8)	O(6)-C(8)	1.449(3)
S(2)-C(3)	1.755(2)	C(2)-C(3)	1.478(3)
S(3)-C(4)	1.740(2)	C(3)-C(4)	1.347(3)
S(3)-C(7)	1.778(2)	C(4)-C(5)	1.437(3)
O(3)-C(7)	1.194(3)	C(5)-C(6)	1.356(3)
O(4)-C(2)	1.198(3)	C(6)-C(7)	1.506(3)
		C(8)-C(9)	1.494(3)
O(2)-S(1)-O(1)	117.27(12)	C(2)-C(3)-S(2)	119.2(2)
O(2)-S(1)-C(5)	111.03(10)	C(3)-C(4)-C(5)	120.2(2)
O(1)-S(1)-C(5)	111.88(10)	C(3)-C(4)-S(3)	127.0(2)
O(2)-S(1)-S(2)	109.29(8)	C(5)-C(4)-S(3)	112.8(2)
O(1)-S(1)-S(2)	108.87(8)	C(6)-C(5)-C(4)	114.5(2)
C(5)-S(1)-S(2)	96.46(7)	C(6)-C(5)-S(1)	133.4(2)
C(3)-S(2)-S(1)	93.21(7)	C(4)-C(5)-S(1)	112.2(2)
C(4)-S(3)-C(7)	90.95(10)	O(6)-C(6)-C(5)	135.1(2)
C(2)-O(5)-C(1)	115.0(2)	O(6)-C(6)-C(7)	113.3(2)
C(6)-O(6)-C(8)	120.4(2)	C(5)-C(6)-C(7)	111.7(2)
O(4)-C(2)-O(5)	125.6(2)	O(3)-C(7)-C(6)	124.8(2)
O(4)-C(2)-C(3)	122.9(2)	O(3)-C(7)-S(3)	125.0(2)
O(5)-C(2)-C(3)	111.5(2)	C(6)-C(7)-S(3)	110.2(2)
C(4)-C(3)-C(2)	123.2(2)	O(6)-C(8)-C(9)	106.0(2)
C(4)-C(3)-S(2)	117.6(2)		

Table 3c

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters (Å^{2}x10^3) for **23**

	x	y	z	U(eq)
S(1)	4301(1)	-981(1)	1702(1)	36(1)
S(2)	1970(1)	359(1)	926(1)	50(1)
S(3)	2808(1)	3347(1)	3634(1)	54(1)
O(1)	6235(3)	-490(3)	1314(1)	54(1)
O(2)	3488(3)	-3155(3)	1817(1)	59(1)
O(3)	5832(3)	2762(3)	4916(1)	71(1)
O(4)	-838(3)	3915(3)	2359(1)	58(1)
O(5)	-776(2)	3389(2)	860(1)	42(1)
O(6)	7199(3)	-97(3)	3869(1)	51(1)
C(1)	-2448(4)	4607(4)	682(2)	56(1)
C(2)	-153(3)	3177(3)	1734(1)	39(1)
C(3)	1518(3)	1878(3)	1854(1)	36(1)
C(4)	2776(3)	1847(3)	2641(1)	36(1)
C(5)	4370(3)	545(3)	2709(1)	34(1)
C(6)	5609(3)	742(3)	3520(1)	39(1)
C(7)	4991(4)	2306(4)	4160(2)	49(1)
C(8)	7869(4)	-1776(4)	3376(2)	51(1)
C(9)	9540(5)	-2508(5)	4006(2)	74(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

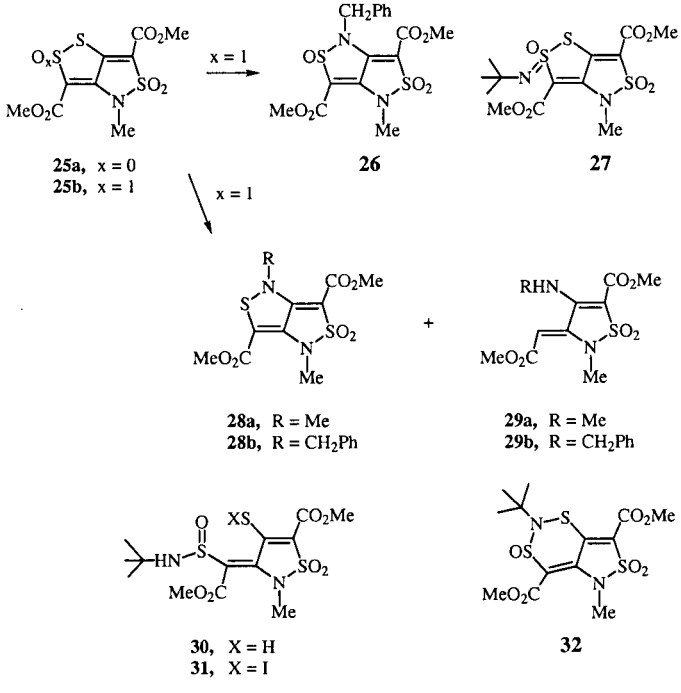
The measured bond lengths and angles of **23** are all within the expected range. Interestingly, the thiolactone carbonyl group has essentially the same bond length as the corresponding lactam carbonyl groups in compounds **6a** and **7**. In the dithiole part of the molecule the distances C(3)-S(2) and C(5)-S1 are comparable within experimental errors. Here again the sulphonyl SO_2 group is twisted out of the otherwise flat bicycle by 6.32°. The measured S(1)-S(2) distance of 2.110 Å is only marginally smaller than the one observed with the structurally related dithiolopyrrole dioxide **7**.

The intended stepwise oxidation of the amino-substituted dithiole **16a** finally led to the isolation of all possible *S*-oxides. With equimolar amounts of *m*-chloroperbenzoic acid the main products were the *S*(2)-oxide **18** already mentioned above and the *S*(1)-oxide **24a** in a ratio of 2:3 (hplc). In this case the ^{1}H nmr spectrum of the latter isomer was sufficient for structure elucidation. Due to their proximity to the chiral sulphur the two benzylic hydrogens are magnetically anisochronous and hence exhibit a characteristically crowded signal pattern [54]. This assignment separately proved the former structure assignment of thiosulphinate **18** and hence of its synthetic congener **15b**. If the dithiole **16a** was reacted with excess *m*-chloroperbenzoic acid a mixture of the isomeric dioxides **24b** and **24c** in a ratio of 3:1 (hplc) was obtained which could be separated by flash chromatography. The structures of these compounds could again be clarified by comparison of their nmr data. Compared to dioxide **24b** the benzylic hydrogen nmr peaks of its isomer **24c** are shifted downfield by 0.22 ppm whereas the ester methoxy signal displays a diamagnetic shift of 0.10 ppm. In addition, the

proximity of the sulphonyl moiety to the amine group in **24c** effects deshielding of the nitrogen-bound hydrogen as evidenced by a paramagnetic shift by 0.66 ppm in comparison to **24b** and its markedly lowered ir frequency (3279 cm^{-1} *vs.* 3372 cm^{-1} for **24b**). The *S*-oxide **20b** expectedly displayed the same reactivity against amines as its aza analogue **15b**. Hence simple nucleophilic substitution of the ethoxyl group with methylamine gave thiolactone **21**, which upon treatment with methylamine/iodine furnished isothiazole oxide **22**.

Finally, the scope of this novel *S/N*-exchange reaction could successfully be extended also to structurally related dithiolosultames, *e.g.* monoxide **25b**, obtained regioselectively by oxidation of dithiole **25a** with *m*-chloroperbenzoic acid without concomitant dioxide formation, upon treatment with benzylamine/iodine smoothly produced the desired isothiazole oxide **26** in a yield exceeding 90% (Scheme 4).

Scheme 4



In the absence of iodine *S*-oxide **25b** reacted with either methyl- or benzylamine to give the expected mixture of the fluorescent isothiazoles **28a,b** and the sultames **29a,b**, respectively [55].

The analogous reaction of **25b** with *tert*-butylamine, however, surprisingly took another course. Instead of the expected isothiazolosultame the bicyclic imidothiosulphonate **27** was formed, whose structure was unambigously clarified by X-ray diffraction analysis (Figure 4). However, due to poor crystal quality (very thin needles) the data obtained allowed only the determination of the compounds topology and prohibit a detailed discussion of atomic parameters or bond lengths of **27**.

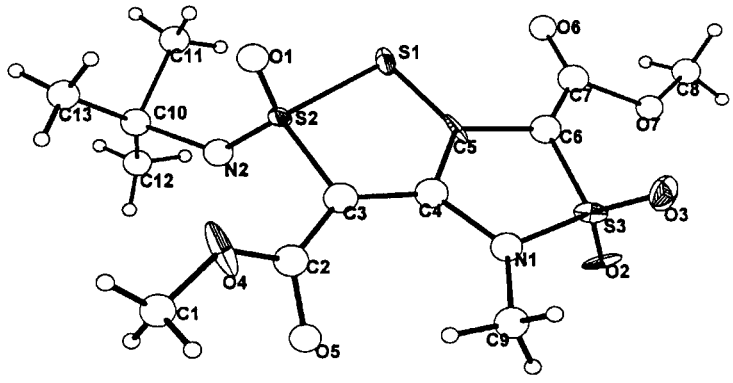


Figure 4. ORTEP plot of thiosulphonate **27**.

Table 4a

Single Crystal X-Ray Crystallographic Analysis of **27**

A. Crystal Parameters	
Formula	$C_{13}H_{18}N_2O_7S_3$ (410.49)
Crystallisation medium	Diisopropyl ether/ ethyl acetate
Crystal form	yellow, very thin needles
Crystal size, mm	0.5 x 0.03 x 0.01
Temperature	183 K
Space group	$P2_1$
cell dimension	a = 6.0967(2) Å
	b = 8.2413(1) Å
	c = 19.5179(2) Å
	β = 96.342(2)°
Volume	974.68(4) $Å^3$
Molecules/unit cell	2
Density calcd, g/cm^3	1.399
absorption coefficient, mm^{-1}	0.415
Index ranges	$-6 \le h \le 4$, $-9 \le k \le 9$, $-21 \le l \le 21$
B.Refinement Parameters	
Reflections collected	4071
Independent reflections	2254 [R(int) = 0.0883]
Number of unique refl. ($I>4\sigma(I)$)	1970
Max./min.transmission	1.000/ 0.3907
Goodness-of-fit on F^2	0.996
R-index [a]	0.186
Flackparameter	0.0(6)
Program used	SHELXL-97

[a] $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$

Table 4b

Selected Bond Lengths (Å) and Bond Angles (°) for **27**

S(1)-C(5)	1.74(2)	S(1)-S(2)	2.214(11)
S(2)-O(1)	1.47(3)	S(2)-N(2)	1.49(2)
S(2)-C(3)	1.80(3)	S(3)-O(2)	1.39(3)
S(3)-C(6)	1.90(3)	S(3)-N(1)	1.72(2)
C(5)-S(1)-S(2)	89.1(8)	O(1)-S(2)-N(2)	122.3(14)
O(1)-S(2)-C(3)	105.3(I4)	N(2)-S(2)-C(3	107.4(13)
O(1)-S(2)-S(1)	103.5(11)	N(2)-S(2)-S(1)	116.4(11)
C(3)-S(2)-S(1)	99.1(10)	O(2)-S(3)-O(3	115.8(16)
O(2)-S(3)-N(1)	107.9(13)	O(3)-S(3)-N(1)	110.0(13)
O(2)-S(3)-C(6)	117.3(14)	O(3)-S(3)-C(6)	108.6(13)
N(1)-S(3)-C(6)	95.2(12)	C(4)-N(1)-S(3)	111.1(18)

Table 4c

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for **27**

	x	y	z	U(eq)
S(1)	8721(17)	5077(10)	2342(4)	65(3)
S(2)	6462(15)	6685(7)	2842(4)	55(3)
S(3)	11007(13)	8564(8)	937(4)	53(3)
O(1)	4270(05)	6030(03)	2610(12)	75(7)
O(2)	12960(04)	9410(03)	1092(11)	67(6)
O(3)	10220(05)	8470(03)	239(11)	79(8)
O(4)	3840(03)	9730(02)	2729(9)	49(5)
O(5)	6740(05)	11440(03)	629(12)	79(7)
O(6)	11900(04)	3910(03)	1400(11)	65(6)
O(7)	13840(04)	5710(02)	741(10)	60(6)
N(1)	9040(04)	9430(03)	1394(10)	44(5)
N(2)	7150(04)	7120(03)	3578(11)	54(6)
C(1)	2700(09)	11290(05)	2930(02)	95(1)
C(2)	5750(06)	10080(04)	2581(14)	54(7)
C(4)	8280(05)	8320(03)	1855(13)	47(7)
C(5)	9320(04)	6690(03)	1816(10)	32(5)
C(6)	10820(05)	6470(03)	1333(13)	47(7)
C(3)	6710(05)	8490(03)	2336(13)	48(7)
C(7)	11750(05)	5350(04)	1077(14)	52(7)
C(8)	15320(06)	4450(04)	559(17)	70(9)
C(9)	8030(07)	12020(05)	1173(19)	77(1)
C(10)	6550(07)	6100(04)	4251(17)	70(9)
C(11)	7050(06)	4210(04)	3999(18)	68(9)
C(12)	8320(08)	6600(06)	4800(02)	91(1)
C(13)	4010(07)	6120(05)	4215(19)	77(1)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

The formation of **27** may be understood on the basis of the proposed mechanism of the *S/N*-exchange reaction mentioned above. Due to steric reasons the action of *tert*-butylamine upon the thiosulphinate **25b** is limited to formation of the sulphinamide **30** analogous to the primary step in the usual reaction sequence. The enthiol group of **30** is oxidized by iodine to furnish the sulphenyl halide as the first intermediate [56]. This may be used up intramolecularly by forming the cyclic *N*-alkylthiosulphinamide **32** which might undergo further ionic rearrangement to compound **27**. There is an analogy to the postulated thermal rearrangement of *N*-alkoxysulphinamides to not isolated *O*-alkylsulphonimidates [57,58]. As far as we know there is no literature report dealing with either *N*-alkylthiosulphinamides or *S*-alkylthiosulphonimidates. An alternative route to **27** may be direct cyclization of the sulphenyl iodide **31**. This reaction may be seen in analogy to the formation of thiosulphonates by sulphenylation of sulphinate salts [59], but then this would imply the existence of an ambident anion of sulphinamide **31**. To the best of our knowledge **27** represents the first example of an imidothiosulphonic acid ester [60].

In summary, we have demonstrated that by chemical oxidation of acceptor-substituted as well as donor-substituted fused 1,2-dithioles preferentially *S*(2)-oxides are formed. These monoxides display high reactivity against *N*-nucleophiles and can be easily transformed by *S/N*-exchange reactions into bicyclic isothiazoles. In contrast, amino-substituted dithioles lack the same regioselectivity upon oxidation and the *S*-oxides obtained show far less reactivity against *N*-nucleophiles. This is in agreement with the findings in the antimycobacterial testing regarding the substituent effects. Here, despite of different lipophilicity, dithioles with acceptor-substituents in the 6-position showed similar minimum inhibition concentration values as ethoxy-substituted compounds did. The only amino-substituted substance tested, however, was far less active in comparison [8]. Hence these results seem to support the hypothesis discussed at the outset that cellular oxidative activation might be a prerequisite for antimicrobial activity of fused 1,2-dithioles of the pyrrothine-type **1**. Because of the assumed high reactivity of the thiosulphinates against bionucleophiles it is not surprising that **25b**, the only tested *S*-oxide so far [8], displayed weaker antimycobacterial activity than the parent compound **25a**.

EXPERIMENTAL

Melting points were determined using a Gallenkamp Melting Point apparatus and are uncorrected. Flash chromatography was performed using silica gel (230-400 mesh) from Merck. The ^1H nmr spectra were recorded at 400 MHz using tetramethylsilane as internal standard on a JEOL GSX 400 Spectrometer. The solvent was deuteriochloroform if not indicated otherwise. Mass spectra were obtained with a Hewlett Packard 5989A Mass Spectrometer employing both EI and CI mode. Infrared spectra were measured as potassium bromide plates using a FT-IR-Spectrometer PARAGON 1000 (Perkin-Elmer). The uv analysis was performed in methanolic solutions on Uvikon 810 Anakomp 220 (Kontron) and UV/VIS Spectrometer Lambda 20 (Perkin Elmer). The hplc analysis was made employing Merck-Hitachi L-6000A/L-4000A and LiChrospher® 100 DIOL, 10 µm (Merck). Microanalyses were carried out applying an Analysator CHN-O-Rapid from Heraeus or were done by I. Beetz, Mikroanalytisches Laboratorium, Kronach, Germany. Dichloromethane was freshly distilled from calcium hydride and ethanol from magnesium turnings under nitrogen. Tetrahydofuran was distilled from sodium benzophenone ketyl under nitrogen immediately prior to use. All moisture-sensitive reactions were run with flame-dried glassware.

General Procedure A. Synthesis of Thiosulphinates from Dithioles.

To an ice-cooled solution of the dithiole (1.0 mmole) in dichloromethane (15 ml) was added a cooled solution of *m*-chloroperbenzoic acid (1.1 mmoles) in dichloromethane (10 ml). After two hours the solution was allowed to reach room temperature, washed rapidly with saturated aqueous sodium bicarbonate solution (10 ml) and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue, containing mainly the *S*-monoxide and in some cases minor amounts of the corresponding *S*-dioxides, recrystallized without or after purification by flash chromatography.

General Procedure B. Synthesis of Thiosulphonates from Dithioles.

To an ice-cold solution of the dithiole (1.0 mmole) in dichloromethane (15 ml) was added a cooled solution of

m-chloroperbenzoic acid (2.1 mmoles) in dichloromethane (10 ml). After two hours the solution was allowed to reach room temperature and kept at this temperature for the time indicated. Then the solution was washed rapidly with saturated aqueous sodium bicarbonate solution (10 ml) and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue recrystallized without or after purification by flash chromatography.

General Procedure C. Synthesis of Isothiazole *S*-Oxides by *S/N*-Exchange Reaction.

To a dry ice-cooled solution of the corresponding *S*-monoxide (1 mmole) in dry tetrahydrofuran (100 ml) was added portionwise iodine (2 mmoles). To this mixture a solution of the corresponding primary amine (2 mmoles) in tetrrahydrofuran (5 ml) was added dropwise. The mixture was allowed to reach ambient temperature, then acidified with dilute sulfuric acid and extracted thrice with dichloromethane. The combined organic extracts were washed successively with saturated aqueous sulfurous acid solution, water and brine and finally dried over sodium sulfate. The volatile products were removed *in vacuo* and the residue purified by flash chromatography.

General Procedure D. Reaction of Thiosulphinates with Primary Amines.

To a dry ice-cooled solution of the corresponding *S*-monoxide (1 mmole) in dry tetrahydrofuran (20 ml) was added dropwise a solution of the primary amine (2 mmoles) in tetrahydrofuran (2 ml). The solution was kept for one hour at -78°, allowed to reach ambient temperature, then diluted with ethyl acetate (50 ml) and washed with dilute sulfuric acid. The aqueous layer was extracted with ethyl acetate (30 ml), the combined organic phases were dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography.

General Prcoedure E. Reduction of Thiosulphinates or Isothiazole Oxides with 1,2-Dimethylhydrazine.

To a solution of 1,2-dimethylhydrazine dihydrochloride (15 mmoles) and 1,8-diazabicyclo[5.4.0]undec-7-ene (30 mmoles) in dry dichloromethane (40 ml) was added the *S*-oxide (1 mmole) in dichloromethane (10 ml). After one hour at room temperature another portion of 15 mmoles of both 1,2-dimethylhydrazine dihydrochloride and 1,8-diazabicyclo(5.4.0(undec-7-ene was added and the mixture stirred for another hour. After dilution with dichloromethane (50 ml) the organic phase was washed with dilute sulfuric acid and dried with sodium sulfate. The volatile products were evaporated and the residue subjected to flash chromatography.

Ethyl 4,5-Dihydro-3-methoxycarbonyl-4-methyl-2,5-dioxo-1,2-dithiolo[4,3-*b*]pyrrole-6-carboxylate (**6a**).

This compound was prepared following general procedure A from dithiole **5a** [61] (0.301 g, 1.0 mmole). Twofold recrystallization from diisopropyl ether/ethyl acetate gave light orange crystals (30%), mp 180°; ir: ν 2957, 1748, 1725, 1684, 1611 cm^{-1}; uv: λ max (log ε) 315 nm (4.055); ^1H nmr: δ 4.39 (q, 2 H, J = 7.3 Hz), 3.96 (s, 3 H), 3.48 (s, 3 H), 1.37 (t, 3 H, J = 7.3 Hz); ms: m/z 317 [M^+].

Anal. Calcd. for $C_{11}H_{11}NO_6S_2$ (317.34): C, 41.63; H, 3.49; N, 4.41; S, 20.21. Found: C, 41.72; H, 3.47; N, 4.34; S, 19.97.

X-ray Diffraction Analysis of Thiosulphinate **6a**.

Data collection: CAD4 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, ω-scan, scan width (1.09 + 0.52 tan Θ)°, maximum measuring time 60 s, intensity of three standard reflections checked every two hours. Structure solution by SHELXS-86 [62] and refinement by SHELXL-93 [63], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2 \times U_{eq}$ of the adjacent carbon atom. Full-matrix refinement against F^2. Weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis 0.302 and -0.261 e $Å^{-3}$. The deposition number of the complete data at the Cambridge Crystallographic Data Centre is 102635. The drawing was made by ZORTEP [64].

Dimethyl 4,5-Dihydro-4-methyl-2,5-dioxo-1,2-dithiolo[4,3-*b*]-pyrrole-3,6-dicarboxylate (**6b**).

This compound was prepared following general procedure A from dithiole **5b** [61] (0.287 g, 1.0 mmole) to give 0.120 g of a yellow solid. The purity >90% was shown by ^1H nmr analysis, yield 35% (based upon pure product); ^1H nmr: δ 3.97 (s, 3 H), 3.93 (s, 3 H), 3.49 (s, 3 H); ms: m/z 303 [M^+].

Ethyl 4,5-Dihydro-3-methoxycarbonyl-4-methyl-2,2,5-trioxo-1,2-dithiolo[4,3-*b*]pyrrole-6-carboxylate (**7**).

1. This compound was prepared following general procedure B from dithiole **5a** [61] (0.301 g, 1.0 mmole). A reaction time of seven days was reqired followed by purification by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.22), yield 15%. 2. A solution of dithiole **5a** (0.301 g, 1.0 mmole) and trifluoroperoxyacetic acid (from trifluoroacetic acid anhydride and hydrogen peroxide, 3 mmoles [65]) in dichloromethane (20 ml) was allowed to stand at ambient temperature for three days and worked up as described above to give dioxide **7** in 13% yield, yellow powder, mp 176° (diisopropyl ether); ir: ν 2958, 1756, 1723, 1678, 1636, 1220 cm^{-1}; uv: λ max (log ε) 208 (4.238), 317 nm (4.338); ^1H nmr: δ 4.41 (q, 2 H, J = 7.3 Hz), 3.98 (s, 3 H), 3.50 (s, 3 H), 1.38 (t, 3 H, J = 7.3 Hz); ms: m/z 333 [M^+].

Anal. Calcd. for $C_{11}H_{11}NO_7S_2$ (333.34): C, 39.63; H, 3.33; N, 4.20; S, 19.24. Found: C, 39.71; H, 3.38; N, 4.27; S, 19.36.

X-ray Diffraction Analysis of Thiosulphonate **7**.

Data collection: CAD4 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, ω-scan, scan width (0.77 + 0.59 tan Θ)°, maximum measuring time 60 s, intensity of three standard reflections checked every two hours. Structure solution by SHELXS-86 [62] and refinement by SHELXL-93 [63], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2 \times U_{eq}$ of the adjacent carbon atom. Full-matrix refinement against F^2. Weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis 0.199 and -0.234 e $Å^{-3}$. The deposition number of the complete data at the Cambridge Crystallographic Data Centre is 102636. The drawing was made by ZORTEP [64].

(*Z*)-Methyl 2-(2,5-Dihydro-4-ethoxycarbonyl-1-methyl-3-methylamino-5-oxo-2-pyrrolylidene)acetate (**8a**).

This compound was prepared following general procedure D from thiosulphinate **6a** (0.317 g, 1.0 mmole) and methylamine (8.0 *M* in ethanol, 2.0 ml, 16 mmoles), requiring two hours at room temperature. Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.40), yield 30%, deep yellow crystals, mp 119° (diisopropyl ether); ir: ν 3420, 2950, 1720, 1691, 1606 cm^{-1}; uv: λ max (log ε) 213 (4.180), 237 (4.043), 308 nm (4.305); ^1H nmr: δ 10.94 (s, br, 1 H, N*H*), 4.23

(q, 2 H, J = 7.3 Hz), 3.72 (s, 3 H), 3.12 (d, 3 H, J = 6.2 Hz), 1.30 (t, 3 H, J = 7.3 Hz); ms: m/z 268 [M+].

Anal. Calcd. for $C_{12}H_{16}N_2O_5$ (268.27): C, 53.73; H, 6.01; N, 10.44. Found: C, 54.00; H, 5.60; N, 10.36.

(*Z*)-Methyl 2-(3-Benzylamino-2,5-dihydro-4-ethoxycarbonyl-1-methyl-5-oxo-2-pyrrolylidene)acetate (**8b**).

This compound was prepared following general procedure D from thiosulphinate **6a** (0.317 g, 1.0 mmole) and benzylamine (0.214 g, 2 mmoles), requiring four hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.07), yield 35%, yellow crystals, mp 114° (diisopropyl ether); ir: n 3448, 2952, 1716, 1688, 1599, 1205 cm^{-1}; uv: λ max (log ε) 211 (4.373), 240 (4.129), 308 (4.351), 407 nm (3.407); ^1H nmr: δ 11.36 (s, br, 1 H, N*H*), 7.43-7.29 (m, 5 H), 5.48 (s, 1 H), 4.80 (d, 2 H, J = 5.6 Hz), 4.25 (q, 2 H, J = 7.3 Hz), 3.74 (s, 3 H), 3.04 (s, 3 H), 1.30 (t, 3 H, J = 7.3 Hz); ms: m/z 344 [M+].

Anal. Calcd. for $C_{18}H_{20}N_2O_5$ (344.37): C, 62.78; H, 5.85; N, 8.13. Found: C, 62.96; H, 5.79; N, 8.00.

Ethyl 1,5-Dihydro-1,4-dimethyl-3-methoxycarbonyl-5-oxo-1*H*-2λ⁴-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**9a**).

1. This compound was isolated as a by-product in the synthesis of **8a**. Purification was by flash chromatography eluting with dichloromethane/methanol 9:1 (R_f 0.75), yield 12%.

2. Alternatively compound **9a** can be prepared following general procedure E from *S*-oxide **10a** (0.314 g, 1.0 mmole), yield 75%, deep yellow powder, mp 180° (ethyl acetate); ir: ν 2977, 1731, 1694, 1668, 1630, 1579 cm^{-1}; uv: λ max (log ε) 248 (4.025), 340 (3.897), 379 nm (4.019); ^1H nmr: δ 4.23 (q, 2 H, J = 7.3 Hz), 4.07 (s, 3 H), 3.82 (s, 3 H), 3.51 (s, 3 H), 1.30 (t, 3 H, J = 7.3 Hz); ms: m/z 298 [M+].

Anal. Calcd. for $C_{12}H_{14}N_2O_5S$ (298.31): C, 48.32; H, 4.73; N, 9.39; S, 10.75. Found: C, 48.10; H, 4.79; N, 9.55; S, 10.70.

Ethyl 1-Benzyl-1,5-dihydro-3-methoxycarbonyl-4-methyl-5-oxo-1*H*-2λ⁴-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**9b**).

1. This compound was obtained as a by-product in the synthesis of **8b**. Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.20), yield 15%.

2. Alternatively compound **9b** can be prepared following general procedure E from *S*-oxide **10b** (0.390 g, 1.0 mmole), yield 93%, bright yellow crystals, mp 160° (ethyl acetate); ir: ν 2949, 1730, 1687, 1628, 1562 cm^{-1}; uv: λ max (log ε) 208 (4.442), 248 (4.065), 384 nm (4.118); ^1H nmr: δ 7.38-7.34 (m, 5 H), 5.87 (s, 2 H), 4.32 (q, 2 H, J = 7.3 Hz), 3.83 (s, 3 H), 3.57 (s, 3 H), 1.37 (t, 3 H, J = 7.3 Hz); ms: m/z 374 [M+].

Anal. Calcd. for $C_{18}H_{18}N_2O_5S$ (374.41): C, 57.74; H, 4.84; N, 7.48; S, 8.56. Found: C, 57.71; H, 4.89; N, 7.46; S, 8.67.

Dimethyl 1,5-Dihydro-1,4-dimethyl-3-methoxycarbonyl-5-oxo-1*H*-2λ⁴-pyrrolo[3,2-*c*][1,2]thiazole-3,6-dicarboxylate (**9c**).

This compound was prepared following general procedure D from thiosulphinate **6b** (0.303 g, 1.0 mmole) and methylamine (8.0 *M*, 2.0 ml, 16 mmoles), requiring a total reaction time of three hours at room temperature. Purification was by flash chromatography eluting with chloroform/ethyl acetate 2:1 (R_f 0.15), yield 12%, yellow crystals, mp 212° (diethyl ether); ir: ν 2951, 1730, 1685, 1582, 1445, 1210, 1144 cm^{-1}; uv: λ max (log ε) 215 (4.339), 248 (4.333), 340 (4.210), 384 nm (4.341); ^1H nmr: δ 4.17 (s, 3 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.60 (s, 3 H); ms: m/z 284 [M+].

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$ (284.29): C, 46.47; H, 4.25; N, 9.85; S, 11.28. Found: C, 46.60; H, 4.30; N, 10.01; S, 11.51.

Ethyl 1-Hydroxy-4,5-dihydro-3-methoxycarbonyl-4-methyl-5-oxo-1*H*-pyrrolo[3,2-*c*][1,2]dithiole-6-carboxylate (**9d**).

A solution of either **10d** (0.356 g, 1.0 mmole) or **10e** (0.300 g, 1.0 mmole) in trifluoroacetic acid (5 ml) was allowed to stand at room temperature for three days and thereupon evaporated to dryness. Dry chloroform was added and distilled *in vacuo* in order to remove trace amounts of residual acid. The remaining solid was washed with a small amount of ice-cold diethyl ether to give **9d** in 76% yield from either educt. Bright yellow crystals, mp 231° dec (ethyl acetate/acetonitrile); ir: ν 3307 br, 2989, 2956, 1776, 1717, 1703, 1643, 1099 cm^{-1}; uv: λ max (log ε) 216 (4.126), 306 nm (4.214); ^1H nmr: δ 8.60 (s, br, 1 H, OH), 4.36 (q, 2 H, J = 7.3 Hz), 3.94 (s, 3 H), 3.50 (s, 3 H), 1.37 (t, 3 H, J = 7.3 Hz); ms: m/z 284 [M+ -16, 100%].

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$ (300.29): C, 44.00; H, 4.03; N, 9.33; S, 10.68. Found: C, 44.39; H, 4.06; N, 8.92; S, 10.56.

Ethyl 4,5-Dihydro-1-methoxy-3-methoxycarbonyl-4-methyl-5-oxo-1*H*-pyrrolo[3,2-*c*][1,2]dithiole-6-carboxylate (**9e**).

To an ice-cooled solution of **9d** (1 mmole) in tetrahydrofuran/methanol (1:1, 50 ml) was added dropwise an ethereal solution of diazomethane. After nitrogen evolution had ceased the volatile products were removed *in vacuo* and the residue subjected to flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.26), yield 50%, bright yellow crystals, mp 113-114° (diisopropyl ether/ethyl acetate); ir: ν 2956, 1750, 1723, 1697, 1650, 1619, 1441 cm^{-1}; uv: λ max (log ε) 221 (4.171), 310 (4.265), 383 nm (2.948); ^1H nmr: δ 4.32 (q, 2 H, J = 7.3 Hz), 3.92 (s, 3 H), 3.75 (s, 3 H), 3.49 (s, 3 H), 1.36 (t, 3 H, J = 7.3 Hz); ms: m/z 314 [M+].

Anal. Calcd. for $C_{12}H_{14}N_2O_6S$ (314.32): C, 45.85; H, 4.49; N, 8.91; S, 10.20. Found: C, 45.93; H, 4.55; N, 8.77; S, 9.91.

Ethyl 1,5-Dihydro-1,4-dimethyl-3-methoxycarbonyl-2,5-dioxo-1*H*-2λ⁴-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**10a**).

This compound was prepared following general procedure C from *S*-oxide **6a** (0.317 g, 1.0 mmole) and methylamine (8.0 *M* in ethanol, 2.0 ml, 16 mmoles). Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.25), yield 45%, faintly yellow crystals, mp 125° (diisopropyl ether/ethyl acetate); ir: ν 2955, 1749, 1722, 1696, 1648, 1620 cm^{-1}; uv: λ max (log ε) 220 (4.158), 309 (4.260), 393 nm (3.020); ^1H nmr: δ 4.31 (q, 2 H, J = 7.3 Hz), 3.91 (s, 3 H), 3.74 (s, 3 H), 3.49 (s, 3 H), 1.36 (t, 3 H, J = 7.3 Hz); ms: m/z 314 [M+].

Anal. Calcd. for $C_{12}H_{14}N_2O_6S_2$ (314.31): C, 45.86; H, 4.49; N, 8.91; S, 10.20. Found: C, 45.79; H, 4.42; N, 8.74; S, 10.34.

Ethyl 1-Benzyl-1,5-dihydro-3-methoxycarbonyl-4-methyl-2,5-dioxo-1*H*-2λ⁴-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**10b**).

This compound was prepared following general procedure C from *S*-oxide **6a** (0.317 g, 1.0 mmole) and benzylamine (0.214 g, 2 mmoles). Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.12), yield 51%, light yellow needles, mp 94° (diisopropyl ether); ir: ν 3033, 2984, 2950, 1751, 1711, 1686, 1646, 1616, 1244, 1216, 1128, 1038 cm^{-1}; uv: λ max (log ε) 209 (4.267), 309 nm (4.214); ^1H nmr: δ 7.35-7.29 (m, 5 H), 6.01 (d, 1 H, J = 15.4 Hz), 5.00 (d, 1 H, J = 15.4 Hz), 4.27 (q, 2 H, J = 7.3 Hz), 3.89 (s, 3 H), 3.49 (s, 3 H), 1.29 (t, 3 H, J = 7.3 Hz); ms: m/z 390 [M+].

Anal. Calcd. for $C_{18}H_{18}N_2O_6S$ (390.41): C, 55.38; H, 4.65; N, 7.18; S, 8.21. Found: C, 55.36; H, 4.64; N, 7.10; S, 7.98.

Ethyl 1-(1-Adamantyl)-1,5-dihydro-3-methoxycarbonyl-4-methyl-2,5-dioxo-1*H*-2λ^4-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**10c**).

This compound was prepared following general procedure C from *S*-oxide **6a** (0.317 g, 1.0 mmole) and 1-adamantylamine (0.450 g, 3 mmoles), requiring one hour reaction time at room temperature. Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.30), yield 35%. Light yellow crystals, mp 142° (hexane); ir: ν 2910, 2945, 1743, 1717, 1656, 1613, 1451, 1214 cm^{-1}; uv: λ max (log ε) 214 (4.003), 304 nm (4.220); ^{1}H nmr: δ 4.34 (q, 2 H, J = 7.3 Hz), 3.89 (s, 3 H), 3.46 (s, 3 H), 2.32 (s, br, 3 H), 2.21 (s, br, 6 H), 1.70 (s, br, 6 H), 1.35 (t, 3 H, J = 7.3 Hz); ms: m/z 434 [M$^+$].

Anal. Calcd. for $C_{21}H_{26}N_2O_6S$ (434.51): C, 58.05; H, 6.03 N, 6.45; S, 7.38. Found: C, 58.04; H, 6.09; N, 6.40; S, 6.95.

Ethyl 1-*tert*-Butyl-1,5-dihydro-3-methoxycarbonyl-4-methyl-2,5-dioxo-1*H*-2λ^4-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**10d**).

This compound was prepared following general procedure C from *S*-oxide **6a** (0.317 g, 1 mmole) and *tert*-butylamine (0.365 g, 5 mmoles), requiring six hours reaction time at room temperature. Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.13), yield 33%, yellow crystals, mp 138° (diisopropyl ether); ir: ν 2969, 1746, 1713, 1654, 1606 cm^{-1}; uv: λ max (log ε) 214 (4.087), 304 nm (4.300); ^{1}H nmr: δ 4.34 (q, 2 H, J = 7.3 Hz), 3.90 (s, 3 H), 3.47 (s, 3 H), 1.65 (t, 3 H, J = 7.3 Hz); ms: m/z 356 [M$^+$].

Anal. Calcd. for $C_{15}H_{20}N_2O_6S$ (356.39): C, 50.55; H, 5.66 N, 7.86; S, 8.99. Found: C, 50.37; H, 5.46; N, 7.56; S, 8.80.

Ethyl 1,5-Dihydro-3-methoxycarbonyl-4-methyl-2,5-dioxo-1*H*-2λ^4-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**10e**).

This compound was prepared following general procedure C from *S*-oxide **6a** (0.317 g, 1 mmole) and ammonia (25%, aqueous solution, 3.0 ml, 44 mmoles), requiring two hours reaction time at room temperature. Purification was by flash chromatography eluting with ethyl acetate/formic acid 40:1 (R_f 0.30), yield 15%, light yellow crystals, mp 157° dec (ethyl acetate); ir: ν 3500-3400 br, 2981, 1689, 1654, 1566 cm^{-1}; uv: λ max (log ε) 224 (3.887), 252 (4.139), 295 (3.956), 416 nm (3.379); ^{1}H nmr: δ 8.35 (s, br, 1 H, NH), 4.04 (q, 2 H, J = 7.3 Hz), 3.74 (s, 3 H), 3.22 (s, 3 H), 1.17 (t, 3 H, J = 7.3 Hz); ms: m/z 300 [M$^+$].

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$ (300.29): C, 44.00; H, 4.03 N, 9.33; S, 10.68. Found: C, 44.16; H, 4.05; N, 8.96; S, 10.76.

Ethyl 1-(1-Adamantyl)-3-iodo-4-methyl-2,5-dioxo-1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole-6-carboxylate (**12**).

This compound was obtained as a by-product in the synthesis of **10c**. Purification was by flash chromatography using hexane/ethyl acetate 3:1 (R_f 0.71), yield 16%, yellow crystals, mp 143° (hexane); ir: ν 2911, 2854, 1735, 1679, 1641, 1436 cm^{-1}; uv: λ max (log ε) 314 nm (4.261); ^{1}H nmr: δ 4.33 (q, 2 H, J = 7.3 Hz), 3.19 (s, 3 H), 2.21 (s, br, 6 H), 2.12 (s, br, 3 H), 1.68 (s, br, 6 H), 1.35 (t, 3 H, J = 7.3 Hz); ms: m/z 482 [M$^+$].

Anal. Calcd. for $C_{20}H_{23}N_2O_4I$ (482.32): C, 49.81; H, 4.81; N, 5.81. Found: C, 49.82; H, 4.87; N, 5.74.

Ethyl 4,5-Dihydro-4-methyl-2,2,5-trioxo-1,2-dithiolo[4,3-*b*]-pyrrole-6-carboxylate (**13b**).

This compound was prepared following general procedure B from dithiole **13a** [1] (0.243 g, 1.0 mmole), requiring five hours reaction time, yield 27%, faintly orange needles, mp 123° (diisopropyl ether/ethyl acetate); ir: ν 3043, 2931, 1729 br, 1681, 1651, 1589, 1464, 1321 br, 1185, 1150 br cm^{-1}; uv: λ max (log ε) 205 (4.157), 301 nm (4.247); ^{1}H nmr: δ 6.52 (s, 1 H), 4.43 (q, 2 H, J = 7.3 Hz), 3.28 (s, 3 H), 1.43 (t, 3 H, J = 7.3 Hz); ms: m/z 275 [M$^+$].

Anal. Calcd. for $C_9H_9NO_5S_2$ (275.30): C, 39.27; H, 3.29; N, 5.09; S, 23.29. Found: C, 39.22; H, 3.40; N, 5.04; S, 23.62.

N-(4,5-Dihydro-4-methyl-2,2,5-trioxo-1,2-dithiolo[4,3-*b*]-pyrrole-6-yl) acetamide (**14**).

This compound was prepared following general procedure B from thiolutin **2** (0.228 g, 1.0 mmole) with the exception that the amount of *m*-chloroperbenzoic acid was doubled. The reaction time was three days. Purification was by flash chromatography eluting with ethyl acetate (R_f 0.66), yield 30%, light-yellow powder, mp 255° dec (diisopropyl ether); ir: ν 3309, 3282, 3077, 3016 w, 2941, 1737, 1721, 1686, 1646, 1631, 1522, 1440, 1141 cm^{-1}; uv: λ max (log ε) 301 (4.138), 385 nm (3.250); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.67 (s, 1 H, N*H*), 7.56 (s, 1 H), 3.11 (s, 3 H), 2.10 (s, 3 H); ms: m/z 260 [M$^+$].

Anal. Calcd. for $C_8H_8N_2O_4S_2$ (260.30): C, 36.91; H, 3.10; N, 10.76; S, 24.64. Found: C, 37.16; H, 3.20; N, 10.41; S, 24.26.

Methyl 4,5-Dihydro-6-ethoxy-4-methyl-2,5-dioxo-1,2-dithiolo-[4,3-*b*]pyrrole-3-carboxylate (**15b**).

This compound was prepared following general procedure A from dithiole **15a** [1] (0.273 g, 1.0 mmole), yield 77%, deep orange needles, mp 129° (diisopropyl ether/ethyl acetate); ir: ν 2995, 1740, 1721, 1636, 1295, 1209 cm^{-1}; uv: λ max (log ε) 314 nm (4.206); ^{1}H nmr: δ 4.37 (q, 2 H, J = 7.3 Hz), 3.92 (s, 3 H), 3.42 (s, 3 H), 1.45 (t, 3 H, J = 7.3 Hz); ms: m/z 289 [M$^+$].

Anal. Calcd. for $C_{10}H_{11}NO_5S_2$ (289.33): C, 41.51; H, 3.83; N, 4.84; S, 22.16. Found: C, 41.55; H, 3.88; N, 4.75; S, 22.35.

Methyl 4,5-Dihydro-6-ethoxy-4-methyl-2,2,5-trioxo-1,2-dithiolo-[4,3-*b*]pyrrole-3-carboxylate (**15c**).

This compound was prepared following general procedure B from dithiole **15a** [1] (0.273 g, 1.0 mmole), requiring six hours reaction time, yield 54%, yellow crystals, mp 172° (diisopropyl ether/ethyl acetate); ir: ν 2999, 1757, 1723, 1640, 1617, 1296 cm^{-1}; uv: λ max (log ε) 310 (4.256), 399 nm (3.015); ^{1}H nmr: δ 4.35 (q, 2 H, J = 7.3 Hz), 3.96 (s, 3 H), 3.42 (s, 3 H), 1.43 (t, 3 H, J = 7.3 Hz); ms: m/z 305 [M$^+$].

Anal. Calcd. for $C_{10}H_{11}NO_6S_2$ (305.33): C, 39.33; H, 3.63; N, 4.61; S, 21.00. Found: C, 39.41; H, 3.67; N, 4.46; S, 21.06.

Methyl 6-*tert*-Butylamino-4,5-dihydro-4-methyl-5-oxo-1,2-dithiolo[4,3-*b*]pyrrole-3-carboxylate (**16b**).

This compound was prepared following general procedure D from *S*-oxide **15b** (0.273 g, 1.0 mmole) and *tert*-butylamine (0.219 g, 3.0 mmoles), requiring 16 hours reaction time, yield 40%, orange crystals, mp 210° (diisopropyl ether/ethyl acetate); ir: ν 3318, 1742, 1644, 1593, 1231 cm^{-1}; uv: λ max (log ε) 249 (3.613), 319 (4.109), 451 nm (3.627); ^{1}H nmr: δ 5.38 (s, 1 H, N*H*), 3.86 (s, 3 H), 3.34 (s, 3 H), 1.30 (s, 9 H); ms: m/z 300 [M$^+$].

Anal. Calcd. for $C_{12}H_{16}N_2O_3S_2$ (300.40): C, 47.98; H, 5.37; N, 9.32; S, 21.35. Found: C, 48.30; H, 5.33; N, 9.02; S, 21.46.

(*E*)-3-Benzylamino-5-benzylimino-1-methyl-4,5-dihydro-1*H*-pyrrol-2-one (**17**).

This compound was obtained as a by-product in the synthesis of **16a**. Purification was by flash chromatography eluting with hexane/ethyl acetate 5:1 (R_f 0.20), yield 28%, orange crystals, mp 104° (hexane/diisopropyl ether); ir: ν 3320, 3021, 2870, 1716, 1668, 1627, 1604 sh, 1582, 1517, cm^{-1}; uv: λ max (log ε) 205 (4.380), 267 (4.180), 347 nm (3.750); ^1H nmr: δ 7.39-7.29 (m, 10 H), 5.36 (s, br, 1 H, N*H*), 5.30 (s, 1 H), 4.67 (s, 2 H), 4.33 (d, 2 H, J = 5.8 Hz), 3.15 (s, 3 H); NOE: 5.30 and 4.67/4.33; ms: m/z 305 [M^+].

Anal. Calcd. for $C_{19}H_{19}N_3O$ (305.38): C, 74.73; H, 6.27; N, 13.76. Found: C, 74.99; H, 6.41; N, 13.37.

Methyl 6-Benzylamino-4,5-dihydro-4-methyl-2,5-dioxo-1,2-dithiolo[4,3-*b*]pyrrole-3-carboxylate (**18**).

1. This compound was prepared following general procedure A from dithiole **16a** [1] (0.334 g, 1.0 mmole). Purification was by flash chromatography eluting with dichloromethane/ethyl acetate 20:1 (R_f 0.15), yield 33%.

2. Alternatively *S*-oxide **18** can be prepared following general procedure D from **15b** (0.289 g, 1.0 mmole), yield 67%, deep red needles, mp 156-157° (diisopropyl ether, ethyl acetate): ir: ν 3210 br, 3022, 2945, 1741, 1716, 1666, 1570, 1523, 1198, 1067 w, 1052 cm^{-1}; uv: λ max (log ε) 337 (4.151), 471 nm (3.739); ^1H nmr: δ 7.40-7.25 (m, 5 H), 5.43 (t, br, 1 H, N*H*, J = 5.2 Hz), 4.51 (d, 2 H, J = 5.2 Hz), 3.88 (s, 3 H), 3.44 (s, 3 H); ms: m/z 350 [M^+].

Anal. Calcd. for $C_{15}H_{14}N_2O_4S_2$ (350.42): C, 51.41; H, 4.03; N, 7.99; S, 18.30. Found: C, 51.63; H, 4.15; N, 7.64; S, 18.65.

Methyl 6-Benzylamino-1,5-dihydro-1,4-dimethyl-2,5-dioxo-1*H*-2λ^4-pyrrolo[3,2-*c*][1,2]thiazole-6-carboxylate (**19**).

This compound was prepared following general procedure C from *S*-oxide **18** (0.350 g, 1.0 mmole) and methylamine (8.0 *M* in ethanol, 5.0 ml, 40 mmoles), requiring 12 hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.50), yield 40%, faintly orange crystals, mp 188° dec (diisopropyl ether/ethyl acetate); ir: ν 3291, 1724, 1689, 1645, 1560, 1525 cm^{-1}; uv: λ max (log ε) 206 (4.272), 334 nm (4.130), 447 nm (3.814); ^1H nmr: δ 7.32-7.21 (m, 5 H), 5.60 (t, 1 H, N*H*, J = 6.1 Hz), 4.54 (m, 2 H), 3.82 (s, 3 H), 3.05 (s, 3 H), 2.65 (s, 3 H); ms: m/z 347 [M^+].

Anal. Calcd. for $C_{16}H_{17}N_3O_4S$ (347.39): C, 55.32; H, 4.93; N, 12.10; S, 9.23. Found: C, 55.61; H, 4.98; N, 11.85; S, 9.34.

Methyl 4,5-Dihydro-6-ethoxy-2,5-dioxothieno[3,2-*c*][1,2]-dithiole-3-carboxylate (**20b**).

This compound was prepared following general procedure A from dithiole **20a** [2] (0.276 g, 1.0 mmole), yield 73%, orange powder, mp 167° (diisopropyl ether/ethyl acetate); ir: ν 2990, 1702, 1602, 1268, 1035 cm^{-1}; uv: λ max (log ε) 324 (3.973), 424 nm (3.334); ^1H nmr: δ 4.53 (t, 2 H, J = 7.3 Hz), 3.97 (s, 3 H), 1.45 (t, 3 H, J = 7.3 Hz); ms: m/z 292 [M^+].

Anal. Calcd. for $C_9H_8O_5S_3$ (292.35): C, 36.97; H 2.76; S, 32.90. Found: C, 36.92; H, 2.80; S, 33.23.

Methyl 4,5-Dihydro-6-ethoxy-2,2,5-trioxothieno[3,2-*c*][1,2]-dithiole-3-carboxylate (**20c**).

This compound was prepared following general procedure B from dithiole **20a** [2] (0.276 g, 1.0 mmole) with the exception that 3.2 mmoles of *m*-chloroperbenzoic acid were employed. The reaction time was four hours, purification was by flash chromatography eluting with hexane/chloroform 1:1 (R_f 0.12), yield 25%, yellow crystals, mp 231° dec (hexane/diisopropyl ether); ir: ν 2970, 1706, 1610, 1576, 1476, 1331, 1271 cm^{-1}; uv: λ max (log ε) 220 (3.606), 247 (3.383), 320 (3.868), 417 nm (3.036); ^1H nmr: δ 4.54 (q, 2 H, J = 7.3 Hz), 3.99 (s, 3 H), 1.42 (t, 3 H, J = 7.3 Hz); ms: m/z 308 [M^+].

Anal. Calcd. for $C_9H_8O_6S_3$ (308.35): C, 35.06; H, 2.61; S, 31.20. Found: C, 34.93; H, 2.74; S, 31.11.

Methyl 4,5-Dihydro-2,5-dioxo-6-methylaminothieno[3,2-*c*]-[1,2]dithiole-3-carboxylate (**21**).

This compound was prepared following general procedure D from *S*-oxide **20b** (0.276 g, 1.0 mmole) and methylamine (8.0 *M*, 2.0 ml, 16 mmoles), requiring two hours reaction time, yield 55%. Reddish powder, mp 208° (diisopropyl ether/ethyl acetate); ir: ν 3343, 2955, 1682, 1627, 1488 cm^{-1}; uv: λ max (log ε) 260 (3.902), 340 (3.893), 468 nm (3.787); ^1H nmr: δ 5.37 (s, 1 H, N*H*), 3.87 (s, 3 H), 3.17 (d, 3 H, J = 6.1 Hz); ms: m/z 277 [M^+].

Anal. Calcd. for $C_8H_7NO_4S_3$ (277.34): C, 34.65; H, 2.54; N, 5.05; S, 34.68. Found: C, 34.82; H, 2.76; N, 4.75; S, 34.84.

Methyl 1,5-Dihydro-4-methyl-6-methylamino-2,5-dioxo-1*H*-2λ^4-thieno[3,2-*c*][1,2]thiazole-6-carboxylate (**22**).

This compound was prepared following general procedure C from *S*-oxide **21** (0.277 g, 1.0 mmole) and methylamine (8.0 *M* in ethanol, 5.0 ml, 40 mmoles), requiring three hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.05), yield 15%, faintly orange powder, mp 191° dec (diisopropyl ether/ethyl acetate); ir: ν 3255, 2984, 1696, 1652, 1316 cm^{-1}; uv: λ max (log ε) 321 (3.551), 441 nm (3.928); ^1H nmr (dimethyl-d_6 sulphoxide): δ 9.11 (s, br, 1 H, N*H*), 3.82 (s, 3 H), 3.66 (s, 3 H), 2.85 (d, 3 H, J = 5.3 Hz); ms: m/z 274 [M^+].

Anal. Calcd. for $C_9H_{10}N_2O_4S_2$ (274.32): C, 39.41; H, 3.67; N, 10.21; S, 23.38. Found: C, 39.67; H, 3.82; N, 9.80; S, 23.46.

Methyl 4,5-Dihydro-6-ethoxy-1,1,5-trioxothieno[3,2-*c*][1,2]-dithiole-3-carboxylate (**23**).

This compound was obtained as a by-product from the synthesis of **20c**. Purification was by flash chromatography eluting with hexane/ethyl acetate 10:1 (R_f 0.20), yield 4%, yellow crystals, mp 231° dec (diisopropyl ether); ir: ν 2970, 1706, 1610, 1576, 1476, 1331, 1271 cm^{-1}; uv: λ max (log ε) 220 (3.606), 247 (3.383), 320 (3.868), 417 nm (3.036); ^1H nmr: δ 4.54 (q, 2 H, J = 7.3 Hz), 3.99 (s, 3 H), 1.42 (t, 3 H, J = 7.3 Hz); ms: m/z 308 [M^+].

Anal. Calcd. for $C_9H_9O_6S_3$ (308.35): C, 35.06; H, 2.61; S, 31.20. Found: C, 34.93; H, 2.74; S, 31.11.

X-ray Diffraction Analysis of Thiosulphonate **23**.

Data collection was as follows: CAD4 Diffractometer, crystal mounted in a glass capillary, cell constants from 25 centered reflections. Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator, ω-2 T-scan, scan width (0.84 + 0.56 tan Θ)°, maximum measuring time 60 s, intensity of three standard reflections checked every two hours. Structure solution was by SHELXS-86 [62] and refinement by SHELXL-93 [63], non-hydrogen atoms refined anisotropically, hydrogens with $U_i = 1.2 \times U_{eq}$ of the adjacent carbon atom. Full-matrix refinement was against F^2; weight: SHELXL-93. Maximum and minimum of the final difference Fourier synthesis are 0.340 and -0.315 e $Å^{-3}$. The deposition number of the complete data at the Cambridge Crystallographic Data Centre is 102637. The drawing was made by ZORTEP [64].

Methyl 6-Benzylamino-4,5-dihydro-4-methyl-1,5-dioxo-1,2-dithiolo[4,3-*b*]pyrrole-3-carboxylate (**24a**).

This compound was prepared following general procedure A from dithiole **16a** [1] (0.334 g, 1.0 mmole). Purification was by flash chromatography eluting with dichloromethane/ethyl acetate 20:1 (R_f 0.10), yield 50%, glittering orange-red crystals, mp 159-160° (diisopropyl ether, ethyl acetate); ir: ν 3267, 3010, 2952, 1718, 1643, 1583, 1509, 1241, 1202, 1057 cm^{-1}; uv: λ max (log ε) 242 (4.019), 400 nm (3.928); ^1H nmr: δ 7.42-7.33 (m, 5 H), 6.33 (m, br, 1 H, N*H*), 4.77 (dd, 1 H, J_1 = 5.1 Hz, J_2 = 14.9 Hz), 4.61 (dd, 1 H, J_1 = 5.1 Hz, J_2 = 14.9 Hz), 3.80 (s, 3 H), 3.54 (s, 3 H); ms: m/z 350 [M^+].

Anal. Calcd. for $C_{15}H_{14}N_2O_4S_2$ (350.42): C, 51.41; H, 4.03; N, 7.99; S, 18.30. Found: C, 51.43; H, 3.99; N, 8.01; S, 18.65.

Methyl 6-Benzylamino-4,5-dihydro-4-methyl-2,2,5-trioxo-1,2-dithiolo[4,3-*b*]pyrrole-3-carboxylate (**24b**).

This compound was prepared following general procedure B from dithiole **16a** [1] (0.334 g, 1.0 mmole), requiring two hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 5:2 (R_f 0.17), yield 31%, red rods, mp 159-160° (hexane/diisopropyl ether); ir: ν 3372, 2951, 1749, 1713, 1663, 1590, 1498 cm^{-1}; uv: λ max (log ε) 327 (4.175), 460 nm (3.713); ^1H nmr: δ 7.39-7.26 (m, 5 H), 5.50 (t, br, 1 H, N*H*, J = 6.4 Hz), 4.46 (d, 2 H, J = 6.4 Hz), 3.92 (s, 3 H), 3.42 (s, 3 H); ms: m/z 366 [M^+].

Anal. Calcd. for $C_{15}H_{14}N_2O_5S_2$ (366.42): C, 49.17; H, 3.85; N, 7.65; S, 17.50. Found: C, 49.16; H, 3.86; N, 7.65; S, 17.80.

Methyl 6-Benzylamino-4,5-dihydro-4-methyl-1,1,5-trioxo-1,2-dithiolo[4,3-*b*]pyrrole-3-carboxylate (**24c**).

This compound was obtained as a by-product from the synthesis of **24b**. Purification was by flash chromatography eluting with hexane/ethyl acetate 5:2 (R_f 0.17), yield 9%, orange crystals, mp 171-172° dec (diisopropyl ether/ethyl acetate); ir: ν 3279, 3006, 2955, 1716, 1655, 1583, 1509 cm^{-1}; uv: λ max (log ε) 247 (3.995), 404 nm (4.190); ^1H nmr: δ 7.41-7.34 (m, 5 H), 6.16 (t, br, 1 H, N*H*, J = 5.5 Hz), 4.68 (d, 2 H, J = 5.5 Hz), 3.82 (s, 3 H), 3.53 (s, 3 H); ms: m/z 366 [M^+].

Anal. Calcd. for $C_{15}H_{14}N_2O_5S_2$ (366.42): C, 49.17; H, 3.85; N, 7.65; S, 17.50. Found: C, 49.15; H, 3.83; N, 7.69; S, 17.79.

Dimethyl 4-Methyl-2,5,5-trioxo-4*H*-2λ^4,5λ^6-1,2-dithiolo[4,3-*c*]-[1,2]thiazole-3,6-dicarboxylate (**25b**).

This compound was prepared following general procedure A from dithiole **25a** [66] (0.323 g, 1.0 mmole), yield 90%, yellow crystals, mp 226-227° (diisopropyl ether); ir: ν 2957, 1726, 1708, 1609, 1586, 1439, 1111, 1080, 1040 cm^{-1}; uv: λ max (log ε) 205 (4.229), 311 nm (4.092); ^1H nmr: δ 4.00 (s, 3 H), 3.95 (s, 3 H), 3.54 (s, 3 H); ms: m/z 339 [M^+].

Anal. Calcd. for $C_9H_9NO_7S_3$ (339.37): C, 31.85; H, 2.67; N, 4.13; S, 28.35. Found: C, 31.97; H, 2.76; N, 4.21; S, 28.22.

Dimethyl 4-Benzyl-1-methyl-2,2,5-trioxo-1*H*,4*H*-2λ^6,5λ^4-1,2-thiazolo[4,3-*c*][1,2]thiazole-3,6-dicarboxylate (**26**).

This compound was prepared following general procedure C from *S*-oxide **25b** (0.339 g, 1.0 mmole) and benzylamine (0.750 g, 7 mmoles), requiring four hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 3:1 (R_f 0.25), yield 90%, yellow needles, mp 188° (ethyl acetate); ir: ν 2995, 2954, 1717, 1612 cm^{-1}; uv: λ max (log ε) 210 (4.250), 306 nm (4.152); ^1H nmr: δ 7.40-7.30 (m, 5 H), 6.06 (d, 1 H, J = 15.6 Hz), 4.99 (d, 1 H, J = 15.6 Hz), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.67 (s, 3 H); ms: m/z 412 [M^+].

Anal. Calcd. for $C_{16}H_{16}N_2O_7S_2$ (412.47): C, 46.59; H, 3.91; N, 6.79; S, 15.55. Found: C, 46.61; H, 4.06; N, 6.63; S, 15.22.

Dimethyl 2-*tert*-Butylimino-4-methyl-2,5,5-trioxo-4*H*-2λ^6,5λ^6-1,2-dithiolo[4,3-*c*][1,2]thiazole-3,6-dicarboxylate (**27**).

This compound was prepared following general procedure C from *S*-oxide **25b** (0.339 g, 1.0 mmole) and *tert*-butylamine (1.168 g, 16 mmoles), requiring two hours reaction time. Purification was by flash chromatography eluting with hexane/ethyl acetate 5:1 (R_f 0.14), yield 14%, faintly yellow crystals, mp 190° (diisopropyl ether/ethyl acetate); ir: ν 2970, 1718, 1636, 1585, 1439, 1364, 1342, 1282, 1245, 1211, 1181, 1128 cm^{-1}; uv: λ max (log ε) 212 (4.214), 327 nm (4.038); ^1H nmr: δ 3.99 (s, 3 H), 3.95 (s, 3 H), 3.42 (s, 3 H), 1.43 (s, 9 H); ms: m/z 410 [M^+].

Anal. Calcd. for $C_{13}H_{18}N_2O_7S_3$ (410.49): C, 38.04; H, 4.42; N, 6.82; S, 23.43. Found: C, 38.21; H, 4.43; N, 6.77; S, 22.76.

X-ray Diffraction Analysis of Imidosulphonate **27**.

Data collection was as follows: Siemens P4 diffractometer with CCD Area-detector and LT4 device, crystal mounted with perfluoro ether oil on a glass fiber, hemisphere data collection, 1400 frames collected with an exposure of MoK_α radiation, graphite monochromator, 20s/frame, SADABS absorption correction, 122 parameters refined. Data reduction were with SAINT, calculations with SHELXL 97. Sulphur atoms were refined anisotropically. Only a part of the other non-hydrogen atoms did not refine anisotropically and thus was left isotropic. Hydrogen atoms were incorporated in the refinement using their calculated positions. The poor R value presumably results from insufficient absorption correction as well as the extremely thin needles which results in low intensities of the observed reflexes. Hence solely the topology of the examined molecule is secured.

Dimethyl 1,4-Dimethyl-2,2-dioxo-1*H*,4*H*-2λ^6-1,2-thiazolo-[4,3-*c*][1,2]thiazole-3,6-dicarboxylate (**28a**).

This compound was obtained as a by-product in the synthesis of **29a**. Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.21), yield 5%, yellow crystals, mp 250° (methanol); ir: ν 3003, 2948, 1731, 1692, 1585 cm^{-1}; uv: λ max (log ε) 214 (4.513), 253 (4.182), 377 nm (4.543); ^1H nmr: δ 3.93 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.53 (s, 3 H); ms: m/z 320 [M^+].

Anal. Calcd. for $C_{10}H_{12}N_2O_6S_2$ (320.34): C, 37.50; H, 3.78; N, 8.75; S, 20.02. Found: C, 37.55; H, 3.75; N, 8.74; S, 20.29.

Dimethyl 4-Benzyl-1-methyl-2,2-dioxo-1*H*,4*H*-2λ^6-1,2-thiazolo[4,3-*c*][1,2]thiazole-3,6-dicarboxylate (**28b**).

This compound was obtained as a by-product in the synthesis of **29b**. Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.58), yield 7%, yellow crystals, mp 182° (methanol); ir: ν 2950, 1725, 1698, 1612, 1576 cm^{-1}; uv: λ max (log ε) 211 (4.390), 307 (3.691), 379 nm (4.203); ^1H nmr: δ 7.35-7.19 (m, 5 H), 5.67 (s, 2 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.53 (s, 3 H); ms: m/z 396 [M^+].

Anal. Calcd. for $C_{16}H_{16}N_2O_6S_2$ (396.43): C, 48.48; H, 4.07; N, 7.07; S, 16.17. Found: C, 48.59; H, 4.10; N, 6.92; S, 16.28.

(Z)-Methyl 2,3-Dihydro-1,1-dioxo-1λ^6-3-methoxycarbonylmethylene-2-methyl-4-methylamino-1,2-thiazole-5-carboxylate (**29a**).

This compound was prepared following general procedure D from *S*-oxide **25b** (0.339 g, 1.0 mmole) and methylamine (8.0 M,

1.0 ml, 8.0 mmoles). Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.18), yield 20%, cream-coloured crystals, mp 170° (methanol); ir: ν 3293, 3263, 3197, 2958, 1723, 1678, 1610, 1495 cm^{-1}; uv: λ max (log ε) 220 (4.112), 299 nm (4.280); ^1H nmr: δ 8.68 (s, br, 1 H, N*H*), 5.74 (s, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.31 (d, 3 H, J = 6.0 Hz), 3.21 (s, 3 H); ms: m/z 290 [M^+].

Anal. Calcd. for $C_{10}H_{14}N_2O_6S$ (290.29): C, 41.38; H, 4.86; N, 9.65; S, 11.04. Found: C, 41.09; H, 4.59; N, 9.59; S, 11.12.

(*Z*)-Methyl 4-Benzylamino-2,3-dihydro-1,1-dioxo-1λ⁶-3-methoxycarbonylmethylene-2-methyl-1,2-thiazole-5-carboxylate (**29b**).

1. This compound was prepared following general procedure D from *S*-oxide **25b** (0.339 g, 1.0 mmole) and benzylamine (0.428 g, 4 mmoles). Purification was by flash chromatography eluting with hexane/ethyl acetate 1:1 (R_f 0.52), yield 70%.

2. Alternatively compound **29b** can be prepared following general procedure E from *S*-oxide **26** (0.412 g, 1.0 mmole), yield 73%, cream-coloured crystals, mp 176° (methanol); ir: ν 3251, 3119, 2945, 1717, 1673, 1609 cm^{-1}; uv: λ max (log ε) 303 nm (4.173); ^1H nmr: δ 8.67 (s, br, 1 H, N*H*), 7.38-7.19 (m, 5 H), 5.62 (s, 1 H), 4.69 (d, 2 H, J = 5.1 Hz), 3.81 (s, 3 H), 3.68 (s, 3 H), 3.16 (s, 3 H); ms: m/z 366 [M^+].

Anal. Calcd. for $C_{16}H_{18}N_2O_6S$ (366.41): C, 52.45; H, 4.95; N, 7.65; S, 8.75. Found: C, 52.45; H, 5.01; N, 7.63; S, 8.78.

Reduction of Thiosulphinate **20b** with Isonicotinic Acid Hydrazide.

A solution of *S*-oxide **20b** (0.292 g, 1.0 mmole) and isonicotinic acid hydrazide (4.110 g, 30 mmoles) in anhydrous ethanol (70 ml) was refluxed for 20 hours, thereupon adsorbed onto silica gel and chromatographed eluting with hexane/ethyl acetate 10:1 (R_f 0.20), yield 87% of **20a**.

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