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Fused 1,2-dithioles, V: Carbenoid anions as intermediates in reactions of pyrrothines and their heteroanalogues

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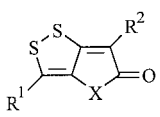
Pyrrothines like thiolutine and other bicyclic 1,2-dithioles of type **1** when unsubstituted in 3-position are marked by their CH acidity. In the presence of weak bases such as triethylamine the pyrrothine **4** degraded via its anion to a thioketene trapped as the 1,3-dithietane **5**. The carbenoid anions of several compounds **1** reacted with elemental sulphur forming enthiolates whose alkylation led to the corresponding thioethers or, in the case of the thiolactam **9**, to the bicyclic trithiones **10** and **11**. In the same manner selenides can be obtained via intermediate selenolate ions. Introduction of an aryl- or heteroarylmercapto group into compounds **1** was achieved directly by reaction of the corresponding anions with suitable disulphides. Though there may be structural limitations, this sulphurization reaction can be extended to 3-unsubstituted trithiones. The new compounds exhibited significant activity against *Mycobacterium tuberculosis* in the primary screening.

1. 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-dithiolofuranes and 1,2-dithiolothiophenes of the general formula **1**. These compounds are structurally related to naturally occuring 1,2-dithiolopyrroles, commonly named pyrrothines, the longest known of which is thiolutine **2**. Thiolutine [4–7] as well as a number of compounds of type **1** display remarkable antiobiotic activity against *Mycobacterium tuberculosis* but also against atypical, non-tuberculosis mycobacteria including *Mycobacterium avium* [8] which causes opportunistic infections complicating AIDS. QSAR calculations revealed the dependency upon substituents in 6-position but no distinction between electron accepting and donating substituents could be found [8] and therefore no clear connection with log *P* values.

From that we concluded that the incorporated alkylidene 1,2-dithiole backbone might be the pharmacophore whereas the heteroatom in 4-position is less important [9]. However, the actual mechanism of physiological action is still obscure. In the preceding paper [10] we developed the hypothesis that *S*-oxides of these dithioles, i.e. the corresponding thiosulphinates, might be active metabolites. In a parallel investigation we focussed on the question of differences between 3-substituted and 3-unsubstituted pyrrothines. *In vitro*-tests revealed only marginal differences in antibacterial activity between 3-unsubstituted dithioles of type **1** ($R^1 = H$) and the corresponding 3-carbonic esters ($R^1 = CO_2R$) with the first-mentioned compounds being slightly more potent [8]. On the other hand, 3-phenyl substituted dithioles seemed to display only very weak activity.



X = NH, NMe, O, S
$R^1 = CO_2R$, H
R^2 = variable

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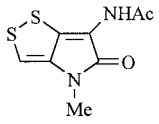


Thiolutine **2**

2. Investigations, results and discussion

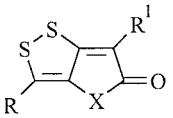
2.1. Chemistry

In contrast to the 3-substituted pyrrothine **3** (Scheme 1) the unsubstituted compound **4** is susceptible to even weak bases such as triethylamine. In solution **4** degrades slowly in the presence of tertiary amines to numerous substances as detected by TLC. Upon addition of methyl iodide to such a solution of **4** and amine the 1,3-dithietane **5** can be isolated as the main product as an equal mixture of (*E*/*Z*)-isomers. The simplicity of the ^{1}H NMR spectrum of **5** contributed to the structure elucidation. Whereas conventional routine mass spectroscopy employing both CI and EI mode displayed solely the corresponding mole peak for the thioketene monomer, FAB mass spectroscopy gave the correct data for the dithietane **5**. 1,3-Dithietanes are known as dimerization products of thioketenes or acylthioketenes and in this case sometimes named desaurins [11, 12]. Hence, the precursor of dithietane **5** is the short-lived anion **6** and finally **4a**, the anion of dithiole **4**.

Basically, deprotonations of suitable substituted alkenes are well known [13, 14], but usually much stronger bases such as lithium alkyls are employed [15, 16]. Dithiole **4** apparently has a higher acidity; the driving force for its deprotonation may be the resonance stabilization of the originating anion **4a**, reminiscent of the conjugate anion of thiazolium salts, e.g. thiamin [17–22].

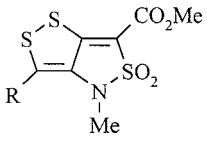
A series of efforts to derivatize the originated anion **4a** by known trapping reagents such as chlorotrimethylsilane [23, 24], methyl trifluoromethanesulphonate ("magic methyl") [13, 14], DMF [13, 14], acrylonitrile and 2,3-dimethyl-2-butene [25, 26] or diazo compounds [27] proceeded without success. Only reaction of **4a** with elemental sulphur proved to be successful, leading to the apparently stable anion **7** [28, 29] (Scheme 2). Thionation is a typical reaction of nucleophilic carbenes and therefore well compatible with a carbenoid character of **4a** as depicted by the resonance structures ([27], for trapping experiments of carbenes with sulphur see [30, 31]).

Upon acidification anion **7** was converted to dithiole **8a**, but unfortunately the substance could not be obtained in analytically pure state. However, because of the lack of a ^{1}H NMR signal for a vinylic hydrogen and the appearance of IR absorption bands at 3416 cm^{-1} (OH) and

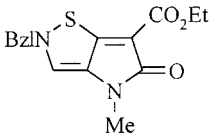


	X	R^1
a	O	CO_2Et
b	S	CO_2Et
c	S	OEt

13a-c: R = H
14a-c: R = SMe



15: R = H
16: R = SMe
17: R = CO_2Me



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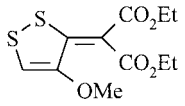

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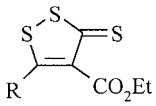


20: R = H
21: R = SMe

1667 cm^{-1} (COOR) we suppose that at least in the solid state **8a** exists as the tautomeric trithione, i.e. the protonated ketene derivative **7**. However, alkylation of **8a** with diazomethane gave rise to the thioether **8b** and reaction with dimethyl(methylmercapto)sulfonium tetrafluoroborate provided the disulphide **8c**. Thioether **8b** in turn is more easily accessible in almost quantitative yield by a one-pot thionation of **4** with elemental sulphur in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and methyliodide. In this manner it was established that anion **7** is present in solutions of dithiole **4** with tertiary amines without added sulphur. In this case the sulphur apparently derived from other degradation products possibly including a thioketene such as **6** [32, 33].

This thionation reaction worked equally well with the corresponding thiolactam **9**. But after methylation of the intermediate salt here the bicyclic trithione **10** was obtained and analogously trithione **11** when the reaction was conducted in dichloromethane as solvent and alkylating agent [34]. As expected for a bicyclic trithione, **10** displayed the C=S signal in the ^{13}C NMR spectrum at 195.2 ppm. The *N*-methyl signal in the ^1H NMR spectrum of pyrrole **10** is shifted downfield to 4.27 ppm. For the purpose of comparison the corresponding isomer **12** was synthesized by thionation of **8b** with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (Lawesson's reagent [35]). In the ^{13}C NMR spectrum of **12** the C=S signal was now observed at 187.1 ppm and the *N*-methyl signal in the ^1H NMR spectrum at 3.95 ppm.

As known from other carbenes, selenylation of anion **4a** should also be possible [36, 37]. However, reaction of **4** with an excess of finely ground selenium in the presence of DBU followed by alkylation furnished an inseparable mixture of both the sulphide **8b** and the desired selenide **8d**. The unwanted formation of **8b** was nearly completely suppressed by performing the selenylation under ultrasonic treatment, by this means enhancing the otherwise poor solubility of selenium in organic solvents.

Not surprisingly, the introduction of an alkylmercapto group into the anion of dithiole **4** could also be performed as an electrophilic substitution reaction with disulphides. Whereas dimethyl disulphide failed to provide **8b** the more electrophilic diphenyl disulphide cleanly gave the thioether **8e** [38, 39]. This substitution reaction also proceeded well with sterically more encumbered bis(1-phenyl-1*H*-tetrazol-5-yl)disulphide [40] to give the new sulphide **8f**. Experiments directed to apply this reaction analogously to the direct selenylation of dithiole **4** with DBU and diphenyl diselenide, however, failed. For other partially unsuccessful selenylation reactions with anions see [41, 42].

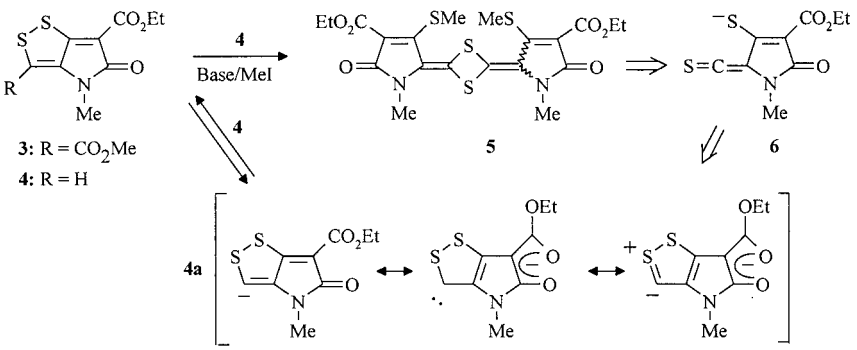
The observed carbene-like reactions took place only with the anion of pyrrothine **4**. The dithiole itself failed to undergo reactions with typical nucleophilic carbene trapping reagents such as isothiocyanates [43]. On the other hand, electrophilic substitution reaction in 3-position was feasible with bromine. In a slow reaction the bromo pyrrothine **8g** was formed.

The thionation procedure employing elemental sulphur and base was found not to be limited to pyrrothine **4** and the thiolactam **9**. The corresponding dithiololactone **13a** as well as the thiolactone **13b** could be converted into the methylthio derivatives **14a** and **14b**, respectively.

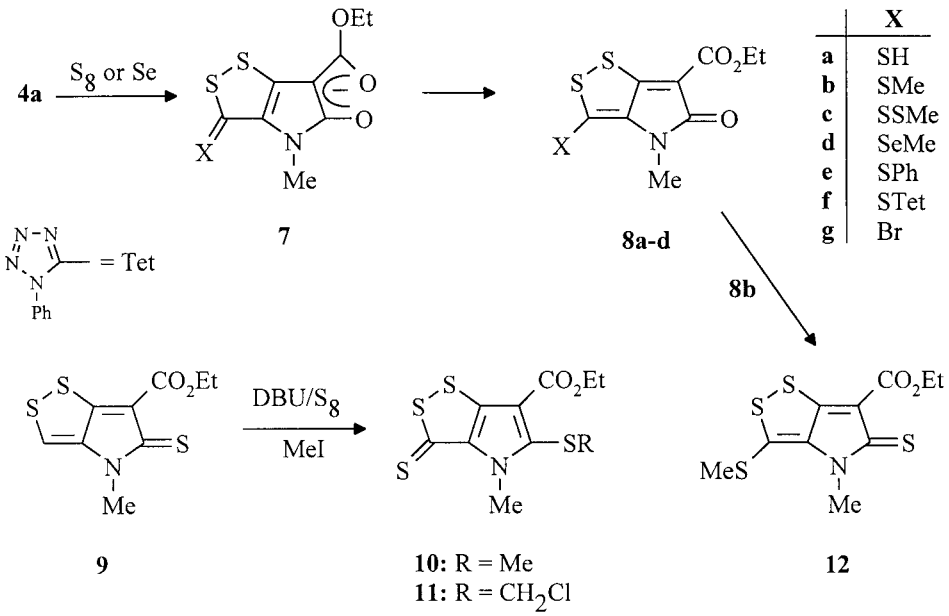
Even the donor-substituted dithiolothiolactone **13c** was cleanly sulphurated to give the sulphide **14a** in excellent yield. In the same way the methylthio group was smoothly introduced into dithiolosultame **15** giving rise to the sulphide **16**. Hence this carbene-like reactivity of pyrrothines and heteroanalogues towards elemental sulphur via their anions appears to be a general feature. But there are exceptions. Thiolutine **2** for instance failed to give the thionation reaction. The same is true for the isothiazolopyrrole **18** [1], an isoster of pyrrothine **4** as well as for the monocyclic dithiole **19**, an open chain analogue of dithiolactone **13a**. On the other hand, trithione **20** was smoothly thionated to sulphide **21**. This is not surprising at all, since **20** may form a conjugate anion with resonance structures very alike to those of **4a**.

In summary, we have found a route to introduce an alkylseleno-, alkylthio-, arylthio- or heteroarylthio group into 3-unsubstituted pyrrothines and their heteroanalogues with apparently only few exceptions. Intermediates are carbenoid anions of the named compounds.

Scheme 1



Scheme 2



2.2. Biological evaluation

Some of the new compounds were evaluated for *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* as part of the TAACF TB Screening Program under direction of the U.S. National Institutes of Health, NIAID division. These compounds displayed significant inhibition effects in the primary screening, conducted at 12.5 μg/ml against *M. tuberculosis* strain H37Rv in BACTEC 12B medium using the BACTEC 460 radiometric system with rifamycin as reference substance (Table). Compounds demonstrating at least 99% inhibition in the primary screen are currently being re-tested in order to determine the actual minimum inhibitory concentration (MIC) against *M. tuberculosis* including different drug resistent strains.

The results show a comparable high activity of thiolutine **2** and the corresponding diester **3** whereas the monoester **4** and its methylthio derivative **8b** are less active in contrast to the highly active methylselenyl derivative **8d** and both the phenylthio and heteroarylthio compounds **8e/8f**. A drop in activity after methylthiolation can likewise be observed by comparing the lactams **3**, **4** and **8b** with the corresponding sultams **17**, **15** and **16**. On the other hand, the methylthio derivatives of the lactone and thiolactone heterologues **14a** and **14c** seemingly do not follow this line because of their high activity. This may partly be due to a generally higher activity of the oxa- and thiaanalogues of pyrrothine derivatives, a conclusion which can cautiously be drawn from earlier screening results [8].

Table: Primary antituberculosis activity *in vitro* screening*

Compd.	MIC (μg/ml)	Inhibition (%)	Compd.	MIC (μg/ml)	Inhibition (%)
2	<12.5	100	**12**	<12.5	13
3	<12.5	98	**14a**	<12.5	99
4	<12.5	73	**14c**	<12.5	100
8b	<12.5	13	**15**	<12.5	100
8d	<12.5	99	**16**	<12.5	12
8e	<12.5	96	**17**	<12.5	100
8f	<12.5	95	**21**	<12.5	12

* MIC rifamycin 0.25 μg/ml; 97% inhibition

Surprisingly, however, is the finding that the methylthio substituted trithione **21** has an activity comparable to the bicyclic methylthio compounds **8b** and **16**. This may constitute a new lead structure.

The biological importance of the carbene-like reactivity of 3-unsubstituted pyrrothines and their heteroanalogues acting as antibacterials appears to be insignificant especially if one takes into account negative experiments with thiolutine. But it is a question still to be examined if pyrrothine anions like **4a** exhibit a catalytic activity in chemical and/or biochemical reactions as they are well documented with thiazolium salts like thiamin [17–22, 44] or with azolium salts [45].

3. Experimental

3.1. General

Melting points were determined using a Gallenkamp apparatus and are uncorrected. Flash chromatography was performed using silica gel (230–400 mesh) from Merck. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard on a JEOL GSX 400. MS were obtained with a Hewlett Packard 5989A Mass Spectrometer employing both EI and CI mode or with a KRATOS MS80RFA using FAB mode. IR spectra were measured as KBr plates for solids using a FT-IR-Spectrometer PARAGON 1000 (Perkin-Elmer). UV analysis was performed unless otherwise stated in methanolic solutions on Uvikon 810 Anakomp 220 (Kontron) and UV/VIS Spectrometer Lambda 20 (Perkin Elmer). 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. All the results were in an acceptable range.

Dichloromethane and toluene were freshly distilled from calciumhydride, ethanol from magnesium turnings under N_2. THF was distilled from sodium benzophenone ketyl under N_2 immediately prior to use. All moisture-sensitive reactions were run with flame-dried glassware.

3.2. Ethyl 4,5-dihydro-4-methyl-5-oxo-1,2-dithiolo[4,3-b]pyrrole-6-carboxylat (4)

To a solution of 1.49 g (5 mmol) of compound **3** [10] in EtOH (50 ml) an ethanolic solution of KOH (0.5 N, 50.0 ml, 25 mmol) was added and the mixture kept at RT for 16 h. After dilution with CH_2Cl_2 (100 ml) the mixture was acidified with dil. H_2SO_4 (50 ml) and the aqueous layer reextracted with CH_2Cl_2 (30 ml). After drying (Na_2SO_4) of the combined organic phases the solvent was removed in vacuo and the residue, containing inter alia enthiol **8a**, purified by CC eluting with $CHCl_3$/ethyl acetate 2:1 (R_f 0.19). Yellow crystals; yield: 661 mg (51%), mp. 189–190 °C from ethyl acetate/acetonitrile, (lit. [10]: m.p. 188 °C).

3.3. (E/Z)-[Bis-(2,5-dihydro-4-ethoxycarbonyl-1-methyl-3-methylthio-5-oxo-2-ylidene]-1,3-dithietane (5)

To a solution of dithiole **4** (243 mg, 1 mmol) and CH_3I (0.5 ml, 8 mmol) in THF/CH_2Cl_2 (30 ml, 1:1) a solution of DBU (1.5 ml, 10 mmol) in THF (3 ml) was added at RT and the mixture stirred for 20 min. After dilution with CH_2Cl_2 (50 ml) the mixture was washed with dil. H_2SO_4 (50 ml) and the aqueous layer reextracted with CH_2Cl_2 (30 ml). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue purified by CC eluting with $CHCl_3$/ethyl acetate 3:2 (R_f 0.16–0.38, tailing) to furnish dithietane **5** (97 mg, 38%). Reddish brown crystals; m.p. 272–276 °C dec. (ethyl acetate/CH_3CN). IR (cm^{-1}): $\nu = 2984$, 2935, 1688 br., 1600, 1522, 1137, 1030; UV (CH_3CN, nm): λ_{max} (lg ε) = 208 (4.017), 245 (4.118), 385 (3.913), 512 (4.545); ^1H NMR ($CDCl_3$): δ = 4.38 (q, 4 H, J = 7.0 Hz), 3.35 (s, 3 H), 3.30 (s, 3 H), 2.63 (s, 3 H), 2.61 (s, 3 H), 1.38 (t, 6 H, J = 7.0 Hz); MS: m/z 515 [M^+, FAB].
$C_{20}H_{22}N_2O_6S_4$ (514.7)

3.4. Ethyl 4,5-dihydro-3-mercapto-4-methyl-5-oxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8a)

A mixture of dithiole **4** (486 mg, 2 mmol), S_8 (520 mg, 16 mmol) and DBU (0.3 ml, 2 mmol) in THF (30 ml) was stirred for 90 min at RT, thereupon diluted with CH_2Cl_2 (30 ml), washed with dil. H_2SO_4 and the aqueous layer re-extracted with CH_2Cl_2 (15 ml). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue purified by CC eluting with ethyl acetate (R_f 0.11) to furnish enthiol **8a** (281 mg, 51%). Yellow powder; m.p. 230 °C dec. (diethyl ether). Blue ferric chloride test. IR (cm^{-1}): $\nu = 3416$, 2929, 2344, 1660, 1561; UV (nm): λ_{max} (lg ε) = 205 (3.793), 239 (3.712), 356 (3.623), 415 (3.882); ^1H NMR ([D_6]-DMSO): δ = 4.15 (q, 2 H, J = 7.3 Hz), 3.52 (s, 3 H), 1.24 (t, 3 H, J = 7.3 Hz).

3.5. Ethyl 4,5-dihydro-4-methyl-3-methylthio-5-oxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8b)

To a mixture of 243 mg (1 mmol) of dithiole **4** and 260 mg (8 mmol) S_8 in dry THF (20 ml) a solution of 0.3 ml (2 mmol) 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in THF (3 ml) was dropwise added under N_2. After 1.5 h (the TLC indicated complete consumption of the dithiol) a solution of 0.2 ml (3.2 mmol) CH_3I in THF (3 ml) was added and the mixture stirred for another 15 min. After dilution with CH_2Cl_2 (50 ml) the mixture was washed with dil. H_2SO_4 (2 N, 15 ml) and the aqueous layer re-extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), concentrated and adsorbed onto silica gel. Purification by flash chromatography eluting with CH_2Cl_2/ethyl acetate 24:1 (R_f 0.12) gave dithiole **8b** (285 mg, 99%). Yellow crystals; m.p. 149 °C (CH_2Cl_2/diethyl ether). IR (cm^{-1}): $\nu = 2975$, 1677, 1581, 1507, 1424; UV (nm): λ_{max} (lg ε) = 209 (4.270), 405 (4.402); ^1H NMR ($CDCl_3$): δ = 4.40 (q, 2 H, J = 7.3 Hz), 3.58 (s, 3 H), 2.69 (s, 3 H), 1.40 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 167.0; 163.5; 162.4; 143.6; 128.5; 106.9; 60.9; 27.1; 20.1; 14.4; MS: m/z 289 [M^+].
$C_{10}H_{11}NO_3S_3$ (289.2)

3.6. Ethyl 4,5-dihydro-4-methyl-3-methyldithio-5-oxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8c)

A suspension of enthiol **8a** (275 mg, 1 mmol) and dimethyl(methylthio)sulphonium tetrafluoroborate (392 mg, 2 mmol) in dry CH_2Cl_2 (30 ml) was refluxed for 2 h, thereupon washed with H_2O (20 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by CC eluting with diisopropyl ether/ethyl acetate 1:1 (R_f 0.39) to give disulphide **8c** (125 mg, 39%). Yellow crystals; m.p. 123 °C (diethyl ether). IR (cm^{-1}): $\nu = 2981$, 1693, 1656, 1577, 1509; UV (nm): λ_{max} (lg ε) = 209 (4.271), 403 (4.334); ^1H NMR ($CDCl_3$): δ = 4.40 (q, 2 H, J = 7.3 Hz), 3.54 (s, 3 H), 2.70 (s, 3 H), 1.40 (t, 3 H, J =7.3 Hz); MS: m/z 321 [M^+].
$C_{10}H_{11}NO_3S_4$ (321.2)

3.7. Ethyl 4,5-dihydro-4-methyl-3-methylseleno-5-oxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8d)

To a suspension of dithiole **4** (486 mg, 2 mmol) and Se (1.34 g, 17 mmol) in THF (100 ml) under ultrasonic treatment a solution of DBU (0.6 ml, 4 mmol) in THF (20 ml) was added under N_2. After 2 h at RT a solution of CH_3I (0.3 ml, 4.8 mmol) in THF (3 ml) was added dropwise and the mixture kept at RT for another 12 h. The suspension was filtered with suction through a small pad of celite, rinsing the filter cake with CH_2Cl_2 (100 ml). The filtrate was washed with dil. H_2SO_4 and the aqueous layer extracted with CH_2Cl_2 (30 ml). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue purified by CC eluting with $CHCl_3$/ethyl acetate 3:1 (R_f 0.29) to furnish selenide **8d** (606 mg, 90%). Light orange platelets; m.p. 148 °C (ethyl acetate). IR (cm^{-1}): $\nu = 2954$ w., 1674, 1640, 1576, 1504, 1421; UV (nm): λ_{max} (lg ε) = 281 (3.347), 383 sh. (4.302), 390 (4.340), 407 (4.365); ^1H NMR ($CDCl_3$): δ = 4.38 (q, 2 H, J = 7.0 Hz), 3.58 (s, 3 H), 2.53 (s, 3 H), 1.38 (t, 3 H, J = 7.0 Hz); MS: m/z 336 [M^+].
$C_{10}H_{11}NO_3S_2Se$ (336.3)

3.8. Ethyl 4,5-dihydro-4-methyl-5-oxo-3-phenylthio-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8e)

To a solution of dithiole **4** (243 mg, 1 mmol) and diphenyl disulphide (770 mg, 3.5 mmol) in THF (75 ml) a solution of DBU (0.4 ml, 2.7 mmol) in THF (5 ml) was added under N_2. After 3 h at RT the mixture was concentrated, adsorbed onto silica gel and purified by CC eluting with $CHCl_3$/ethyl acetate 9:1 (R_f 0.14) to furnish dithiole **8e** (173 mg, 49%). Fine yellow needles; m.p. 198 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): $\nu = 3075$, 2992, 2932, 1660, 1574, 1055, 1478; UV (nm): λ_{max} (lg ε) = 206 (4.460), 400 (4.352); ^1H NMR ($CDCl_3$): δ = 7.49–7.40 (m, 5 H), 4.41 (q, 2 H, J = 7.0 Hz), 3.58 (s, 3 H), 1.40 (t, 3 H, J = 7.0 Hz); MS: m/z 351 [M^+].
$C_{15}H_{13}NO_3S_3$ (351.5)

3.9. Ethyl 4,5-dihydro-4-methyl-5-oxo-3-(1-phenyl-1H-tetrazole-5-thio)-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8f)

To a solution of dithiole **4** (486 mg, 2 mmol) and bis(1-phenyl-1*H*-tetrazole-5-yl)disulphide (1.77 g, 5 mmol) [40] in THF (50 ml) a solution of DBU (2.1 ml, 14 mmol) in THF (5 ml) was added under N_2. After 3 h at RT the mixture was diluted with CH_2Cl_2 (70 ml) and washed with dil. H_2SO_4. After extraction of the aqueous layer with CH_2Cl_2 (30 ml) the combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by CC eluting with $CHCl_3$/ethyl acetate/triethylamine 20:10:1 (R_f 0.48) to furnish dithiole **8f** (150 mg, 18%). Yellow powder; m.p. 119–120 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): $\nu = 3070$, 2984, 2940, 1746, 1702, 1595, 1531, 1498; UV (nm): λ_{max} (lg ε) = 383 (4.169), 398 (4.294); ^1H NMR ($CDCl_3$): δ = 7.62 (m, 3 H), 7.53 (m, 2 H), 4.41 (q, 2 H, J = 7.0 Hz), 3.48 (s, 3 H), 1.40 (t, 3 H, J = 7.0 Hz); MS: m/z 419 [M^+].
$C_{16}H_{13}N_5O_3S_3$ (419.5)

3.10. Ethyl 3-bromo-4,5-dihydro-4-methyl-5-oxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (8g)

A suspension of dithiole **4** (243 mg, 1 mmol) in CH_2Cl_2 (10 ml) was charged with Br_2 (40% in acetic acid, 10.0 ml, 78 mmol) and kept at RT for 48 h. After dilution with CH_2Cl_2 (50 ml) the mixture was washed with H_2O (50 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by CC eluting with CH_2Cl_2 (R_f 0.35) to furnish dithiole **8g** (225 mg, 70%). Yellow crystals; m.p. 187 °C (CH_2Cl_2/diethyl ether). IR (cm^{-1}): $\nu = 2979$, 1716, 1664, 1600, 1497; UV (nm): λ_{max} (lg ε) = 209 (4.261), 239 (3.954), 376 (4.312), 394 (4.293); ^1H NMR ([D_6]-DMSO): δ = 4.26 (q, 2 H, J = 7.3 Hz), 3.41 (s, 3 H), 1.29 (t, 3 H, J = 7.3 Hz); MS: m/z 321/323 [M^+].
$C_9H_8BrNO_3S_2$ (322.8)

3.11. Ethyl 4,5-dihydro-4-methyl-5-thioxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (9)

A solution of dithiole **4** (1.46 g, 6 mmol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (Lawesson's reagent [35]) (4.85 g, 12 mmol) in dry toluene (100 ml) was refluxed for 75 min, there upon concentrated, adsorbed upon silica gel and purified by CC eluting with $CHCl_3$/ethyl with $CHCl_3$/ethyl acetate 9:1 (R_f 0.25) to give thiolactam **9** (0.92 g, 59%). Orange crystals; m.p. 225–230 °C dec. (CH_2Cl_2/diethyl ether). IR (cm^{-1}): $\nu = 3031$, 2980, 1708, 1575, 1486, 1470; UV (nm): λ_{max} (lg ε) = 226 (4.211), 292 (3.971), 438 (4.394); ^1H NMR ([D_6]-DMSO): δ = 8.46 (s, 1 H), 4.28 (q, 2 H, J = 7.3 Hz), 3.63 (s, 3 H), 1.32 (t, 3 H, J = 7.3 Hz); MS: m/z 259 [M^+].
$C_9H_9NO_2S_3$ (259.2)

3.12. Ethyl 4-methyl-5-methylthio-3-thioxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (10)

To a mixture of 259 mg (1 mmol) of dithiole **9** [46] and 260 mg (8 mmol) S_8 a solution of 0.3 ml (2 mmol) DBU in THF (3 ml) was dropwise added under N_2. After 15 min a solution of 0.2 ml (3.2 mmol) CH_3I in THF (3 ml) was added and the mixture stirred for another 15 min. After dilution with CH_2Cl_2 (50 ml) the mixture was washed with dil. H_2SO_4 (2 N, 15 ml) and the aqueous layer re-extracted with CH_2Cl_2 (15 ml). The combined organic phases were dried (Na_2SO_4), concentrated and adsorbed onto silica gel. Purification by CC eluting with hexane/ethyl acetate 8:1 (R_f 0.23) gave dithiole **10** (276 mg, 90%). Yellow crystals; m.p. 92 °C (hexane/diisopropyl ether). IR (cm^{-1}): $\nu = 2977$, 2930, 1720, 1491, 1443, 1387, 1256, 1227, 1064; UV (nm): λ_{max} (lg ε) = 231 (4.148), 290 (3.986), 344 (4.194), 417 (4.126); ^1H NMR ($CDCl_3$): δ = 4.42 (q, 2 H, J = 7.2 Hz), 4.29 (s, 3 H), 2.57 (s, 3 H), 1.43 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 195.2; 162.1; 149.1; 148.7; 138.5; 113.7; 61.6; 32.1; 19.4; 14.7; MS: m/z 305 [M^+].
$C_{10}H_{11}NO_2S_4$ (305.5)

3.13. Ethyl 5-chloromethylenethio-4-methyl–3-thioxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (11)

This compound was prepared in the same manner as compound **10** from 259 mg (1 mmol) of dithiole **9** [46] and S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) with CH_2Cl_2 (40 ml) as solvent. The TLC indicated complete consumption of the dithiole after 60 h at RT. Purification by CC eluting with hexane/ethyl acetate 8:1 (R_f 0.22) gave dithiole **11** (211 mg, 48%). Light orange needles; m.p. 150 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): ν = 2973, 1714, 1672, 1494, 1435, 1278, 1231, 1058; UV (nm): λ_{max} (lg ε) = 230 (4.138), 301 (4.055), 340 (4.170), 421 (4.076); ^{1}H NMR ($CDCl_3$): δ = 5.04 (s, 2 H), 4.40 (q, 2 H, J = 7.2 Hz), 4.32 (s, 3 H), 1.42 (t, 3 H, J = 7.2 Hz); MS: m/z 339/341 [M^+].
$C_{10}H_{10}ClNO_2S_4$ (339.9)

3.14. Ethyl 4,5-dihydro-4-methyl-3-methylthio-3-thioxo-1,2-dithiolo[4,3-b]pyrrrole-6-carboxylate (12)

A solution of 289 mg (1 mmol) of dithiole **8b** and 800 mg (2 mmol) of Lawesson's reagent [35]) in dry toluene (30 ml) was refluxed for 2 h, thereupon adsorbed upon silica gel and purified by CC eluting with hexane/ethyl acetate 1:1 (R_f 0.31) to give thiolactam **12** (256 mg, 84%). Deep orange crystals; m.p. 204 °C (ethyl acetate/CH_3CN). IR (cm^{-1}): ν = 2979, 1721, 1646 w., 1532 w., 1470; UV (nm): λ_{max} (lg ε) = 236 (4.088), 291 (4.106), 362 (3.640), 454 (4.385); ^{1}H NMR ($CDCl_3$): δ = 4.45 (q, 2 H, J = 7.0 Hz), 3.95 (s, 3 H), 2.78 (s, 3 H), 1.43 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 187.1; 164.3; 162.2; 139.2; 131.9; 118.3; 61.5; 31.4, 19.5; 14.8; MS: m/z 305 [M^+].
$C_{10}H_{11}NO_2S_4$ (305.5)

3.15. 6-Ethoxy-5-oxo-5H-thieno[3,2-c][1,2]dithiole (13c)

To a chilled solution of methyl 6-ethoxy-5-oxo-5*H*-thieno[3,2-*c*]-[1,2]dithiole-3-carboxylate [2] (276 mg, 1 mmol) in EtOH (20 ml) an ethanolic solution of KOH (0.5 N in EtOH, 5 ml, 2.5 mmol) was added and the mixture was allowed to reach RT. After another 30 min the solution was acidified with dil. H_2SO_4 (10 ml) and extracted thrice with CH_2Cl_2 (45 ml in total). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue taken up in toluene (20 ml). The mixture was refluxed with *p*-toluenesulphonic acid (20 mg, 0.1 mmol) for 4 h and thereupon adsorbed onto silica gel. Purification by CC eluting with hexane/ethyl acetate 7:1 (R_f 0.25) furnished dithiole **13c** (203 mg, 93% overall). Deep yellow crystals; m.p. 95–96 °C (hexane/diisopropyl ether) ([2]: m.p. 94 °C).

3.16. Ethyl 3-methylthio-5-oxo-5H-1,2-dithiolo[4,3-b]furane-6-carboxylate (14a)

This compound was prepared in the same manner as compound **10** from dithiole **13a** [3] (230 mg, 1 mmol), S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) in THF as solvent. The reaction time was 1 h. Purification by CC eluting with hexane/ethyl acetate 2:1 (R_f 0.30) gave dithiole **14a** (251 mg, 91%). Reddish orange crystals; m.p. 154 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): ν = 2979, 1787, 1755, 1696, 1561, 1488; UV (nm): λ_{max} (lg ε) = 237 (3.916), 317 (3.863), 384 sh. (4.332), 400 (4.368); ^{1}H NMR ($CDCl_3$): δ = 4.39 (q, 2 H, J = 7.2 Hz), 2.80 (s, 3 H), 1.39 (t, 3 H, J = 7.2 Hz); MS: m/z 276 [M^+].
$C_9H_8O_4S_3$ (276.4)

3.17. Ethyl 3-methylthio-5-oxo-5H-thieno[3,2-c][1,2]dithiole-6-carboxylate (14b)

This compound was prepared in the same manner as compound **10** from dithiole **13b** [47] (246 mg, 1 mmol), S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) in THF as solvent. The reaction time was 8 h at RT. Purification by CC eluting with hexane/ethyl acetate 5:2 (R_f 0.16) gave dithiole **14b** (113 mg, 39%). Fine orange needles; m.p. 216 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): ν = 2975, 1651 br., 1496, 1471; UV (nm): λ_{max} (lg ε) = 263 (3.699), 337 (3.784), 409 (4.425); ^{1}H NMR ($CDCl_3$): δ = 4.43 (q, 2 H, J = 7.2 Hz), 2.81 (s, 3 H), 1.41 (t, 3 H, J = 7.2 Hz); MS: m/z 292 [M^+].
$C_9H_8O_3S_4$ (292.4)

3.18. 6-Ethoxy-3-methylthio-5-oxo-5H-thieno[3,2-c][1,2]dithiole (14c)

This compound was prepared in the same manner as compound **10** from dithiole **13c** (218 mg, 1 mmol), S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) in THF as solvent. The reaction time was 15 h at RT. Purification by CC eluting with hexane/ethyl acetate 8:1 (R_f 0.25) gave dithiole **14c** (222 mg, 84%). Deep orange crystals; m.p. 80 °C (hexane/diisopropyl ether). IR (cm^{-1}): ν = 2964, 1618, 1541, 1510, 1466; UV (nm): λ_{max} (lg ε) = 216 (3.871), 275 (3.458), 333 (3.679), 383 (4.074); ^{1}H NMR ($CDCl_3$): δ = 4.29 (q, 2 H, J = 7.3 Hz), 2.61 (s, 3 H), 1.34 (t, 3 H, J = 7.3 Hz); MS: m/z 264 [M^+].
$C_8H_8O_2S_4$ (264.4)

3.19. Methyl 4-methyl-5,5-dioxo-4H-5λ^6-1,2-dithiolo[4,3-c][1,2]thiazole-6-carboxylate (15)

To a chilled solution of diester **17** [48] (323 mg, 1 mmol) in ethanol (20 ml) an ethanolic solution of KOH (0.5 N in EtOH, 5 ml, 2.5 mmol) was added and the mixture allowed to reach RT. After another 5 h the solution was acidified with dil. H_2SO_4 (10 ml) and extracted thrice with CH_2Cl_2 (45 ml in total). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue purified by CC eluting with hexane/ethyl acetate 2:1 (R_f 0.07) to furnish dithiole **15** (191 mg, 72%). Orange needles; m.p. 185–186 °C from hexane/diisopropyl ether, (lit. [48]: m.p. 184 °C).

3.20. Methyl 4-methyl-3-methylthio-5,5-dioxo-4H-5λ^6-1,2-dithiolo[4,3-c][1,2]thiazole-6-carboxylate (16)

The compound was prepared in the same manner as compound **10** from dithiol **15** [48] (265 mg, 1 mmol), S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) in THF as solvent. The reaction time was 1 h at RT. Purification by CC eluting with hexane/ethyl acetate 2:1 (R_f 0.19) gave dithiole **16** (302 mg, 97%). Deep yellow platelets; m.p. 172–173 °C (diisopropyl ether/ethyl acetate). IR (cm^{-1}): ν = 2927, 1670, 1563, 1505, 1436, 1295, 1221, 1147; UV (nm): λ_{max} (lg ε) = 236 (3.793), 383 (4.181), 409 (4.297); ^{1}H NMR ($CDCl_3$): δ = 3.94 (s, 3 H), 3.52 (s, 3 H), 2.61 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ = 161.6; 159.2; 130.8; 126.7; 108.1; 52.8; 28.1; 20.4; MS: m/z 311 [M^+].
$C_8H_9NO_4S_4$ (311.4)

3.21. Diethyl (4-methoxy-3H-1,2-dithiol-3-ylidene)malonate (19)

To a solution of diethyl (5-ethoxycarbonyl-4-methoxy-3*H*-1,2-dithiol-3-ylidene)malonate [49] (724 mg, 2 mmol) in EtOH (30 ml) an ethanolic solution of KOH (0.5 N in EtOH, 20.0 ml, 10 mmol) was added and the mixture was allowed to stand at RT for 15 min. After dilution with CH_2Cl_2 (50 ml) the mixture was acidified with dil H_2SO_4 (50 ml) and the aqueous layer was reextracted with CH_2Cl_2 (30 ml). After drying (Na_2SO_4) of the combined organic phases the solvent was evaporated and the residue redissolved in toluene (30 ml). The solution was refluxed with *p*-toluenesulphonic acid (20 mg, 0.1 mmol) for 90 min, thereupon adsorbed onto silica gel and purified by CC eluting with hexane/ethyl acetate 3:1 (R_f 0.15) to furnish dithiole **19** (452 mg, 78% overall). Bright yellow crystals, m.p. 70 °C (hexane). IR (cm^{-1}): ν = 3064, 2979, 2934, 2902, 2839, 1719 br., 1644, 1552, 1498; UV (nm): λ_{max} (lg ε) = 383 sh. (4.118), 392 (4.159); ^{1}H NMR ($CDCl_3$): δ = 6.71(s, 1H), 4.26 (m, 4 H), 3.82 (s, 3 H), 1.29 (m, 6 H); MS: m/z 290 [M^+].
$C_{11}H_{14}O_5S_2$ (290.4)

3.22. Methyl 5-methylthio-3-thioxo-3H-1,2-dithiole-4-carboxylate (21)

The compound was prepared from dithiole **20** [50] (192 mg, 1 mmol), S_8 (260 mg, 8 mmol) and DBU (0.3 ml, 2 mmol) in THF as solvent. The reaction time was 1 h at RT. Purification by CC eluting with hexane/ethyl acetate 3:1 (R_f 0.29) gave dithiole **21** (655 mg, 55%). Deep yellow crystals; m.p. 152 °C (diisopropyl ether/ethyl acetate) (lit. [32]: m.p. 152 °C). IR (cm^{-1}): ν = 2950, 1681, 1431, 1376, 1255; UV (nm): λ_{max} (lg ε) = 241 (3.844), 295 (3.799), 327 (4.108), 417 (3.832); ^{1}H NMR ($CDCl_3$): δ = 3.93 (s, 3 H), 2.73 (s, 3 H); MS: m/z 238 [M^+].
$C_6H_6O_2S_4$ (238.4)

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