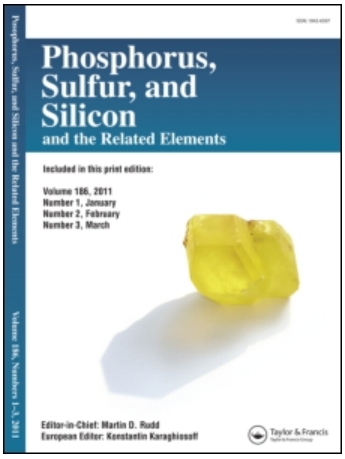


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The 3-Thioxo-1,2-Dithiol-4-yl Group: A Versatile One Endowed Also With a -R Electronic Effect

Marylène Chollet Krugler[a]; Béatrice Legouin[a]; Sylvain Gargadennec[a]; Liza Mouret[b]; Jean-Louis Burgot[a]
[a] Laboratoire de Chimie Analytique, UFR des Sciences Pharmaceutiques et Biologiques, Université de Rennes I, Rennes, France [b] Laboratoire de Mathématiques et Physique Pharmaceutique, UFR des Sciences Pharmaceutiques et Biologiques, Université de Rennes I, Rennes, France

To cite this Article Krugler, Marylène Chollet , Legouin, Béatrice , Gargadennec, Sylvain , Mouret, Liza and Burgot, Jean-Louis(2006) 'The 3-Thioxo-1,2-Dithiol-4-yl Group: A Versatile One Endowed Also With a -R Electronic Effect', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 10, 2307 — 2320
To link to this Article: DOI: 10.1080/10426500600616860
URL: http://dx.doi.org/10.1080/10426500600616860

Phosphorus, Sulfur, and Silicon, 181:2307–2320, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500600616860

The 3-Thioxo-1,2-Dithiol-4-yl Group: A Versatile One Endowed Also With a –R Electronic Effect

Marylène Chollet Krugler
Béatrice Legouin
Sylvain Gargadennec
Laboratoire de Chimie Analytique, UFR des Sciences Pharmaceutiques et Biologiques, Université de Rennes I, Rennes, France

Liza Mouret
Laboratoire de Mathématiques et Physique Pharmaceutique, UFR des Sciences Pharmaceutiques et Biologiques, Université de Rennes I, Rennes, France

Jean-Louis Burgot
Laboratoire de Chimie Analytique, UFR des Sciences Pharmaceutiques et Biologiques, Université de Rennes I, Rennes, France

The pK_a values in an aqueous solution of some 4-aminodithiolethiones, 4-aminodithiolones, 5-phenyl-4-hydroxydithiolethione, and 5-phenyl-4-hydroxydithiolone were determined by UV-VIS spectrophotometry at 298 K. These compounds exhibited unexpectedly very low pK_a values in the range of 0–2 for amino derivatives and in the range of 7 for hydroxy derivatives. Electronic structure calculations by ab initio and DFT methods together with an X-ray measurement indicated that these results may be attributed to a markedly negative π charge on the carbon 5 together with a positive π charge on the basic substituent of the carbon 4. As a result, the dithiole nucleus exerts in this case a strong —R effect. Although they were very low, pK_a values of 4-aminodithiolethiones remained still higher than those found with 5-aminodithiolethiones, which were also determined in this work for comparison. The latter were not unexpectedly in the range $-3 < pH < -2$.

Keywords 1,2-dithiole-3-thione; acidity constant; ab initio Hartree-Fock; electronic structure; density functional theory

Received November 14, 2005; accepted January 30, 2006.

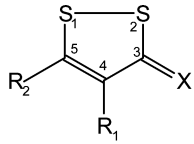
The authors would like to thank Dr. Eric Furet for helpful discussions on the theoretical calculations part of this work. We thank also Mr. G. Bouer for his assistance in preparing the English manuscript.

Address correspondence to Marylène Chollet Krugler, Laboratoire de Chimie Analytique, UFR des Sciences Pharmaceutiques et Biololgiques, Université de Rennes I, Rennes, France. E-mail: marylene.chollet@univ-rennes1.fr

INTRODUCTION

3*H*-1, 2-dithiole-3-thiones (DTT) **1** (X = S) are compounds of growing pharmacological interest. The prevention of cancer through the administration of low-cost non-toxic molecules such as Oltipraz (35972 R.P.) (R_1: methyl; R_2: 2-pyrazinyl)[1] and Anetholtrithione (R_1: H; R_2: *p*-methoxyphenyl) [2] is being intensely investigated.[3] The chemopreventive properties of these two derivatives are also probably shared by the entire class of dithiolethiones.[4] In brief, the family of dithiolethiones is of central interest in the concept of chemoprevention.

In the course of our studies devoted to the physicochemical properties of 3*H*-1, 2-dithiole-3-thiones (DTT) **1** (X = S) and 3*H*-1, 2-dithiole-3-ones (DTO) **1** (X = O) (Scheme 1),[5,6]



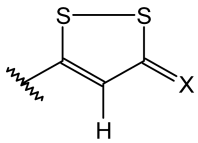
X = O

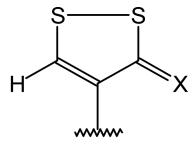
X = S

1

SCHEME 1

we took an interest in the quantitative assessment of the electronic effect of the 3-thioxo-1,2-dithiol-5-yl **2** and 3-thioxo-1,2-dithiol-4-yl **3** groups and of the corresponding oxo ones **2′** and **3′** (Scheme 2).





2 X = S **3** X = S

2' X = O **3'** X = O

SCHEME 2

If the strong withdrawing effect of group **2** (and to a slightly lesser extent of **2′**) both by inductive and resonance effects is now well ascertained,[5] this is not the case of the electronic effects of groups **3** and **3′**. On the one hand, linear free-enthalpy relationships based on pK_a values of 4-(hydroxy or aminophenyl) DTT and DTO indicated a

weak withdrawing effect only by an inductive one, as it was evidenced by the σ_{p-}, σ_p, and σ_m values of Hammett substituent constants.[5,7,8] On the other hand, Voronkow et al., [9] attributed a + R releasing effect of group 3 in 4-phenyl DTT on the basis of theoretical calculations. The discrepancy between these two results evidenced by the values of Hammett substituent constants may be probably due to the fact that the phenyl moiety is sufficiently twisted relatively to the plane of the dithiole nucleus to prevent any conjugation between them, and hence only the −I effect plays a part in the σ values. One finding corroborates indirectly this explanation. It concerns the experimental water/n-octanol log P values of 4-phenyl DTT, and 4-(p-tolyl)-DTT, which strictly obey the additivity rule of the log P fragments, i.e., of the phenyl and of the dithiole fragments determined statistically elsewhere. This precludes any conjugation between them.[10]

However, this + R effect of group 3 must probably exist in some cases as mentioned below. The difficult hydrolysis of 4-ethoxycarbonyl DTT, which occurs only in a very acidic medium, is in agreement with the strong conjugation between the dithiole moiety and the carbonyl of the ester group.[11] For our part, we also explained the anomalous pK_a values of 3-thioxo-1,2-dithiole-4-carboxylic acids by the occurrence of both a −I and a +R effect of group **3**.[12] Let us also recall that charge transfer studies have shown that sulfur atoms 1 and 2 in the dithiole ring play the part of a tank of electrons for the remainder of the group during the first two $\Pi \rightarrow \Pi^*$ transitions of low energy.[13]

Finally, another point remained fully obscure at the beginning of this work. It was whether or not a −R electronic effect of groups **3** and **3′** occurred in some cases. Hence, we decided also to check this possibility.

We took an interest in the determination of the pK_a values of some judiciously substituted DTT and DTO in order to answer these questions.

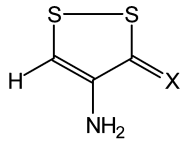
We studied firstly pK_a values of DTT **4**, **5**, **6** and those of their corresponding DTO **4′**, **5′**, **6′** and (Scheme 3).

To compare the electronic effects of groups **2** and **3**, we also determined the pK_a values of DTT **7**, **8**, and **9** and those of DTO **8′** (Scheme 4).

Let us recall that only few functionalized DTT and DTO have so far been described in the literature. However, the chosen derivatives had already been described, except derivatives **5**, **5′**, **6′** and **8**, which were original.

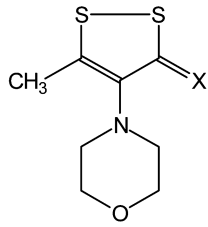
RESULTS AND DISCUSSION

pK_a values are given in the Table I. They were determined by UV-VIS spectrophotometry (see Experimental section).



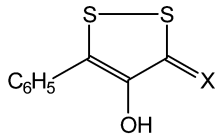
4 X = S

4' X = O



5 X = S

5' X = O



6 X = S

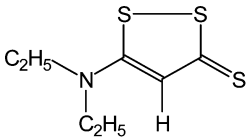
6' X = O

SCHEME 3

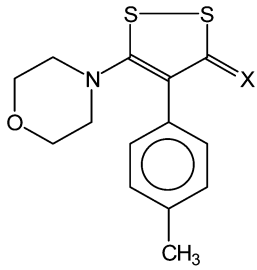
Strikingly anomalous pK_a values are observed in Table I. They are related to those obtained with 4-amino DTT, DTO **4**, **4′**, **5**, and **5′**, and to a lesser extent to those found with 4-hydroxyderivatives **6** and **6′** (pK_a values of DTT and DTO **7**, **8**, **8′** and **9** are not unexpected—see below).

Results obtained with derivatives **4**, **4′**, **5**, **5′**, **6**, and **6′** were very surprising indeed.

Since DTT (and to a slightly lesser extent DTO) have been known for a long time to be aromatic compounds,[14] their pK_a values were expected to be in the range of $4 < pK_a < 5$ for derivatives **4**, **4′**, **5**, **5′** and in the range of $9 < pK_a < 11$ for **6** and **6′** in agreement with those found with anilines and phenols. Actually they were considerably lower. A similar phenomenon is observed with 2-aminotropone and 2-tropolone, the pK_a values of which are respectively in the order of 2.20[15,16] and 6.90.[17,18]

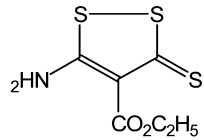


7



8 X = S

8' X = O



9

SCHEME 4

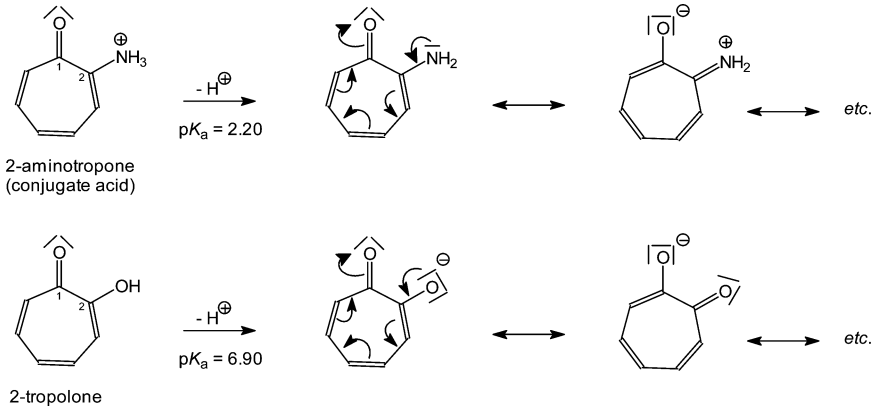
TABLE I pK_a Values[a] of Dithiolethiones 4, 5, 6, 7, 8, and 9 and Dithiolones 4′, 5′, 6′, and 8′

Compound	X	pK_a (Spectrophometry)
4	S	1.06 ± 0.02[b]
4′	O	1.86 ± 0.05[b]
5	S	-0.06 ± 0.05[b]
5′	O	0.21 ± 0.08[b]
6	S	6.93 ± 0.22[c]
6′	O	6.97 ± 0.02[c]
7	S	-2.16 ± 0.08[b]
8	S	-2.32 ± 0.10[b]
8′	O	-2.12 ± 0.30[b]
9	S	-2.47 ± 0.08[d]

[a]The 95% confidence limits on the average value are given by $-\log(K_a \pm 2.447\sigma_{n-1}/n^{1/2})$ according to a student's table.
[b]pK_a determined in methanol-water 2% (v/v) at 298 K.
[c]pK_a determined in ethanol-water 5% (v/v) at 298 K.
[d]pK_a determined in methanol-water 1% (v/v) at 298 K.

This analogy is not surprising because DTT and DTO are considered to be iso-π-electronic of tropones (Scheme 5).[19,20]

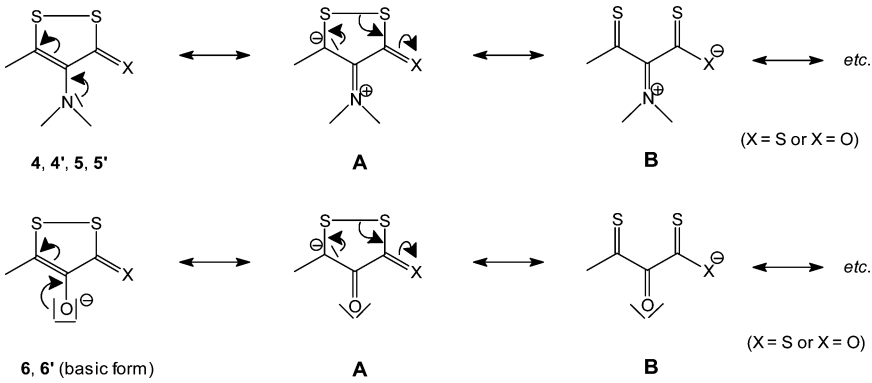
According to this concept, each of the sulfur atoms 1 and 2 plays the part of a double bond in the tropone series. We noticed that the pK_a value of 2-tropolone was identical with those obtained with 4-hydroxy derivatives **6** and **6'**. Amino derivatives **4**, **4′**, **5**, and **5′** exhibited however markedly lower values than 2-aminotropone. In the case of the tropone derivatives, lower pKa values in relation with those of "classical"



SCHEME 5

phenols and anilines can be explained by the resonance delocalization of the electrons of the basic site. In our case, it is hence reasonable to infer from these data that groups **3** and **3′** exhibit likewise a strong −R effect when they are bound to an amino or hydroxylic group. The effect could be attributed to the delocalization of the electrons of the basic site upon the dithiole nucleus as it is in the tropones.

However, it is interesting to emphasize the fact that there may exist a great difference between the resonance schemes of the basic forms of the DTT (DTO) and tropones. DTT and DTO may exhibit a single bond no-bond resonance between sulfur atoms 1 and 2 (Scheme 6). Such a single bond no-bond resonance is not involved at first glance in the chemistry of tropones.



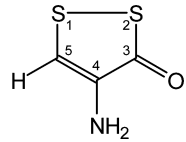
SCHEME 6

The occurrence of a single bond no-bond resonance has been frequently evoked in the chemistry of thio-organic compounds and has been the subject of several studies.[21,22] Moreover, in the case of some 1,2-dithiolylium-4-olates cations, a true equilibrium between the cyclic dithiolylium-4-olate structure and its noncyclic valence isomer does exist, at least with some substituents.[23] Hence, pK_a values obtained with derivatives **4**, **4′**, **5**, **5′** raised the same question for 4-aminodithiolethiones and 4-aminodithiolones.

Actually the following arguments show that the resonance schemes of derivatives **4**, **4′**, **5**, **5′**, **6**, and **6′** must not involve the open form **B** and show that the form **A** is of great weight:

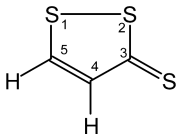
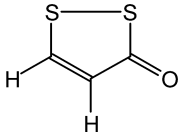
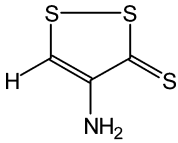
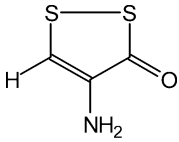
- The length of the disulfide bond in derivative **4′** is quite normal (2.05 Å)[24] as it is indicated by an X-ray measurement (Table II). The length of the disulfide bond in the non cyclic valence isomers of 1,2-dithiolylium-4-olates is indeed markedly longer than the length

TABLE II Bond Lengths (Å) of Compound 4′ Obtained by X-Ray Spectroscopy, Calculated by PM3-MNDO, Ab Initio HF (6-31G*), and DFT (B3LYP, 6-31G*) Methods



	RX	PM3	HF	DFT
S_1-S_2	2.05	2.08	2.07	2.10
S_2-C_3	1.78	—	1.78	1.82
S_1-C_5	1.72	1.73	1.76	1.75
C_3-O	1.22	—	1.17	1.21
C_4-N	1.37	1.42	1.37	1.39
C_3-C_4	1.47	—	1.48	1.47
C_4-C_5	1.34	1.35	1.33	1.35

TABLE III π-Charges of Compounds 4, 4′, Parent Dithiolthione, and Dithiolone, Calculated by PM3-MNDO, Ab Initio HF (6-31G*), and DFT (B3LYP, 6-31G*) Methods

		S_1	S_2	C_3	C_4	C_5	S_6	O	N
	PM3	1.83	1.83	0.94	1.04	1.02	1.33	—	—
	HF	1.83	1.80	0.91	1.05	0.96	1.40	—	—
	DFT	1.75	1.75	1.03	1.03	1.02	1.39	—	—
	PM3	1.88	1.91	0.78	1.08	1.00	—	1.36	—
	HF	1.86	1.87	0.75	1.09	0.95	—	1.45	—
	DFT	1.77	1.81	0.86	1.08	1.01	—	1.44	—
	PM3	1.84	1.81	0.96	1.03	1.13	1.36	—	1.59
	HF	1.85	1.78	0.92	0.99	1.09	1.42	—	1.80
	DFT	1.77	1.73	1.05	1.00	1.13	1.43	—	1.75
4									
	PM3	1.90	1.90	0.78	1.06	1.13	—	1.36	1.60
	HF	1.89	1.85	0.75	1.01	1.10	—	1.46	1.80
	DFT	1.83	1.79	0.88	1.04	1.14	—	1.44	1.76
4′									

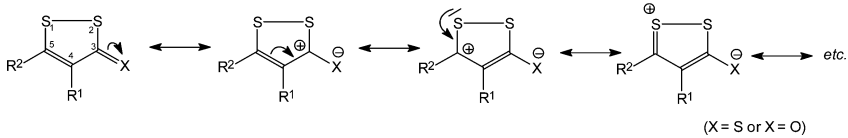
of the disulfide bridge in the cyclic isomer.[25] Hence, the open forms **B** are already ruled out by this finding.

- Calculations of the electronic structures (Table III) by ab-initio HF and DFT methods of derivatives **4**, and **4′** and of parent compounds (for comparison) showed clearly that carbon 5 was markedly more negatively charged in π electrons in the former than in the latter. It also appeared that the amino group was deficient in π electrons as it was the case in aniline (1.63 PM3 – 1.80 HF – 1.76 DFT). This confirms the high weight of structure **A** (Scheme 6) and hence the –R effect of the dithiole nucleus.

It is important to notice that the disulfide bond lengths calculated were in the expected range (Table II).[24]

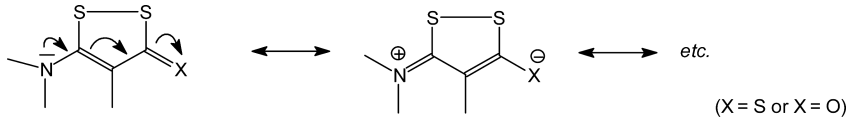
Likewise, the agreement between the experimental and calculated geometry of compound **4′** was good. Here lies a strong argument in favor of the calculations accuracy. It is interesting to notice also that π electronic charges of sulphur 1 and 2 atoms were the same in the 4-amino derivatives as in the parent compounds. The structure of α-thiocarbanions has been the subject of several studies, and this result may be an additional contribution to the debate.[26]

pK_a values found for DTT and DTO **7**, **8**, **8′**, and **9** were not unexpected owing to the well-known resonance scheme of the dithiole nucleus (Scheme 7).



SCHEME 7

One explanation for the pK_a differences between 5- and 4-amino derivatives, lies in the fact that in the latter derivatives, the delocalization of π electrons of the amino group is far less extended, as it has been said, than in the 5-amino compounds. Several canonical forms contribute to the true structure in which the iminium limit form has a very high weight (Scheme 8).



SCHEME 8

pK_a values obtained with these derivatives were in agreement with those exhibited by 2-nitro-aniline (p$K_a = -0.31$) and 2,4-dinitroaniline (p$K_a = -4.42$), two derivatives in which both inductive and resonance withdrawing effects do exist and reinforce themselves. Hence, pK_a values of derivatives **7**, **8**, **8′**, and **9** confirmed that groups **2** and **2'** are endowed with a very strong withdrawing effect.[5] The results of the order of p$K_a \cong -2.20$ induce the question of the protonation site of derivatives **7**, **8**, **8′**, and **9** in a strongly acidic medium. At first insight, it may be either the amino or the thiocarbonyl (carbonyl) group. It is probably on the nitrogen that protonation occurs because pK_a values of protonated thiocarbonyl derivatives given in the literature are in the order of -4.[19]

CONCLUSION

As a result, it can be inferred from this work that the 3-thioxo-1,2-dithiol-4-yl **3** groups and its corresponding oxo groups **3′** are endowed with a powerful −R electronic effect when they are bonded to electron-donating substituents. This −R electronic effect remains, however, still weaker than that exhibited by its isomeric 3-thioxo and 3-oxo-1,2-dithiol-5-yl **2** and **2′** groups.

EXPERIMENTAL

Materials

All commercially available chemicals were of analytical grade. The water used throughout this work was deionized on a set of ion exchanging columns (ELGASTAT UHQ MKII, England) to $\rho > 16$ M$\Omega \cdot$cm^{-1}.

Instrumentation

For analysis, FTIR spectra were recorded on a Perkin-Elmer FTIR 16PC instrument. Mass spectra were recorded on a Varian Mat 311 spectrometer (CRMPO—Rennes). NMR spectra were taken on a 300 MHz Bruker AM 300 instrument; observation frequency were taken at 300 MHz for ^{1}H and 75 MHz for ^{13}C; chemical shifts were referred to tetramethylsilane ($\delta = 0$ ppm) (CRMPO—Rennes). Melting points were determined on an Electrothermal 9200 instrument. Single crystal X-ray diffraction data collection was performed at r.t. with a Nonius CAD4 diffractometer (Centre de Diffractométrie, Université de Rennes I, France), with Mo Kα radiation ($\lambda = 0.71073$ Å). The crystal structure of **4′** has been deposited at the Cambridge Crystallograghic Data Centre and allocated

the deposition number **CCDC 256923**. Absorbances were measured using UV-VIS spectrophotometer (Uvikon Model 922) with 1-cm silica cells.

Spectrophotometric UV-VIS pK_a Determinations

For UV-VIS studies, one or two different working wavelengths corresponding to the maxima of molar absorptivities were selected for each compound. The strategy followed was to select the wavelengths endowed with the larger differences of molar absorptivities between the conjugated acid and base under study (working wavelengths are mentioned with the description of dithiolethiones and dithiolones). The buffer solutions were the Britton and Robinson ones for pH $>$ 2. For pH $<$ 2, Bascombe and Bell's acidity functions were chosen. pK_a were extracted from the pH and absorbance data by using a nonlinear least-squares procedure.[27,28] To obtain significant statistical parameters, 6 independent determinations were performed for each derivative. The molar absorptivity ε of each one was systematically considered as unknown. This strategy allowed a comparison of the molar absorptivity determined through the fitting process with the experimental one. The consistence of both groups of results provided an indirect proof of accuracy of the experiments and of calculations.

Solutions were prepared by dissolving weighed amounts of compounds in a minimum of methanol or ethanol and then by diluting the alcoholic solution in the appropriate buffer. The amount of methanol in the working solutions never exceeded 2% (v/v) except for compounds **6** and **6′**, which were ethanol-water 5% (v/v). In every case, one or several isobestic points were found.

Theoretical Calculations

- PM3-MNDO semi-empirical calculations were carried out within the framework of the MOPAC program.[29] The efficiency of this method has been previously evidenced for the study of electronic and geometric structures of a dithiolthione and a dithiolone series.[30]
- Ab initio Hartree–Fock (HF) and Density Functional Theory (DFT) calculations were performed with the *Gaussian 03* revision B.04 package.[31] DFT calculations use the B3LYP[32] hybrid functional. Both HF and DFT methods were carried out with a 6-31G* basis set, which is now commonly used for such systems. π-charges presented in Table III were obtained with a natural bond orbital analysis.[33]

Synthesis

Dithiolethiones and dithiolones **4**, **4′**, **6**, **7**, **8′**, and **9** are described in this section. Dithiolethiones and dithiolones **5**, **5′**, **6′**, and **8** are novel compounds.

*4-Amino-3*H*-1,2-dithiole-3-thione 4*

This compound is described in the literature. [34]λ (pH = − 1.0)/nm = 400 (ε/dm^3 mol^{-1} cm^{-1} 10527), λ(pH = 3.2)/nm = 425 (11793).

*4-Amino-3*H*-1,2-dithiol-3-one 4′*

This compound is described in the literature. [34]λ(pH = 0.0)/nm = 310 (ε/dm^3 mol^{-1} cm^{-1}6268), λ(pH = 4.0)/nm = 335 (6175).

*5-Methyl-4-morpholin-4-yl-3*H*-1,2-dithiole-3-thione 5*

This product was prepared by sulfuration of ethyl-2-morpholinoacetate[35] (10.79 g; 0.05 mole) with P_4S_{10} (22.00 g; 0.05 mole) in refluxing xylene (500 mL) during 15 min.[36] After cooling, the suspension was washed with an aqueous sodium hydroxide solution 0.2 M and extracted with chloroform. The solvent was dried over sodium sulfate and evaporated in vacuo. The residue was purified by a column chromatography on silica gel, elution with ether/toluene (1%); yield: 12%; yellow crystals, m.p. 134°C (ethyl alcohol anhydrous); EI-MS m/z: 233.0015 (calcd. for $C_8H_{11}NOS_3$:233.0002); ^{1}H NMR ($CDCl_3$, δ ppm): 2.48 (s, 3H, CH_3); 3.41 (s, 4H, morpholino); 3.77 (s, 4H, morpholino), ^{13}C NMR ($CDCl_3$, δ ppm): 18.1 (CH_3); 48.2 (CH_2, morpholino); 67.9 (CH_2, morpholino), 151.8 (C4); 168.4 (C5); 211.7 (C3); λ(pH = − 3)/nm = 398(ε/dm^3 mol^{-1} cm^{-1} 10980), λ(pH = 2.0)/nm = 398 (9192).

*5-Methyl-4-morpholin-4-yl-3*H*-1,2-dithiol-3-one 5′*

To a solution dithiolethione **5** (1 eq, 1.43 g) in ether (600 mL) was added 3 eq of benzhydroxamoyl chloride and 3 eq of triethylamine.[37] After the addition, the solution was stirred at r.t. until discoloration of the mixture. The precipitate was filtered and eliminated, and the ether solution was removed. The residue was purified by a column chromatography on silica gel, elution with ether/toluene (25%); yield: 33%; white crystals, m.p. 89°C (ethyl alcohol anhydrous); EI-MS m/z: 217.0237 (calcd. for $C_8H_{11}NO_2S_2$:217.0231); ^{1}H NMR ($CDCl_3$, δ ppm): 2.41 (s, 3H, CH_3); 3.07 (s, 4H, morpholino); 3.76 (s, 4H, morpholino), ^{13}C NMR ($CDCl_3$, δ ppm): 18.4 (CH_3); 49.4 (CH_2, morpholino); 67.6 (CH_2, morpholino), 138.7 (C4); 161.4 (C5); 190.8 (C3); λ(pH = − 3)/nm = 398(ε/dm^3 mol^{-1} cm^{-1} 10980), λ(pH = 2.0)/nm = 398 (9192); IR (KBr, υ_{max}, cm^{-1}): 1628 (C=O).

*4-Hydroxy-5-phenyl-3*H*-1,2-dithiole-3-thione 6*

This compound is described in the literature.[38] λ(pH = 6.1)/nm = 415 (ε/dm^3 mol^{-1} cm^{-1} 9768), λ(pH = 9.1)/nm = 415 (3322).

*4-Hydroxy-5-phenyl-3*H*-1,2-dithiol-3-one 6′*

To a solution dithiolethione **6** (1 eq, 700 mg) in ether (250 mL) was added 2.5 eq of benzhydroxamoyl chloride and 2 eq of triethylamine.[37] After the addition, the solution was stirred at r.t. until discoloration of the mixture. The precipitate was filtered and eliminated, and the ether solution was removed. The residue was heated in refluxing xylene (100 mL) during 1 h; the solvent was removed, and the residue was purified by a column chromatography on silica gel, elution with toluene; yield: 46%; white crystals, mp 139°C; EI-MS m/z: 209.9817 (calcd. for $C_9H_6O_2S_2$:209.9809). ^{1}H NMR ($CDCl_3$, δ ppm): 6.56 (s, 1H, OH); 7.44–7.87 (m, 5H, C_6H_5), ^{13}C NMR ($CDCl_3$, δ ppm): 127.4, 129.1, 130.4, 131.5 (C_6H_5); 137.0 (C5); 141.4 (C4); 188.5 (C3); λ(pH = 5.1)/nm = 380(ε/dm^3 mol^{-1} cm^{-1} 1098), λ(pH = 9.8)/nm = 380 (9443). IR (KBr, υ_{max}, cm^{-1}): 1717 (C=O), 3352 (OH).

*5-(Diethylamino)-3*H*-1,2-dithiole-3-thione 7*

This compound is described in the literature.[39] λ(pH = −2.9)/nm = 295 (ε/dm^3 mol^{-1} cm^{-1} 12404), λ(pH = 1)/nm = 355 (24642).

*4-(4-Methylphenyl)-5-morpholin-4-yl-3*H*-1,2-dithiole-3-thione 8*

This product was prepared by the sulfuration of compound **8′** (1 eq, 275 mg) with P_4S_{10} (1 eq, 418 mg) in refluxing xylene (45 mL) during 15 min.[36] After cooling, the suspension was washed with an aqueous sodium hydroxide solution 0.2 M and extracted with chloroform. The solvent was dried over sodium sulfate and evaporated in vacuo. The residue was purified by a column chromatography on silica gel, elution with ether/toluene (4%); yield: 55%; orange crystals, m.p. 139°C; EI-MS m/z: 309.0318 (calcd. for $C_{14}H_{15}NOS_3$: 309.0316). ^{1}H NMR ($CDCl_3$, δ ppm): 2.37 (s, 3H, CH_3); 3.26 (s, 4H, morpholino); 3.60 (s, 4H, morpholino) 7.21–7.27 (m, 4H, C_6H_4), ^{13}C NMR ($CDCl_3$, δ ppm): 21.4 (CH_3); 51.1 (CH_2, morpholino); 65.9 (CH_2, morpholino) 128.5, 129.8, 130.1, 132.8 (C_6H_4); 138.3 (C4); 178.9 (C5); 207.5 (C3); λ(pH = −4.0)/nm = 313(ε/dm^3 mol^{-1} cm^{-1} 9547), λ(pH = 0.0)/nm = 374 (13339).

*4-(4-Methylphenyl)-5-morpholin-4-yl-3*H*-1,2-dithiol-3-one 8′*

This compound is described in the literature.[40] λ(pH = −4.0)/nm = 322 (ε/dm^3 mol^{-1} cm^{-1} 14121), λ(pH = 1.0)/nm = 322 (11167).

*Ethyl 5-amino-3-thioxo-3*H*-1,2-dithiole-4-carboxylate 9*

This product is described in the literature.[41] $\lambda(pH = -4.0)/nm = 251$ (ε/dm^3 mol^{-1} cm^{-1} 7526), $\lambda(pH = 0.0)/nm = 251$ (10400).

REFERENCES

[1] J. P. Leroy, M. Barreau, C. Cotrel, C. Teanmart, M. Nesser, and F. Benazet, *Curr. Chemother*., **1,** 148 (1978).
[2] S. Lam, C. Mac Aulay, J. C. Le Riche, Y. Dyachkova, A. Coldman, M. Guillaud, E. Hawk, M. O. Christen, and A. Gadzar, *J. Natl. Conc. Inst*., **94,** 1001 (2002).
[3] M. Sporn and N. Suh, *Nat. Rev. Cancer*, **2,** 537 (2002).
[4] B. D. Roebuck, J. J. Curphey, Y. Li, K. Baumgartner, S. Bodreddigary, J. Yan, S. J. Gange, T. W. Kensler, and T. R. Sutter, *Carcinogenesis*, **24,** 1919 (2003).
[5] M. Chollet, B. Legouin, and J. L. Burgot, *J. Chem. Soc., Perkin Trans*., **2,** 2227 (1998).
[6] S. Gargadennec, G. Burgot, J. L. Burgot, R. Mannhold, and R. F. Rekker, *Pharmaceutical Research*, **22,** 875 (2005).
[7] M. Saidi, Ph. D. Thesis, University of Rennes I, Rennes (1988).
[8] J. L. Burgot, A. Darchen, and M. Saidi, *Comm. Section Ouest de la Société Française de Chimie* (1988).
[9] M. G. Voronkow, V. I. Minkin, O. A. Osipov, M. G. Kogan, and T. V. Lapina, *Khim. Geterosikl. Soedin*, **3,** 758 (1967).
[10] M. Bona, P. Boudeville, O. Zekri, M. O. Christen, and J. L. Burgot, *J. Pharm. Sci*., **87,** 1107 (1995).
[11] C. Trebaul and J. Teste, *Bull. Soc. Chim. Fr*., **7,** 2456 (1969).
[12] M. Chollet and J. L. Burgot, *J. Chem. Soc., Perkin Trans*., **2,** 387 (1998).
[13] A. Botrel, B. Illien, P. Rajczy, I. Ledoux, and J. Zyss, *Theor. Chim. Acta*., **87,** 175 (1993).
[14] Ph. Landis, *Chem. Rev*., **65,** 237 (1965).
[15] S. Seto, T. Hiratsuka, and H. Toda, *Yakugaku Zusshi*, **89,** 1673 (1969).
[16] K. Imafuku, Y. Takata, and H. Matsumura, *Bull. Chem. Soc. Jap*., **47,** 1809 (1974).
[17] K. Takahashi, K. Morita, and K. Takase, *Chem. Letters*, 1505 (1977).
[18] H. C. Ko and W. F. O'Hara, *Thermochimica Acta*, **11,** 94 (1975).
[19] R. Mayer and H. Hartmann, *Zeitschrift für Chemie*., **6,** 209 (1967).
[20] F. Boberg, *Liebigs Ann. Chem*., **693,** 212 (1966).
[21] C. L. Perrin, Y. J. Kim, and J. Kuperman, *J. Phys. Chem*., **105,** 11383 (2001).
[22] J. K. Bjernemose, E. Frandsen, F. Jensen, and C. Th. Pedersen, *Tetrahedron*, **59,** 10255 (2003).
[23] D. Barillier, *Phosphorus and Sulfur*, **8,** 79 (1980).
[24] N. Lozac'h and J. Vialle, in *The Chemistry of organic sulfur compounds*, vol. 2, 257–285 (Pergamon Press, Oxford, 1966).
[25] R. Mayer, J. Fabian, H. Viola, and L. Jakisch, *Phosphorus and Sulfur*, **31,** 109 (1987).
[26] F. Bernardi, I. G. Csizmadia, A. Mangini, H. B. Schlegel, M. H. Whangbo, and S. Wolfe, *J. Am. Chem. Soc*., **97,** 2209 (1975).
[27] O. Zekri, P. Boudeville, P. Genay, B. Perly, P. Braquet, P. Jouenne, and J. L. Burgot, *Anal. Chem*., **68,** 2598 (1996).
[28] B. Legouin and J. L. Burgot, *Analyst (London)*, **121,** 43 (1996).
[29] J. J. P. Stewart, MOPAC, *A Semi-Empirical Molecular Orbital Program*, QCPE, Program n°455 (1983).
[30] M. Chollet-Krugler, A. Botrel, J. J. Charbit, J. Barbe, and J. L. Burgot, *Phosphorus, Sulfur, and Silicon*, **166,** 27 (2000).

[31] G aussian 03, Revision B.04, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, et al. Gaussian (Wallingford, CT, 2004).
[32] A. D. Becke, *J. Chem. Phys.*, **98,** 5648 (1993).
[33] A. E. Reed, L. A. Curtiss, and F. Weinhold, *Chem. Rev*., **88,** 899 (1988).
[34] R. F. C. Brown and I. D. Rae, *Aust. J. Chem*., **17,** 447 (1964).
[35] A. Etienne and G. Izoret, *Bull. Soc. Chim. Fr*., 2897 (1964).
[36] L. Legrand and N. Lozac'h, *Bull. Soc. Chim*., 79 (1955).
[37] F. Boberg and J. Knoop, *Liebigs Ann. Chem*., **708,** 148 (1967).
[38] D. Barillier, P. Rioult, and J. Vialle, *Bull. Soc. Chim. Fr*., 659 (1977).
[39] C. Cotrel, D. Farge, and G. Taurand, *Eur. Pat. Appl*., EP 82-401502 19820806 (1963).
[40] F. Boberg and A. Marei, *Liebigs Ann. Chem*., **666,** 88 (1963).
[41] R. Wagner and R. Mayer, *Zeitschrift für Chemie*., **3,** 26 (1963).