Synthesis of (4-Methylpiperazin-1-yl)carbodithioates and of their 1,3-Dithiolium Derivatives

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A series of new phenacyl carbodithioates containing 4-methylpiperazine have undergone cyclocondensation reactions under acidic conditions. The newly in situ formed 1,3-dithiolium salts have been directly converted to the corresponding mesoionic 2-[2-(4-methylpiperazin-1-yl)-1,3-dithiolium-2-yl]phenolates by treatment with aqueous sodium carbonate.

Keywords: N-methylpiperazine, carbodithioates, 1,3-dithiolium salt, mesoionic phenolates, FTIR, NMR

The great diversity, as well as heterocycles numerous biological activities, makes them indispensable to modern day medicine [1-5]. Within this class, heterocyclic compounds containing nitrogen or/and sulfur have maintained a high interest of researchers [6-14]. A variety of drugs designed to be used in antifilarial chemotherapy contain a thiocarbonylamide group as a common structural element. One group of these compounds is based on a 2-*t*-butylbenzothiazole ring in which the carbonylamide linkage is present as an isothiocyanate, dithiocarbamic acid ester or thioureea **1** derivative. The single representative of another series is an *N*-methylpiperazine adduct of amorcazine **2** [15]. Dithiocarbamic acid esters are important precursors for 1,3-dithiolium salts [16-18]. The 1,3-dithiolium ring contains a positively charged carbon atom which is prone to nucleophilic attack [19], giving 1,3-dithiolium cationss the potential to interact with biological molecules like proteins or DNA. 1,3-Dithiolium rings can also be converted to tetrathiafulvalenes, compounds that can be used in intramolecular charge-transfer complexes or as π-electron donors for metals [20, 21]. Although tetrathiafulvalenes are well-known electron donor systems, a variety of acceptor units have also been investigated. Thus, of special interest are systems where the donor moiety is linked through a *p*- or *s*-bonded bridge to the acceptor moiety [22-29]. Taking these facts into consideration, we decided to investigate the synthesis of several combined systems with a direct link between the *N*-methylpiperazine and the corresponding dithiocarbamic acid derivatives and 1,3-dithiolium systems (fig. 1).

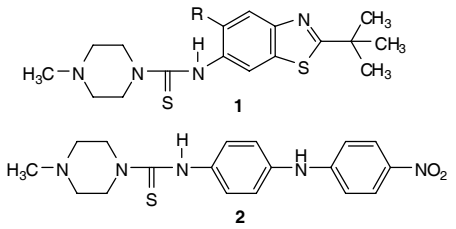


Fig. 1. Antifilarial drugs containing *N*-methylpiperazine

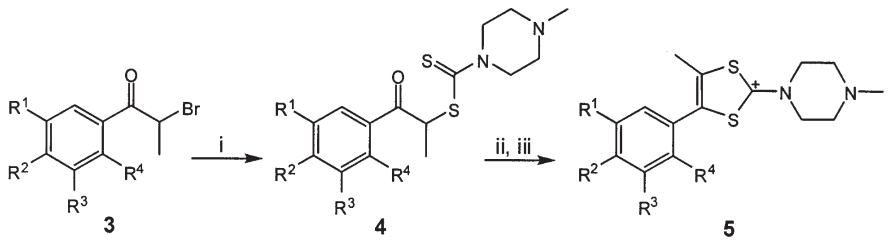
Experimental part

Equipment and methods

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS.

Synthesis

The synthetic pathway used to obtain carbodithioates **4a-c** and their corresponding mesoionic derivatives **5a-c** is described in scheme 1:



i: N-methylpiperazine-carbodithioate, acetone, rt 24h; ii: H_2SO_4/AcOH 1:1 (v/v), 80 °C; iii: Na_2CO_3 (aq).

3, 4	R^1	R^2	R^3	R^4
a	Br	H	Br	OH
b	I	H	I	OH
c	Br	OH	Br	H

5	R^1	R^2	R^3	R^4
a	Br	H	Br	O^-
b	I	H	I	O^-
c	Br	O^-	Br	H

Scheme 1. The synthesis of carbodithioates **4a-c** and of mesoionic phenolates **5a-c**

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1-(3,5-Dibromo-4-hydroxyphenyl)-1-oxapropan-2-yl-(N-methylpiperazine)-1-carbodithioate (**4c**);
General Procedure

To a solution of 2-bromo-1-(3,5-dibromo-4-hydroxyphenyl)propan-1-one **3c** (3.87g, 0.01mol) in acetone (100mL), 4-methylpiperazinium 4-methylpiperazine-1-carbodithioate (2.77g, 0.01mol) was added and the reaction mixture was stirred for 24h at room temperature. The reaction product was then precipitated with water (400mL), vacuum filtered and recrystalized from a mixture of ethanol/dioxane (160mL/ 40mL). Analytical and spectral data of carbodithioates **4** are presented in table 1.

2,6-Dibromo-4-[2-(4-methylpiperazin-1-yl)-5-methyl-1,3-dithiol-2-ylium-4-yl]phenolate **5c**;
General Procedure

Carbodithioate **4c** (0.482g, 0.001mol) was added to a mixture of sulfuric acid/acetic acid (1mL/1mL). The resulting solution is then heated at 80°C for 30 min, allowed to cool down to room temperature and then poured into water (100mL). A solution of sodium carbonate in water (6g in 100mL) was then slowly added and carbon dioxide begins to evolve. Upon complete addition of the sodium carbonate solution, the *p*H level reaches 8-9 and a yellow precipitate starts to form. The resulting solution was stirred for 24 h, after which the precipitate was vacuum filtered, washed thoroughly with water and left to dry. The analytical and spectral data for mesoionic derivatives **5a-c** are presented in table 2.

Results and discussions

The salts of dithiocarbamic acid are readily available from the reaction of secondary amine with carbon disulfide, under various experimental conditions [30, 31]. The reactions of these compounds with α-bromophenones consist in a straightforward synthesis for a large number of phenacyl carbodithioates [32-36]. These compounds are useful intermediates for the synthesis of 1,3-dithiolium salts and of their derivatives. Thus, we decided to react various substituted *ω*-bromo-propiophenones with 4-methylpiperazinium 4-methylpiperazine-1-carbodithioate in order to produce the corresponding carbodithioates. 2-Bromo-1-(3,5-dibromo-2-hydroxyphenyl)propan-1-one **3a** and 2-bromo-1-(3,5-diiodo-2-hydroxyphenyl)propan-1-one **3b** have been synthesized using a consequent bromination protocol, according with the reported procedures [37, 38]; 2-bromo-1-(3,5-dibromo-4-hydroxyphenyl)propan-1-one **3c** has been obtained from 4-hydroxypropiophenone following the literature procedure [39]. Through a S_N2 mechanism, carbodithioates **4a-c** have been obtained in 63-85% isolated yields. Their formation is supported by analytical and spectral data (table 1). Thus, the ^{1}H NMR spectra indicate a shift in value for the quartet belonging to the α-carbonyl proton from around 2.5ppm to ca. 5.7ppm. Also, a new singlet appears at 3.4ppm corresponding to the methyl protons, as well as three new signals between 2.5-4.5ppm, belonging to the rest of the protons in the 4-methylpiperazine moiety. ^{13}C NMR spectra indicate the appearance of three new aliphatic signals, belonging to the 4-methylpiperazine moiety: one at around 18.5ppm, belonging to the methyl carbon atom and two found between 50-55ppm, belonging to the piperazine carbon atoms. Also, a new signal appears at around 194.4ppm, attributed to the thiocarbonyl group.

One of the most important synthetic application of phenacyl dithiocarbamates consists in the synthesis of 2-dialkylamino-1,3-dithiolium salts. This involves the 1,3-dithiolium ring closure under acid catalysis [40-44]; special methods have been also reported for sensitive substrates [45]. Following one of the reported method, the cyclization of carbodithioates **4a-c** has been performed in a sulfuric acid/acetic acid mixture, at a temperature of 80°C. This leads to the closure of a 1,3-dithiolium ring, where the positive charge at the C(2) position is counterbalanced by a hydrogensulfate anion. When perchloric acid is added to the reaction mixture after the cyclization step [46], the

	M.p. (°C)	η (%)	IR-ATR (cm^{-1})	NMR (ppm)
4a	160-162	74	2798, 1646, 1428, 1249, 1143, 1030, 987, 779, 546	*^{1}H NMR* ($CDCl_3$) δ : 1.63 (3H, d, CH_3), 2.35 (3H, s, CH_3), 2.44-2.60 (4H, m, $2CH_2$), 3.85-4.05 (2H, m, CH_2), 4.22-4.46 (2H, m, CH_2), 5.78 (1H, q, CH), 7.88 (1H, d, ^4J=2.2 Hz, CHar), 8.12 (1H, d, H-4, J_{H4-H6}=2.2 Hz), 12.63 (1H, bs, OH). *^{13}C NMR* ($CDCl_3$) δ : 16.7, 45.5, 50.8, 54.3, 110.7, 113.3, 119.6, 131.8, 141.6, 158.4, 193.4, 202.7
4b	180-182	63	2802, 1636, 1420, 1248, 1146, 1030, 995, 777, 670	*^{1}H NMR* (DMSO-*d6*) δ : 1.51 (3H, d, CH_3), 2.65 (3H, s, CH_3), 2.98-3.13 (4H, m, $2CH_2$), 3.93-4.56 (4H, m, $2CH_2$), 5.77 (1H, q, CH), 8.33 (1H, d, ^4J=1.8 Hz, CHar), 8.39 (1H, d, ^4J=1.8 Hz, CHar). *^{13}C NMR* (DMSO-*d6*) δ : 16.8, 43.3, 51.0, 52.8, 83.1, 90.1, 120.8, 138.8, 152.3, 160.2, 194.4, 202.5.
4c	152-154	85	3384, 1654, 1561, 1421, 1327, 1279, 1174, 973, 638	*^{1}H NMR* ($CDCl_3$) δ : 1.60 (3H, d, CH_3), 2.39 (3H, s, CH_3), 2.53-2.65 (4H, m, $2CH_2$), 3.91-4.12 (2H, m, CH_2), 4.26-4.58 (2H, m, CH_2), 5.73 (1H, q, CH), 8.24 (2H, m, H-2 + H-6). *^{13}C NMR* ($CDCl_3$) δ : 16.9, 45.4, 51.0, 54.2, 110.4, 129.8, 133.1, 153.9, 194.2, 194.4.

Table 1
ANALYTICAL AND SPECTRAL DATA OF CARBODITHIOATES **4a-c**

	M.p. (°C)	η (%)	IR-ATR (cm^{-1})	NMR (ppm)
5a	108-110 (dec)	44	1563, 1496, 1452, 1256, 1153, 987, 869, 690	*^{1}H NMR* ($CDCl_3$) δ : 2.39 (3H, s, CH_3), 2.55 (3H, s, CH_3), 2.60-2.68 (4H, m, $2CH_2$), 3.60-3.99 (4H, m, $2CH_2$), 7.33 (1H, d, ^4J =2.5 Hz, CHar), 7.49 (1H, d, ^4J=2.5 Hz, CHar). *^{13}C NMR* ($CDCl_3$) δ : 17.3, 45.6, 53.2, 99.4, 115.9, 120.1, 123.1, 128.4, 134.8, 135.2, 163.1, 187.3.
5b	148-150 (dec)	53	1550, 1428, 1255, 1143, 990, 863, 638	*^{1}H NMR* ($CDCl_3$) δ : 2.40 (3H, s, CH_3), 2.57 (3H, s, CH_3), 2.60-2.69 (4H, m, $2CH_2$), 3.62-3.96 (4H, m, $2CH_2$), 7.50 (1H, d, ^4J =2.0 Hz, CHar), 7.86 (1H, d, ^4J=2.0 Hz, CHar). *^{13}C NMR* ($CDCl_3$) δ : 17.3, 45.6, 53.2, 94.7, 119.1, 123.1, 135.0, 135.3, 146.2, 165.3, 187.1.
5c	165-167 (dec)	90	1570, 1497, 1264, 1146, 985, 865, 737, 626	*^{1}H NMR* (DMSO-*d6*) δ : 2.27 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.57-2.63 (4H, m, $2CH_2$), 3.74-3.84 (4H, m, $2CH_2$), 7.29 (2H, m, H-2 + H-6). *^{13}C NMR* (DMSO-*d6*) δ : 15.0, 45.3, 52.9, 53.0, 54.1, 106.7, 115.4, 123.4, 131.8, 132.6, 163.7, 183.7.

Table 2
ANALYTICAL AND SPECTRAL DATA OF MESOIONIC DERIVATIVES **5a-c**

hydrogensulfate anion is replaced by a perchlorate anion. Attempts to isolate either of the two salts by precipitating them with water have been unsuccessful. This is probably due to the 4-methylpiperazine moiety, which contains a tertiary sp^3 nitrogen atom, that can also react with acids, forming a water-soluble ammonium salt. We therefore decided to convert the soluble 1,3-dithiolium salts into their corresponding mesoionic derivatives in order to isolate them. This was achieved by raising the *p*H of the reaction mixture to around 8-9, using sodium carbonate to first neutralize the acids used in the cyclization step and then to provide the necessary base to deprotonate the phenolic group of the 1,3-dithiolium salts. This lead to the formation of a yellow precipitate which could be filtered, dried and characterized from a spectral and analytical point of view. Prompted by the successfully isolation of mesoionic phenolates **5** we decided to investigate the *one-pot* synthesis of phenolates **5** from dithiocarbamates **4**. Thus, by decreasing the amount of acetic acid to the volume of H_2SO_4 and heating the mixture for 30 min at 80°C, we obtained a homogeneous solution that contains the 1,3-dithiolium cation; treatment of this solution with a saturated aqueous Na_2CO_3 directly provided compounds **5**. The closure of the 1,3-dithiolium ring is supported by analytical and spectral data (table 2). The IR spectra show the disappearance of the carbonyl band at around 1650-1630cm^{-1}. The ^{1}H NMR spectra show the disappearance of the quartet at around 5.70-5.80ppm belonging to the α-carbonyl proton. The signal corresponding to the β-carbonyl protons is shifted from around 1.50-1.60ppm to about 2.30-2.40ppm and its multiplicity changes from doublet, to singlet. The ^{13}C NMR spectra show the disappearance of the carbonyl and thiocarbonyl signals from 194.0-202.0ppm and the appearance of a new signal at around 183.0-187.0ppm, corresponding to the positively charged C(2) atom of the 1,3-dithiolium ring. As mentioned before, phenolates **5** have been isolated as yellow products that present the features of mesoionic compounds [47]. The colour of this class of compounds has been reported to be the result of an intramolecular charge transfer between electron-rich and electron-deficient regions of the molecules and not to the contribution of a quinoid structures in the ground states [16, 17]. The presence of a hydroxy substituent in the *ortho*- or *para*-positions of the aryl ring induces an extended delocalization of the negative charge up to the C(5) atom of the dithiolium ring.

Conclusions

The synthesis of some new 4-methylpiperazine phenacyl carbodithioates has been achieved. These were converted into 1,3-dithiolium salts and then into the corresponding mesoionic compounds, in order to isolate them. A *one-pot* synthetic procedure for the synthesis of the mesoionic phenolates has been also developed. All new compounds were characterized by NMR and IR spectroscopy.

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