

# SYNTHESIS OF 1,3-DITHIOLIUM SALTS CONTAINING *N*-METHYLPIPERAZINE

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**Abstract:** The synthesis of 4-aryl-2-(*N*-methylpiperazin-1-yl)-1,3-dithiol-2-ylum perchlorates has been accomplished by the acid catalyzed heterocyclocondensation of the corresponding substituted phenacyl *N*-methylpiperazin-1-carbodithioates. The later have been obtained from the reaction of various substituted *o*-bromoacetophenones with a salt of *N*-methylpiperazine carbodithioic acid. The structures of new synthesized *N*-methylpiperazine derivatives have been proved by analytical and spectral data.

**Keywords:** Carbodithioates; 1,3-Dithiolium salts; *N*-Methylpiperazine

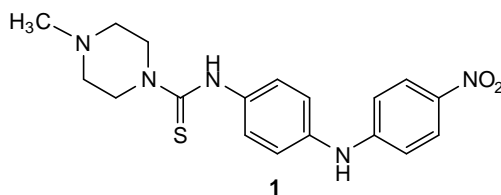
## Introduction

An important structural features of heterocyclic compounds, which continues to be exploited by the drug industry, lies in their ability to manifest substitutes around a core scaffold in defined three dimensional representations.<sup>1,2</sup> Heterocyclic compounds are known to exhibit a wide variety of application in therapeutics, such as antibacterial, anti-inflammatory, antifungal, anticancer and lipid peroxidation inhibitor, and antitubercular.<sup>3-7</sup> Between them, heterocyclic compounds containing nitrogen or/and sulfur have maintained a high interest of researchers.<sup>8-11</sup> The piperazine nucleus is an important heterocycle, exhibiting remarkable pharmacological activities.<sup>12</sup> A slight change in the substitution pattern on

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the piperazine moiety causes significant difference in pharmacological activities. For example, piperazine and substituted piperazines are important precursors for the synthesis of quinolone-type antibacterial compounds. *N*-methylpiperazine is used in the synthesis of ofloxacin, amifloxacin, fleroxacin and difloxacin antibacterial drugs.<sup>13</sup> A variety of recently developed drugs, designed to be used in antifilarial chemotherapy, contain a thiocarbonylamide group as a common structural element.<sup>14</sup> 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 thiourea derivative. The single representative of another series is an *N*-methylpiperazine adduct of amoscanate. This compound (amocarzine) has been clinical tested on patients suffering from onchocercosis (**1**, Figure 1).



**Figure 1.** Antifilarial drug amocarzine.

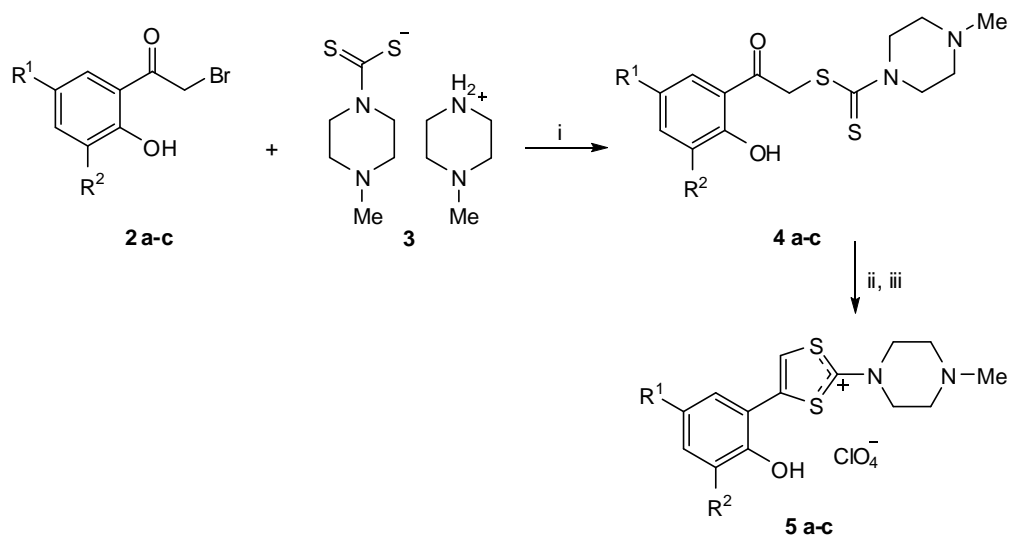
1,3-Dithiolium systems are known for their reactivity at the C(2)-position towards nucleophiles.<sup>15</sup> Besides the synthetic interest for these reactions, it should be noted that the nucleophilic addition of the purinic bases of DNA to the model compounds was postulated as the Maxam-Gilbert mechanism for the biological activity of electrophilic substrates.<sup>16</sup> Moreover, 1,3-dithiolium salts are important precursors of tetrathiafulvalenes (TTF), which in turn are notable  $\pi$ -electron donors in organic metals.<sup>17</sup> Although tetrathiafulvalenes are well-known electron donor systems, a variety of acceptor units has been investigated, special attention being devoted to the nature of cationic systems.<sup>18,19</sup> Accounting

the above 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.

## Results and Discussion

The stable derivatives of dithiocarbamic acid are readily available from the reaction of secondary amine with carbon disulfide, under various experimental conditions.<sup>20</sup> The reactions of these compounds with  $\omega$ -bromophenones consist in a direct method for the synthesis of phenacyl carbodithioates.<sup>21-23</sup> These compounds are useful intermediates for the synthesis of 1,3-dithiolium salts and of their derivatives.<sup>24</sup> Thus, we are reporting here the reaction of various substituted  $\omega$ -bromo-acetophenones **2** with *N*-methylpiperazinium *N*-methylpiperazin-1-carbodithioate (**3**)<sup>25</sup> in order to produce the corresponding carbodithioates **4** (Scheme 1). The synthesis of 2-bromo-1-(3,5-dibromo-2-hydroxyphenyl)ethan-1-one **2a**, 2-bromo-1-(3-bromo-5-methyl-2-hydroxyphenyl)ethan-1-one **2b** and 2-bromo-1-(3,5-diiodo-2-hydroxyphenyl)ethan-1-one **2c** has been accomplished according with the previous reported procedures.<sup>26</sup> Following a  $S_N2$  mechanism, carbodithioates **4a-c** have been obtained in 71-83% isolated yields (Scheme 1). The structure of dithiocarbamates **4** has been proved by analytical and spectral data. Thus, the <sup>1</sup>H NMR spectra indicate a shift in value for the  $\alpha$ -carbonyl proton to ca. 4.90 ppm. Also, a new singlet appears at 2.37 ppm corresponding to the methyl protons, as well as three new signals between 2.38-4.36 ppm, belonging to the rest of the protons in the 4-methylpiperazine moiety. <sup>13</sup>C NMR spectra indicate the appearance of three new aliphatic signals, belonging to the 4-methylpiperazine moiety: one

around 45 ppm, belonging to the methyl carbon atom and two found between 50-55 ppm, belonging to the piperazine carbon atoms. Also, a new signal appears around 198 ppm, attributed to the thiocarbonyl group.



<b>2, 4, 5</b>	<b>R<sup>1</sup></b>	<b>R<sup>2</sup></b>
<b>a</b>	Br	Br
<b>b</b>	CH <sub>3</sub>	Br
<b>c</b>	I	I

**Scheme 1.** Synthesis of 1,3-dithiolium perchlorates **5 a-c**.

i. acetone, reflux; ii. H<sub>2</sub>SO<sub>4</sub>/AcOH 1:3 (v/v), 80 °C; iii. 70% HClO<sub>4</sub>

Using a concentrated sulfuric acid-glacial acetic acid (1:3 v/v) mixture the cyclization of dithiocarbamates **4a-c** takes place under mild reaction conditions (Scheme 1). After 10 min at 80 °C the homogeneous reaction mixture was cooled to room temperature, 70% perchloric acid was added and then poured into water. Filtration and recrystallization of the precipitate gives the corresponding perchlorates **5a-c** as colorless crystals, in

good yields (71-84%). The cyclization of phenacyl carbodithioates **4** to the corresponding 1,3-dithiolium perchlorates **5** was accompanied by significant changes in the spectral features. The IR spectra revealed the disappearance of the carbonyl absorption band (ca. 1640 cm<sup>-1</sup>) and the appearance of a new broad band centered at 1076 cm<sup>-1</sup> corresponding to the perchlorate anion. Heterocyclization of dithiocarbamates **4** is also supported by the NMR spectra. Thus, the <sup>1</sup>H NMR spectra indicated that the heterocyclocondensation has occurred through the disappearance of the signal for aliphatic hydrogens (4.90 ppm). <sup>13</sup>C NMR spectra also support the synthesis of 1,3-dithiolium salts **5** by the disappearance of the carbonyl and thiocarbonyl carbon atoms present in the dithiocarbamates spectra and the appearance of a new signal at a very low field (ca. 191 ppm) which correspond to the electron deficient C(2) atom.

## Experimental

**General remarks:** Melting points were obtained on a KSPI melting-point meter and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on a Thermo Scientific ISQ LT instrument.

### **1-(3,5-Dibromo-2-hydroxyphenyl)-1-oxoethan-2-yl-(*N*-methylpiperazin)-1-carbodithioate (4a); General Procedure:**

To a solution of 2-bromo-1-(3,5-dibromo-4-hydroxyphenyl)ethan-1-one **2a** (0.746 g, 2 mmol) in acetone (20 mL), a solution of 4-methylpiperazin-1-carbodithioate (0.552 g, 2 mmol) in acetone (25 mL) was added and the reaction mixture was refluxed for 60 minutes. After

cooling to room temperature, the reaction product was precipitated with water (200 mL), vacuum filtered and recrystallized from a mixture of ethanol/dioxane (60 mL/20 mL) yielding 0.660 g (71%) of pink crystals. M.p. = 179–180 °C. IR (ATR,  $\text{cm}^{-1}$ ): 2935, 2793, 1640, 1433, 1246, 1140, 1030, 990, 789, 695.  $^1\text{H}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.37 (3H, s,  $\text{CH}_3$ ), 2.56 (4H, t,  $J = 4.5$  Hz,  $2\text{CH}_2$ ), 4.05 (2H, s,  $\text{CH}_2$ ), 4.35 (2H, d,  $J = 0.5$  Hz,  $\text{CH}_2$ ), 4.88 (2H, s,  $\text{CH}_2$ ), 7.91 (H, d,  $J = 2.5$  Hz,  $\text{CH}_{\text{ar}}$ ), 8.11 (H, d,  $J = 2.5$  Hz,  $\text{CH}_{\text{ar}}$ ), 12.45 (H, bs, OH).  $^{13}\text{C}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 43.6, 45.6, 50.3, 52.0, 54.3, 110.8, 113.4, 120.7, 131.7, 141.8, 158.0, 194.1, 198.0. MS (EI):  $m/z = 466$  ( $\text{M}^+$  for  $\text{C}_{14}\text{H}_{16}^{79}\text{Br}_2\text{N}_2\text{O}_2\text{S}_2$ ).

**1-(3-Bromo-5-methyl-2-hydroxyphenyl)-1-oxoethan-2-yl-(*N*-methylpiperazin)-1-carbodithioate (4b)**

Colorless crystals, 0.306 g, 76 %. M.p. = 178–179 °C. IR (ATR,  $\text{cm}^{-1}$ ): 2907, 2794, 1643, 1434, 1226, 1140, 1033, 992, 771, 695.  $^1\text{H}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.37 (6H, s,  $2\text{CH}_3$ ), 2.56 (4H, s,  $2\text{CH}_2$ ), 4.06 (2H, t,  $J = 1.0$  Hz,  $\text{CH}_2$ ), 4.36 (2H, s,  $\text{CH}_2$ ), 4.95 (2H, s,  $\text{CH}_2$ ), 7.64 (H, d,  $J = 2.0$  Hz  $\text{CH}_{\text{ar}}$ ), 7.77 (H, d,  $J = 0.5$  Hz,  $\text{CH}_{\text{ar}}$ ), 12.32 (H, bs, OH).  $^{13}\text{C}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 20.4, 44.0, 45.6, 50.1, 52.0, 54.3, 112.0, 119.5, 129.3, 140.8, 156.7, 194.6, 198.5. MS (EI):  $m/z = 402$  ( $\text{M}^+$  for  $\text{C}_{15}\text{H}_{19}^{79}\text{Br N}_2\text{O}_2\text{S}_2$ ).

**1-(3,5-Diiodo-2-hydroxyphenyl)-1-oxoethan-2-yl-(*N*-methylpiperazin)-1-carbodithioate (4c)**

Colorless crystals, 0.468 g, 83 %. M.p. = 183–184 °C. IR (ATR,  $\text{cm}^{-1}$ ): 2797, 1637, 1423, 1226, 1142, 989, 776, 684, 534.  $^1\text{H}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 2.38 (3H, s,  $\text{CH}_3$ ), 2.57 (4H, s,  $2\text{CH}_2$ ), 4.05 (2H, t,  $J = 0.5$  Hz,  $\text{CH}_2$ ), 4.36 (2H, s,  $\text{CH}_2$ ), 4.88 (2H, s,  $\text{CH}_2$ ), 8.27 (2H, dd,  $J = 2.0$  Hz,  $\text{CH}_{\text{ar}}$ ), 12.68 (H, bs, OH).  $^{13}\text{C}$  RMN ( $\text{CDCl}_3$ ),  $\delta$  (ppm): 43.4, 45.6, 50.2, 52.0, 54.3,

54.4, 80.7, 88.4, 120.7, 138.6, 153.0, 160.7, 194.2, 198.0. MS (EI):  $m/z = 562$  ( $M^+$  for  $C_{14}H_{16}I_2N_2O_2S_2$ ).

**4-(3,5-Dibromo-2-hydroxyphenyl)-2-(*N*-methylpiperazin-1-yl)-1,3-dithiol-2-ylum perchlorate (5a); General Procedure:**

To a mixture of 1 mL concentrated sulfuric acid and 3 mL glacial acetic acid 0.141 g of 1-(3,5-dibromo-2-hydroxyphenyl)-1-oxaethan-2-yl-(*N*-methylpiperazin)-1-carbodithioate (**4a**, 0.3 mmol) was added in small portions. The reaction mixture was heated at 80 °C for 10 min and then cooled to room temperature. To the homogenous solution 0.5 mL of 70%  $HClO_4$  was added and then the reaction mixture was diluted with 100 mL of water. The obtained precipitate was filtered and dried off. Recrystallization from 15 mL of ethanol gave colorless crystals; yield (40%). M.p. = 246–247 °C dec. IR (ATR,  $cm^{-1}$ ): 3072, 1556, 1520, 1452, 1265, 1077, 964, 621.  $^1H$  RMN ( $DMSO-d_6$ )  $\delta$  (ppm): 2.90 (3H, s,  $CH_3$ ), 3.39 – 3.46 (4H, m,  $J = 7$  Hz,  $2CH_2$ ), 4.12 (4H, d,  $J = 0.5$  Hz,  $2CH_2$ ), 7.90 (H, d,  $J = 2.5$  Hz,  $CH_{ar}$ ), 7.93 (H, d,  $J = 2.5$  Hz,  $CH_{ar}$ ), 8.20 ppm (H, s, CH).  $^{13}C$  RMN ( $DMSO-d_6$ )  $\delta$  (ppm): 42.7, 51.0, 56.5, 63.2, 114.7, 122.7, 130.7, 133.8, 136.8, 150.8, 190.9. MS (EI):  $m/z = 449$  ( $M^+ - ClO_4$  for  $C_{14}H_{15}^{79}Br_2N_2OS_2$ ).

**4-(3-Bromo-5-methyl-2-hydroxyphenyl)-2-(*N*-methylpiperazin-1-yl)-1,3-dithiol-2-ylum perchlorate (5b)**

Colorless crystals, 0.074 g, 51 %. M.p. = 285–286 °C dec. IR (ATR,  $cm^{-1}$ ): 3452, 3111, 1562, 1480, 1275, 1075, 963, 628.  $^1H$  RMN ( $DMSO-d_6$ )  $\delta$  (ppm): 2.28 (3H, s,  $CH_3$ ), 2.51 (2H, d,  $J = 1.5$  Hz,  $2CH_2$ ), 2.89 (3H, s,  $CH_3$ ), 4.12 (4H, m,  $J = 1.5$  Hz,  $2CH_2$ ), 7.49 (H, d,  $J = 1.5$  Hz,  $CH_{ar}$ ), 7.56

(H, s, CH<sub>ar</sub>), 8.09 ppm (H, s, CH). <sup>13</sup>C RMN (DMSO-*d*<sub>6</sub>), δ (ppm): 20.0, 42.7, 51.0, 51.3, 51.5, 51.8, 113.4, 120.9, 121.3, 128.8, 132.4, 135.1, 135.7, 148.3, 190.9. MS (EI): *m/z* = 385 (M<sup>+</sup>-ClO<sub>4</sub> for C<sub>15</sub>H<sub>18</sub><sup>79</sup>BrN<sub>2</sub>OS<sub>2</sub>).

**4-(3,5-Diiodo-2-hydroxyphenyl)-2-(*N*-methylpiperazin-1-yl)-1,3-dithiol-2-ylum perchlorate (5c)**

Colorless crystals, 0.195 g, 66 %. M.p. = 234–235 °C dec. IR (ATR, cm<sup>-1</sup>): 3059, 1512, 1436, 1269, 1076, 967, 530. <sup>1</sup>H RMN (DMSO-*d*<sub>6</sub>) δ (ppm): 2.81 (3H, s, CH<sub>3</sub>), 3.40 (4H, s, 2CH<sub>2</sub>), 4.08 (4H, d, *J* = 0.5 Hz, 2CH<sub>2</sub>), 7.92 (H, d, *J* = 1.5 Hz, CH<sub>ar</sub>), 8.02 (H, d, *J* = 2.0 Hz, CH<sub>ar</sub>), 8.06 (H, s, CH). <sup>13</sup>C RMN (DMSO-*d*<sub>6</sub>), δ (ppm): 43.0, 51.3, 51.6, 93.7, 121.7, 135.7, 147.3, 190.8. MS (EI): *m/z* = 545 (M<sup>+</sup>-ClO<sub>4</sub> for C<sub>14</sub>H<sub>15</sub>I<sub>2</sub>N<sub>2</sub>OS<sub>2</sub>).

### Conclusions

The synthesis of some new 4-methylpiperazine phenacyl carbodithioates has been achieved. These were converted through an acid catalyzed heterocyclocondensation into the corresponding 4-aryl-2-(*N*-methylpiperazin-1-yl)-1,3-dithiol-2-ylum cations. The combination between *N*-methylpiperazine moiety and 1,3-dithiolium ring might provide promising biological activities. All new compounds were characterized by IR and NMR spectrometry.

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