

Synthesis of 4-(2-hydroxyphenyl)-2-dialkylamino-1,3-dithiolium Salts and Corresponding Mesoionic Derivatives

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The synthesis of various 1,3-dithiolium salts has been accomplished through a combined procedure of acid catalyzed cyclocondensation of various substituted 2-(2-hydroxyphenyl)-1-oxoethylthiocarbamates and the interconversion of mesoionic 2-(1,3-dithiol-2-ylum)phenolates with the corresponding salts. A new class of 1,3-dithiolium chlorides is reported as compounds with a good solubility in water. UV-Vis properties of these compounds are also presented.

Keywords: dithiocarbamates, 1,3-dithiolium salts, mesoionic compounds, internal charge transfer

Heterocyclic compounds present a great importance, from both a biological and an industrial point of view. The versatility presented by a core scaffold, which can be variously substituted within a well defined three dimensional space, represents one of their most important features [1, 2]. Heterocycles are being widely used by the drug industry for their antitubercular, anti-HIV, antiinflammatory, analgesic, antimalarial, muscle relaxant, anticonvulsant, anticancer and lipid peroxidation inhibitor, antidepressant, hypnotic, antibacterial, antifungal, antimycobacterial, trypanocidal, herbicidal activities [3-9]. Research-wise, a great deal of attention is focused on nitrogen and sulfur-containing heterocycles [10-17]. The way the body absorbs any drug is directly influenced by the method used to administer it. With the exception of intravenous administering, drugs usually have to pass at least one body membrane before reaching the circulatory system. The absorption rates are affected by various factors [18]. Water soluble drugs are more easily absorbed than lipid soluble ones. Therefore, finding and synthesizing water soluble, biologically active heterocycles is of general interest. Amongst the great variety of heterocycles, 1,3-dithiolium have also been found to present biological activity, in this particular case, against gram-positive and gram-negative bacteria [19].

In view of these facts, we decided to investigate the synthesis of a series of 4-(2-hydroxyphenyl)-2-dialkylamino-1,3-dithiolium salts as potential water soluble compounds.

Experimental part

Analysis methods

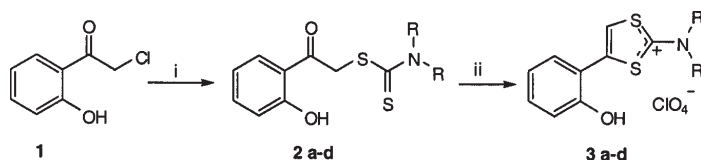
Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Elemental analyses (C, H, N, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement ($\pm 0.3\%$) with the calculated values.

Synthesis

w-Chloro-2-hydroxyacetophenone **1** [20] has been treated with various salts of dialkylaminodithiocarbamic acids in order to provide aminocarbodithioates **2a-d**, in good isolated yields (fig. 1).

1-(2-Hydroxyphenyl)-1-oxaethan-2-yl-*N,N*-dimethyldithiocarbamate (**2a**);

To a 2 g solution of 2-chloro-1-(2-hydroxyphenyl)ethan-1-one (**1**, 0.0117 mol) in 35 mL acetone, a solution of 1.68



i. $R_2NC(S)S^-$, acetone, reflux; ii. $H_2SO_4/AcOH$ 1:3 (v/v), 80 °C, 70% $HClO_4$

| 2, 3, 4, 5 | R | R |
|------------|--|---------------------------------|
| a | CH ₃ | CH ₃ |
| b | CH ₂ CH ₃ | CH ₂ CH ₃ |
| c | (CH ₂) ₅ | |
| d | (CH ₂) ₂ -O-(CH ₂) ₂ | |

Fig. 1. Synthesis of dithiocarbamates **2** and 1,3-dithiolium perchlorates **3**

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| | M.p., °C | η , % | IR-ATR, cm ⁻¹ | NMR (CDCl ₃) |
|-----------|-----------|------------|--|--|
| 2a | 119 - 120 | 86 | 2946, 1638, 1450, 1274, 1101, 988, 749, 621 | ¹ H NMR δ : 3.42 (3H, s, CH ₃); 3.51 (3H, s, CH ₃); 4.89 (2H, s, CH ₂); 6.90 (1H, m, H-5); 6.97 (1H, d, H-3); 7.47 (1H, m, H-4); 7.94 (1H, m, H-6); 11.80 (1H, s, OH). ¹³ C NMR δ : 41.7, 43.4, 46.0, 118.8, 120.4, 121.6, 131.4, 136.5, 162.3, 194.1, 198.5 |
| 2b | 78 - 79 | 86 | 2963, 1641, 1462, 1252, 1201, 1169, 975, 855, 748, 674, 623 | ¹ H NMR δ : 1.28 (6H, t, 2CH ₃); 3.89 (2H, q, CH ₂); 3.96 (2H, q, CH ₂); 4.94 (2H, s, CH ₂); 6.90 (1H, m, H-5); 6.96 (1H, d, H-3); 7.50 (1H, m, H-4); 7.95 (1H, d, H-6); 11.82 (1H, s, OH). ¹³ C NMR δ : 11.2, 12.5, 43.5, 47.0, 49.2, 118.7, 120.5, 121.7, 131.5, 136.4, 162.4, 194.3, 198.7 |
| 2d | 171 - 172 | 86 | 2938, 1640, 1482, 1432, 1224, 1192, 1107, 1017, 873, 745, 716, 651 | ¹ H NMR δ : 3.76 (4H, m, CH ₂ -O-CH ₂); 4.14 (4H, m, CH ₂ -N-CH ₂); 4.95 (2H, s, CH ₂); 6.90 (1H, m, H-5); 6.97 (1H, d, H-3); 7.50 (1H, m, H-4); 7.95 (1H, m, H-6); 11.75 (1H, s, OH). ¹³ C NMR δ : 43.6, 50.7, 51.6, 65.7, 118.9, 120.3, 121.6, 131.1, 136.8, 162.1, 194.5, 198.8 |

Table 1
ANALYTICAL AND SPECTRAL DATA
OF DITHIOCARBAMATES **2**

| | M.p., °C | η , % | IR-ATR, cm ⁻¹ | NMR (DMSO- <i>d</i> ₆) |
|-----------|----------|------------|--|--|
| 3a | 171-172 | 85 | 3185, 1578, 1453, 1256, 1064, 759, 621 | ¹ H NMR δ : 3.53 (3H, s, CH ₃); 3.57 (3H, s, CH ₃); 6.89 (2H, m, H-3 + H-5); 7.27 (1H, m, H-4); 7.56 (1H, m, H-6); 7.97 (1H, s, H-5); 10.90 (1H, s, OH). ¹³ C NMR δ : 47.0, 47.2, 117.9, 119.1, 122.7, 124.5, 128.7, 131.0, 133.3, 154.5, 188.8 |
| 3b | 167-168 | 84 | 3171, 1563, 1447, 1068, 766, 622 | ¹ H NMR δ : 1.42 (6H, t, 2CH ₃); 3.87 (2H, q, CH ₂); 3.93 (2H, q, CH ₂); 6.87 (2H, m, H-3 + H-5); 7.17 (1H, m, H-4'); 7.46 (1H, m, H-6); 7.88 (1H, s, H-5); 10.87 (1H, s, OH). ¹³ C NMR δ : 10.5, 10.9, 51.7, 52.5, 117.9, 119.0, 122.5, 124.8, 128.9, 131.1, 133.6, 154.4, 188.4 |
| 3c | 124-125 | 87 | 3174, 1553, 1441, 1251, 1069, 1008, 769, 620 | ¹ H NMR δ : 1.82 (6H, m, 3CH ₃); 3.85 (4H, m, 2CH ₂ -N); 6.85 (2H, m, H-3 + H-5); 7.02 (1H, m, H-4); 7.75 (1H, d, H-6); 7.72 (1H, s, H-5); 10.62 (1H, s, OH). ¹³ C NMR δ : 21.7, 24.7, 25.1, 56.3, 57.9, 117.8, 118.6, 122.2, 124.8, 128.5, 130.3, 133.3, 154.5, 188.7 |
| 3d | 120-121 | 71 | 3169, 1555, 1453, 1253, 1070, 1022, 770, 619 | ¹ H NMR δ : 3.86 (8H, m, 4CH ₂); 6.85 (2H, m, H-3 + H-5); 6.92 (1H, m, H-4); 7.65 (1H, d, H-6); 7.77 (1H, s, H-5); 10.60 (1H, s, OH). ¹³ C NMR δ : 53.8, 54.5, 64.5, 118.2, 118.6, 122.9, 125.3, 128.3, 130.6, 133.7, 154.4, 188.5 |

Table 2
ANALYTICAL AND SPECTRAL DATA
OF 1,3-DITHIOLIUM
PERCHLORATES **3**

g sodium *N,N*-dimethyldithiocarbamate (0.0117 mol) in 20 mL acetone-water (1:1 v/v) was added. The reaction mixture was heated under reflux for 10 min, cooled to room temperature and then poured in water. The precipitate was filtered, washed with water and dried off. Recrystallization from 50 mL EtOH gave colorless crystals; yield 2.6 g (86%). Analytical and spectral data of carbodithioates **2** are presented in table 1.

2-(N,N-Dimethylamino)-4-(2-hydroxyphenyl)-1,3-dithiol-2-ylum perchlorate (3a);

To a mixture of 2 mL concentrated sulfuric acid and 6 mL glacial acetic acid 2 g of 1-(2-hydroxyphenyl)-1-oxaethan-2-yl-*N,N*-dimethyldithiocarbamate (**2a**, 7.8 mmol) was added in small portions. The reaction mixture was heated at 80°C for 10 min, cooled and 1 mL of perchloric acid was added. The precipitate obtained after water addition (150 mL) was filtered and dried off. Recrystallization from 50 mL of EtOH gave colorless crystals; yield 2.25 g (85%). Analytical and spectral data of 1,3-dithiolium perchlorates **3** are presented in table 2.

2-[2-(N,N-Dimethyl)-1,3-dithiol-2-ylum-4-yl]phenolate (4a);

To 20 mL saturated sodium hydrogencarbonate solution 1 g of perchlorate **3a** (2.96 mmol) was added. Carbon dioxide evolved and the reaction mixture became yellow. After 2 h under vigorous stirring at room temperature, the yellow solid was filtered off, washed with water, and dried. Recrystallization from DMF gave yellow crystals; yield 0.7 g (100%). Analytical and spectral data of 1,3-dithiolium phenolates **4** are presented in table 3.

2-(N,N-Dimethylamino)-4-(2-hydroxyphenyl)-1,3-dithiol-2-ylum chloride (5a);

To 1 g suspension of mesoionic phenolate **4a** (4.2 mmol) in 10 mL acetone a solution of 1.77 mL HCl (37%, 21 mmol)

was added. The reaction mixture was vigorously stirred at rt for 2 h, then filtered and washed with acetone. Recrystallization from ethanol gave colorless crystals; yield 1.13 g (98%). Analytical and spectral data of 1,3-dithiolium chlorides **5** are presented in table 4.

Results and discussions

The synthesis of the desired 1,3-dithiolium salts involves two major steps: the construction of the 1,3-dithiolium ring, followed by the interconversion reactions between related species of the 1,3-dithiolium derivatives. The first step can be accomplished following two consecutive reactions as described in figure 1. ω -Chloro-2-hydroxyacetophenone **1** [20] has been treated with various salts of dialkylaminodithiocarbamic acids in order to provide amino-carbodithioates **2a**, **b**, **d**, in good isolated yields (fig. 1). Dithiocarbamate **2c** has been prepared following a reported experimental procedure [21]. The structure of dithiocarbamates **2a**, **b**, **d** has been proved by analytical and spectral data (table 1).

Phenacyl carbodithioates are important precursors of various substituted 1,3-dithiol-2-ylum cations, by heterocyclocondensation under acidic conditions. Using a concentrated sulfuric acid-glacial acetic acid (1:3 v/v) mixture [22, 23] the cyclization of dithiocarbamates **2a-d** takes place under mild reaction conditions. After 10 min at 80 °C the homogeneous reaction mixture was cooled to room temperature, 70% perchloric acid was added and the reaction mixture was poured into water. Filtration and recrystallization of the precipitate gives perchlorates **3a-d** as colorless crystals, in good to excellent yields (table 2). The cyclization of dithiocarbamates **2** is confirmed by important spectral changes. The IR spectra revealed the disappearance of the absorption band corresponding to the carbonyl group (ca. 1640 cm⁻¹) and the presence of a new, strong and broad absorption band at ca. 1070 cm⁻¹, corresponding to the perchlorate anion.

| | M.p., °C | η , % | IR-ATR, cm ⁻¹ | NMR (DMSO- <i>d</i> ₆) |
|-----------|-----------------|------------|---|--|
| 4a | 148-149 dec. | 100 | 1568, 1451, 1249, 760, 621 | ¹ H NMR δ : 3.50 (3H, s, CH ₃); 3.54 (3H, s, CH ₃); 6.82 (2H, m, H-3 + H-5); 7.23 (1H, m, H-4); 7.51 (1H, m, H-6); 7.95 (1H, s, H-5). ¹³ C NMR δ : 46.9, 47.1, 118.0, 119.2, 122.6, 124.9, 128.7, 130.9, 133.4, 154.9, 188.3 |
| 4b | 223-224 dec. | 100 | 1558, 1446, 1358, 1188, 933, 759, 620 | ¹ H NMR δ : 1.36 (6H, t, 2CH ₃); 3.82 (2H, q, CH ₂); 3.87 (2H, q, CH ₂); 6.71 (2H, m, H-3 + H-5); 7.10 (1H, m, H-4); 7.41 (1H, m, H-6); 7.84 (1H, s, H-5). ¹³ C NMR δ : 10.3, 10.6, 51.4, 52.5, 117.9, 118.7, 122.4, 124.4, 128.8, 130.7, 133.6, 154.6, 188.1 |
| 4c | 146-147 dec. | 100 | 1559, 1440, 1252, 990, 765, 621 | ¹ H NMR δ : 1.79 (6H, m, 3CH ₂); 3.81 (4H, m, 2CH ₂ -N); 6.70 (2H, m, H-3 + H-5); 6.99 (1H, m, H-4); 7.70 (1H, m, H-6); 7.70 (1H, s, H-5). ¹³ C NMR δ : 21.6, 24.8, 25.0, 56.4, 57.8, 117.7, 118.5, 122.3, 124.7, 128.6, 130.4, 133.4, 154.3, 188.3 |
| 4d | 128-129 dec. | 100 | 1560, 1454, 1257, 769, 622 | ¹ H NMR δ : 3.86 (8H, m, 4CH ₂); 6.74 (2H, m, H-3 + H-5); 6.92 (1H, m, H-4); 7.65 (1H, m, H-6); 7.77 (1H, s, H-5). ¹³ C NMR δ : 53.6, 54.6, 64.5, 118.1, 118.5, 122.7, 125.1, 128.3, 130.8, 133.9, 154.1, 188.3 |

Table 3
ANALYTICAL AND SPECTRAL DATA
OF MESOIONIC 1,3-DITHIOLIUM
PHENOLATES **4**

| | M.p., °C | η , % | IR-ATR, cm ⁻¹ | NMR (DMSO- <i>d</i> ₆) |
|-----------|-----------------|------------|--|---|
| 5a | 228-229 dec. | 98 | 3204, 1561, 1444, 1351, 1255, 796, 620 | ¹ H NMR δ : 3.49 (3H, s, CH ₃); 3.52 (3H, s, CH ₃); 6.88 (2H, m, H-3 + H-5); 7.28 (1H, m, H-4); 7.55 (1H, m, H-6); 8.08 (1H, s, H-5); 11.65 (1H, s, OH). ¹³ C NMR δ : 46.9, 47.2, 118.1, 119.0, 122.5, 124.8, 128.8, 130.8, 133.5, 154.8, 188.2 |
| 5b | 163-164 | 97 | 3198, 1564, 1449, 1356, 1258, 799, 622 | ¹ H NMR δ : 1.40 (6H, t, 2CH ₃); 3.85 (2H, q, CH ₂); 3.91 (2H, q, CH ₂); 6.75 (2H, m, H-3 + H-5); 7.16 (1H, m, H-4); 7.44 (1H, m, H-6); 7.96 (1H, s, H-5); 11.70 (1H, s, OH). ¹³ C NMR δ : 10.3, 10.8, 51.5, 52.6, 117.8, 118.8, 122.3, 124.6, 128.7, 130.9, 133.7, 154.5, 188.3 |
| 5c | 205-206 | 96 | 3194, 1568, 1448, 1358, 1261, 798, 621 | ¹ H NMR δ : 2.30 (4H, m, 2CH ₂); 3.73 (4H, m, 2CH ₂ -N); 6.79 (2H, m, H-3 + H-5); 7.47 (1H, m, H-4); 7.84 (1H, d, H-6); 8.05 (1H, s, H-5); 11.54 (1H, s, OH). ¹³ C NMR δ : 21.4, 24.9, 25.1, 56.3, 57.7, 117.9, 118.4, 122.6, 124.9, 128.5, 130.3, 133.7, 154.5, 188.4 |
| 5d | 198-199 | 98 | 3201, 1566, 1452, 1355, 1261, 802, 620 | ¹ H NMR δ : 3.95 (8H, m, 4CH ₂); 6.77 (2H, m, H-3 + H-5); 7.45 (1H, m, H-4); 7.82 (1H, d, H-6); 8.01 (1H, s, H-5); 11.59 (1H, s, OH). ¹³ C NMR δ : 53.7, 54.5, 64.6, 118.0, 118.4, 122.8, 125.0, 128.5, 130.5, 133.8, 154.2, 188.6 |

Table 4
ANALYTICAL AND SPECTRAL DATA
OF 1,3-DITHIOLIUM CHLORIDES **5**

The NMR spectra also support the heterocyclization of dithiocarbamates **2**. Thus, the ¹H NMR spectra of 1,3-dithiol-2-ylum perchlorates indicate the absence of the methylene hydrogens from compounds **2** (ca. 4.9 ppm) and appearance of a new signal at a low field (ca. 8 ppm) corresponding to the hydrogen atom from the 5-position of the heterocycle. ¹³C NMR spectra also prove the synthesis of 1,3-dithiolium perchlorates **3** 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. 188 ppm) which correspond to the electron deficient C-2 atom. Treatment of perchlorates **3a-d**, under heterogeneous conditions, with saturated aqueous sodium hydrogencarbonate solution provides [2-(dialkylamino)-1,3-dithiol-2-ylum-4-yl]phenolates **4a-d**, in quantitative yields (fig. 2). These compounds were isolated as yellow crystalline products that present the features of mesoionic compounds (fig. 3) [24, 25]. The molecular structure of the new compounds was proved by analytical and spectral data (table 3) and

by the following chemical transformation: treatment of an acetone suspension of the mesoionic compounds **4** with perchloric acid regenerates the 1,3-dithiolium perchlorates **3** in quantitative yields (fig. 2).

Using the interconversion possibilities between the mesoionic phenolates and their salts, we have been able to isolate the 1,3-dithiolium chlorides **5a-d**. Thus, 4-(2-hydroxyphenyl)-1,3-dithiol-2-ylum chlorides have been isolated as colorless crystalline products by the treatment of an acetone suspension of mesoionic phenolates **4** with 37% hydrochloric acid (fig. 2). This is a new class of isolable 1,3-dithiolium chlorides. The interest for organic chlorides raised from their good solubility in water, which makes these compounds attractive for biological investigation. The structure of these water soluble 1,3-dithiolium salts was proved by analytical and spectral data (table 4).

The interconversion between mesoionic phenolates **4** and 1,3-dithiolium salts was also confirmed by UV-Vis absorption spectra. As shown in figure 4 deprotonation of 1,3-dithiolium salts is accompanied by the appearance of

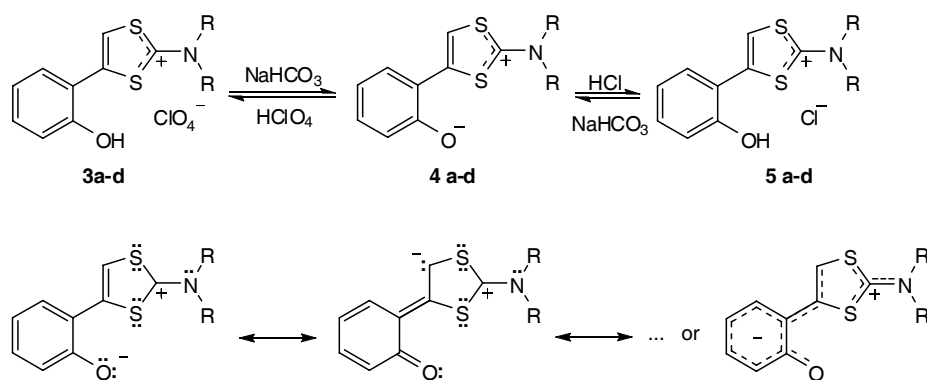


Fig. 2. Synthesis of mesoionic phenolates **4** and 1,3-dithiolium chlorides **5**.

Fig. 3. Extended delocalization charge in mesoionic phenolates **4**

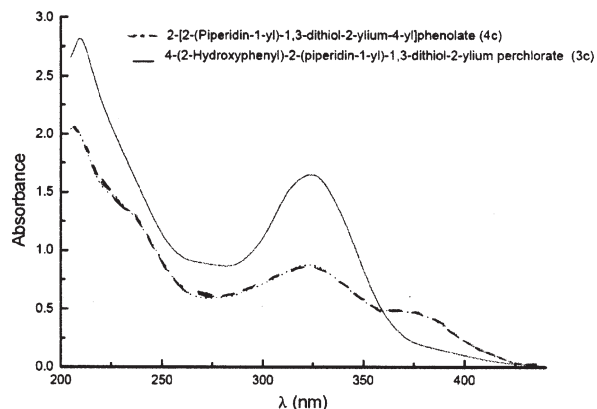


Fig. 4. UV/Vis absorption spectra of 4-(2-hydroxyphenyl)-2-(piperidin-1-yl)-1,3-dithiol-2-ylum perchlorate (**3c**) and 2-[2-(piperidin-1-yl)-1,3-dithiol-2-ylum-4-yl]phenolate (**4c**) in ethanol

a new absorption band at 372 nm, associated with the yellow color of these compounds. The comparative study of the two spectra presented in figure 4 indicate that both mesoionic phenolate **4c** and 1,3-dithiolium perchlorate **3c** exhibit the same absorption bands at 210 nm and 325 nm, corresponding to the $\pi \rightarrow \pi^*$ transition of aromatic core and $n \rightarrow \pi^*$ for electron deficient area, respectively. However, mesoionic phenolate **4c** presents a new absorption band at 235 nm that corresponds to the contribution of the quinoid form to the ground state. As previously reported by us [22], the absorption band at 372 nm originates from an internal charge transfer between electron-rich and electron-deficient regions of the molecules.

Conclusions

The synthesis of 4-(2-hydroxyphenyl)-2-dialkylamino-1,3-dithiol-2-ylum perchlorates has been accomplished by heterocondensation of 1-(2-hydroxyphenyl)-2-(*N,N*-dialkylaminocarbodithioate)-1-ethanones. The corresponding 1,3-dithiolium chlorides were prepared using the interconversion properties of mesoionic 2-(1,3-dithiol-2-ylum)phenolates with the corresponding salts. The former compounds represent a new class of 1,3-dithiolium chlorides with a good solubilities in water. UV-Vis investigations of the reported compounds revealed the presence of an internal charge transfer in mesoionic phenolates, which is responsible for their yellow color.

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