Synthesis and Structural Characterization of a New Iodine-containing Phenacyl *N,N*-Diethylamino Carbodithioate

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*The synthesis of 1-(2-hydroxy-5-iodophenyl)-1-oxaethan-2-yl-N,N-diethylamino-1-carbodithioate was achieved from w-bromo-2-hydroxy-5-iodoacetophenone and sodium N,N-diethyldithiocarbamate, and the structure of the new phenacyl carbodithioate was confirmed by X-ray analysis. Upon acid-catalyzed cyclization of dithiocarbamate **3**, the corresponding 1,3-dithiolium perchlorate **4** was obtained. Conversion of the latter into mesoionic derivative **5** was achieved in a basic environment. All new compounds were characterized using NMR spectroscopy.*

Keywords: dithiocarbamate, 1,3-dithiolium salt, mesoionic phenolate, X-ray crystallography

An important structural feature of heterocyclic compounds, which continues to be exploited by the drug industry, lies in their ability to distribute substituents around a core scaffold in well-defined three-dimensional patterns [1]. Heterocyclic derivatives have widespread therapeutic applications, such as antibacterial, antifungal, anti-HIV activity, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants, anticonvulsant, antidepressant, and antitumoral agents [2]. In particular, sulfur- and nitrogen-containing heterocyclic compounds have maintained the continuous interest of researchers [3-13].

Furthermore, 1,3-dithiolium salts are well-known precursors of tetrathiafulvalenes (TTF), which in turn are notable π-electron donors in organic metals [14, 15]. While tetrathiafulvalenes are well-known electron donor systems, a variety of acceptor units have been investigated, special attention being paid to cationic systems [16]. In this context, investigations on a series of (1,3-dithiolium-2-yl)phenolates showed that 1,3-dithiolium ions can also serve as acceptor moieties in intramolecular charge-transfer systems [17]. *N,N*-Dialkylamino carbodithioates represent the main precursors for 1,3-dithiol-2-ylium systems bearing a dialkylamino moiety at the 2-position [18]. In view of the above facts, we report here the synthesis of an iodine-containing phenacyl *N,N*-diethylamino carbodithioate and its conversion to the corresponding 1,3-dithiolium systems.

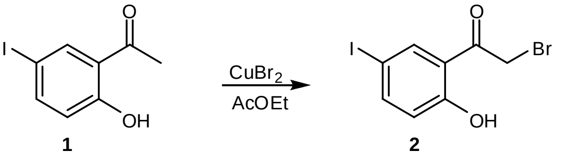
Experimental part

Analysis methods

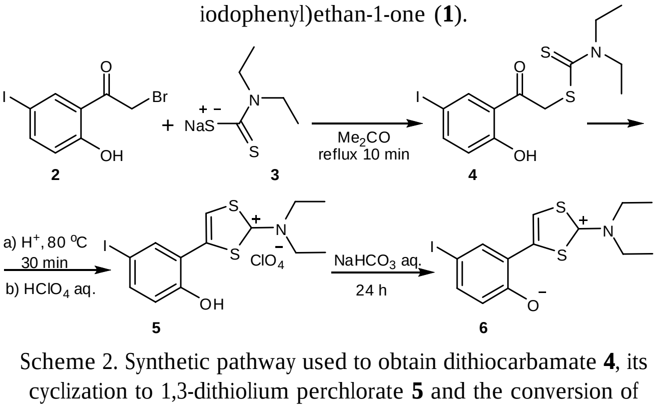
Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. NMR spectra were recorded on a Bruker AV-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. MS: Finnigan MAT 90X, electron impact (EI, 70 eV). Electrospray ionization (ESI): ThermoFisher Scientific LTQ-Orbitrap Velos. Typical spray voltage in positive ion mode was 2.3-2.8 kV.

Synthesis

The synthesis of the target compounds involves a method previously described [19-22] and is presented in schemes 1 and 2.



Scheme 1. The synthesis of 2-bromo-1-(2-hydroxy-5-iodophenyl)ethan-1-one (**1**).



Scheme 2. Synthetic pathway used to obtain dithiocarbamate **4**, its cyclization to 1,3-dithiolium perchlorate **5** and the conversion of the latter to mesoionic derivative **6**

2-Bromo-1-(2-hydroxy-5-iodophenyl)ethan-1-one **2**

To a solution of 1-(2-hydroxy-5-iodophenyl)ethan-1-one (2.62g, 10mmol) in ethyl acetate (100mL), copper (II) bromide (4.46g, 20mmol) was added and the resulting suspension was refluxed for 8 h, during which the color changed from green to yellow. The white precipitate that formed was then filtered and the solvent was removed under reduced pressure. The residue, a dark-orange oil, was dissolved in hexane, kept at 0°C overnight and then filtered, yielding 2.32g (68%) of yellow crystals. ^{1}H NMR ($CDCl_3$) δ 4.43 (s, 2H), 6.84 (d, 1H, ^3J = 8.8 Hz), 7.77 (dd,

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1H, ^3J= 8.8 Hz, ^4J = 2.0 Hz), 8.03 (d, 1H, ^4J = 2.0 Hz), 11.69 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.8, 80.0, 119.1, 121.4, 138.6, 145.7, 162.7, 196.1.

1-(2-Hydroxy-5-iodophenyl)-1-oxaethan-2-yl-N,N-diethylamino-1-carbodithioate **4**

To a solution of 2-bromo-1-(2-hydroxy-5-iodophenyl) ethan-1-one (1.02g, 3mmol) in acetone (10mL), a solution of sodium *N,N*-diethyldithiocarbamate trihydrate (0.68g, 3mmol) in acetone/water (5mL/5mL) was added. The resulting mixture was refluxed for 10 min, cooled to room temperature and poured into water (200mL) with vigorous stirring. The precipitate thus formed was vacuum-filtered and recrystallized from ethanol, yielding 1.07g (87%) of yellow crystals; m.p. = 119-120°C. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, ^3J = 7.1 Hz), 1.37 (t, 3H, ^3J = 7.1 Hz), 3.82 (q, 2H, ^3J = 7.1 Hz), 4.02 (q, 2H, ^3J = 7.1 Hz), 4.86 (s, 2H), 6.80 (d, 1H, ^3J = 8.8 Hz), 7.73 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.2 Hz), 8.27 (d, 1H, ^4J = 2.2 Hz), 11.81 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 11.9, 13.0, 44.4, 47.6, 50.8, 80.4, 121.4, 121.5, 138.9, 145.4, 162.3, 193.5, 198.6 ppm. EI-MS (*m/z*): 409.0 (M^+), 247.0, 218.0, 148.0, 116.0 .

4-(2-Hydroxy-5-iodophenyl)-2-N,N-diethylamino-1,3-dithiol-2-ylium perchlorate **5**

Dithiocarbamate **4** (0.41g, 1mmol) was added to a mixture of sulfuric and acetic acid (0.5mL/1.5mL) and the resulting mixture was heated at 80°C for 30 min. The resulting solution was then allowed to cool to room temperature and poured into an aqueous solution of perchloric acid (0.5mL $HClO_4$ 70% and 50mL H_2O) with vigorous stirring. The resulting white precipitate was then filtered and recrystallized from ethanol, yielding 0.29g (60%) of white crystalline solid; m.p. = 174-175°C. ^{1}H NMR (DMSO-*d*6) δ 1.31-1.41 (m, 6H), 3.80-3.96 (m, 4H), 6.85 (d, 1H, ^3J=8.6 Hz), 7.63 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.1 Hz), 7.90 (d, 1H, ^4J = 2.1 Hz), 8.12 (s, 1H), 11.38 (s, 1H) ppm. ^{13}C NMR (DMSO-*d*6) δ10.3, 53.0, 53.5, 82.0, 118.9, 119.5, 120.3, 133.4, 136.2, 139.8, 153.7, 186.2 ppm. ESI -MS (*m/z*): [M-ClO_4^-]: 391.9634 (calcd. 391.9638).

4-Iodo-2-[2-N,N-diethylamino-1,3-dithiol-2-ylium-4-yl]phenolate **6**

1,3-Dithiolium perchlorate **5** (0.49g, 1mmol) was added to a saturated solution of sodium hydrocarbonate and the resulting suspension was stirred vigorously for 24h. The solid was then filtered and air-dried, yielding 0.37g (94%) of yellow amorphous powder; m.p. = 177-178°C. ^{1}H NMR (DMSO-*d*6) δ1.29-1.40 (m, 6H), 3.75-3.94 (m, 4H), 6.45-6.74 (m, 1H), 7.32-7.43 (m, 1H), 9.81-7.95 (m, 1H), 7.94 (s, 1H) ppm. ^{13}C NMR (DMSO-*d*6) δ10.2, 53.1, 53.8, 81.8, 119.2, 119.7, 120.1, 133.1, 136.0, 140.1, 153.5, 186.0 ppm.

X-ray Structure Determination of ***4***

Crystal data are summarized in table 1. The crystal was mounted in inert oil on a glass fibre and transferred to the cold gas stream of an Oxford Diffraction Nova E diffractometer. Intensity measurements were performed using mirror-focused Cu Kα radiation (λ = 1.54184 A°). Absorption corrections were based on multi-scans. The structure was refined anisotropically on F^2 using the program SHELXL-97 [23]. The hydroxyl hydrogen was refined freely; other hydrogens were included using a riding model or rigid methyl groups.

CCDC-1439856 contains the supplementary crystallo-graphic data for compound **4**. These data can be obtained free of charge from The Cambridge Crystallo-graphic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussions

Phenacyl carbodithioates, which are important precursors for 1,3-dithiolium salts, are easily available from the reaction of *a*-bromophenones with salts of dithiocarbamic acid. 2-Bromo-1-(2-hydroxy-5-iodophenyl) ethan-1-one (**2**) has been synthesized by regioselective side-chain bromination of 1-(2-hydroxy-5-iodophenyl) ethan-1-one (**1**) [24], using $CuBr_2$ as brominating agent.

2-Bromo-1-(2-hydroxy-5-iodophenyl)ethan-1-one (**2**) readily undergoes nucleophilic substitution in the presence of the diethyldithiocarbamate anion, in acetone, yielding the desired phenacyl carbodithioate. The incorporation of the diethyldithiocarbamic unit is confirmed by NMR spectral

Empirical formula	$C_{13}H_{16}INO_2S_2$	
Formula weight	409.29	
Temperature	103 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P(-1)	
Unit cell dimensions	a = 8.3749(4) Å	α = 75.782(4)°
	b = 8.7242(4) Å	β = 83.988(4)°
	c = 11.8908(4) Å	γ = 65.595(5)°
Volume	766.92(6) $Å^3$	
Z	2	
Density (calculated)	1.772 Mg/m^3	
Absorption coefficient	18.9 mm^{-1}	
F(000)	404	
Crystal size	0.20 x 0.04 x 0.04 mm^3	
Theta range for data collection	3.83 to 75.64°	
Reflections collected	31496	
Independent reflections	3174 [R(int) = 0.039]	
Completeness to theta = 75.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.370	
Data/restraints/parameters	3174/0/178	
Goodness-of-fit on F^2	1.05	
Final R indices [I >2sigma(I)]	R1 = 0.0215, wR2 = 0.0550	
R indices (all data)	R1 = 0.0216, wR2 = 0.0551	
Largest diff. peak and hole	0.58 and -0.63 e.$Å^{-3}$	

Table 1
CRYSTAL DATA AND STRUCTURE REFINEMENT

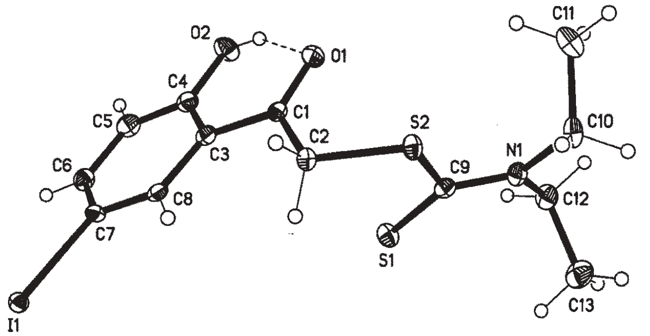

Fig. 1. Molecular structure of compound **4**. Ellipsoids represent 50% probability levels. Selected molecular dimensions (Å, °): N(1)-C(9) 1.327(3), S(1)-C(9) 1.680(2), S(2)-C(9) 1.784(2), N(1)-C(9)-S(2) 113.52(17), N(1)-C(9)-S(1) 124.52(17), S(2)-C(9)-S(1) 121.95(13)

data. Thus the ^{1}H NMR spectrum indicates the presence of two triplets, at 1.29 ppm and 1.37 ppm, corresponding to the two methyl groups, and also two quartets, 3.82 ppm and 4.02 ppm, provided by the two methylene units directly bound to the nitrogen atom. The ^{13}C NMR spectrum confirms the presence of the two methyl groups (11.9 ppm and 13.0 ppm), the two nitrogen-bound methylene groups (47.6 ppm and 50.8 ppm) and the thiocarbonyl carbon atom (193.5 ppm). Moreover, single crystals suitable for X-ray determinations were obtained for dithiocarbamate **4**. The results, which confirm the proposed structure, are presented in figure 1.

A strong intramolecular hydrogen bond O(2)–H(02). . . O(1), with H-O 0.86(5) A^o, angle 152(4)°, is observed in the molecule of **4**. The data confirm the extended p-π conjugation at the level of dithiocarbamic group [25]; the N(1)–C(9) bond length is 1.327(3) A^o, shorter than N(1)–C(10) and N(1)–C(12), which are essentially σ-bonds (1.479(3), 1.476(3) A^o). The torsion angle between the plane of the aromatic ring and that of the planar section of the diethyldithiocarbamate moiety [C(1)-C(2)-S(2)-C(9)] is -64.98(18) °.

Despite previously encountered problems [26, 27], the cyclization of dithiocarbamate **4** to 1,3-dithiolium perchlorate **5** proceeded without any substrate decomposition in a sulfuric acid/acetic acid mixture. The chemical transformation is accompanied by important spectral changes. Thus, the ^{1}H NMR spectrum indicates the disappearance of the singlet at 4.86 ppm, corresponding to the sulfur-bound methylene, and the appearance of a new singlet at 8.12 ppm, attributed to the H-5 hydrogen atom of the 1,3-dithiolium ring. The ^{13}C NMR spectrum reveals the disappearance of the carbonyl and thiocarbonyl signals (198.6 ppm and 193.5 ppm) and the appearance of a new signal at 186.2 ppm, belonging to the positive C-2 carbon atom of the 1,3-dithiolium ring. Also, a broadening of the signal at 11.38, corresponding to the hydroxyl hydrogen atom is observed. This is attributable to the disappearance of the carbonyl group, and with it, the ability of the above-mentioned hydrogen atom to form a hydrogen bond.

The conversion of 1,3-dithiolium perchlorate **5** to 4-iodo-2-[2-*N*,*N*-diethylamino-1,3-dithiol-2-ylium-4-yl]phenolate (**6**) is achieved in a basic environment, necessary for the conversion of the hydroxyl group to a phenoxide group. During the course of the reaction, carbon dioxide gas is produced in the reaction medium and the color of the suspension changes from white to pale yellow; this compound presents the features of mesoionic derivatives [28, 29]. The ^{1}H NMR spectrum indicates the disappearance of the hydroxyl hydrogen atom at 11.38 ppm, together with a slight broadening of the other signals.

Conclusions

The synthesis of a new phenacyl carbodithioate was achieved by reacting the corresponding brominated acetophenone with sodium diethyldithiocarbamate. The structure of 1-(2-hydroxy-5-iodophenyl)-1-oxaethan-2-yl-*N*,*N*-diethylamino-1-carbodithioate was confirmed by X-ray analysis. Acid-catalyzed cyclization of this dithiocarbamate has provided the corresponding 1,3-dithiolium perchlorate, which was converted to the corresponding mesoionic phenolate in a basic environment.

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