SYNTHESIS AND SPECTROSCOPY OF NEW 4-ARYL-2(3*H*)-THIAZOLETHIONES AND DERIVED THIAZOLES

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Abstract: The optimized preparation of four new 4-aryl-2(3*H*)-thiazolethiones and three new phenacylthiothiazoles is described. Since the 2(3*H*)-thiazolethiones contain three functional groups in their ring: an enamine, a thiolactam, and a dithiolactone, their influence was studied by alkylation/aromatization reactions and by ^{1}H-NMR experiments on deuterium exchange with DMSO-d_6/D_2O, $CDCl_3$/CF_3COOD, CF_3COOD and CF_3COOD/D_2O.
Among these new compounds we have found intramolecular weak hydrogen bonding, as well as deuterium exchange involving hydrogens bound to sp^2 carbon atoms.

Introduction

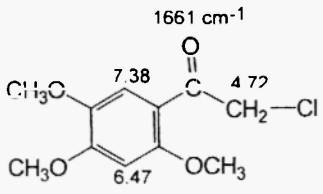
The compounds under study have been registered in *Chemical Abstracts* as 4-thiazoline-2-thiones from 1951 to 1971, and as 2(3*H*)-thiazolethiones onwards. The earlier works considered these compounds as 2-mercapto-thiazoles.

The papers related to these thioxo compounds have been reviewed several times (1-8).

The reaction of an α-halo ketone with a dithiocarbamate (3) to obtain a 2(3*H*)-thiazolethione has been employed with rather simple ketone derivatives. We have prepared four new 4-aryl-2(3*H*)-thiazolethiones having di- or trisubstituted phenyl groups.

Results and Discussion

We tried the reaction of 2,4,5-trimethoxyphenacyl chloride (9), **1**, with ammonium dithiocarbamate (10,11). A mixture dioxane-ethanol (3:5) was employed as solvent due to the low solubility of the chloride **1** in EtOH. However, instead of the expected heterocycle, bis(2,4,5-trimethoxyphenacyl) disulfide, **2**, was formed via the α-mercaptoketone and air oxidation. The IR (KBr wafer) and ^{1}H-NMR data ($CDCl_3$, 300 MHz) are given in the formulas.



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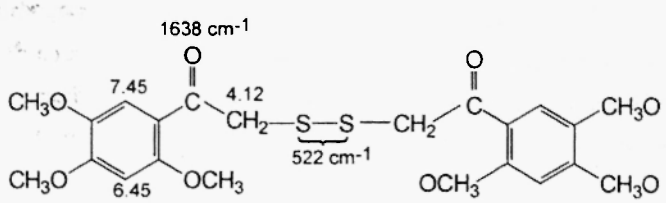
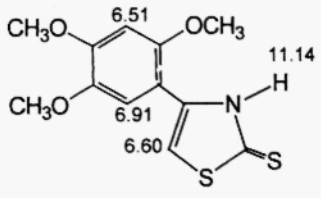


2

The 4-(2,4,5-trimethoxyphenyl)-2(3*H*)-thiazolethione, **3**, was obtained in 93% yield when the above reaction was carried on in pyridine as solvent and at 40°C instead of 50°C. We have found that the H-5 NMR signal in thiazole derivatives shows *ringing* in the spectra at 90 MHz (12). This can be accounted for by the presence of a near heteroatom (H–C–S).

The tautomeric structure of 2-mercaptothiazole was discarded since the H-5 signal would appear at about 7.6 ppm (12,13), instead of at 6.60 ppm.



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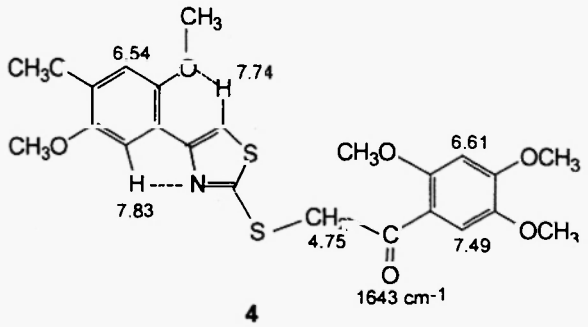
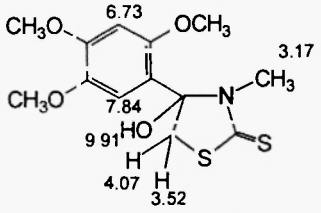


4

The test with $FeCl_3/K_3Fe(CN)_6$ described to detect enols and cryptophenols (14) was applied to the thiazolethione **3**, in order to know if this reagent also detects the isomeric thioenol structure due to a possible prototropy in this compound. We obtained the characteristic blue colour of a positive reaction.

Compound **3** reacted with the phenacyl halide **1**, in N,N-dimethylacetamide as solvent, to yield the thiazole derivative 4. The low field shifted singlets for H-6 in the 4-aryl group and for the thiazolic proton are due to weak hydrogen bonding (15).



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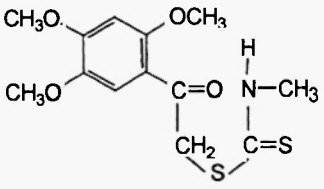

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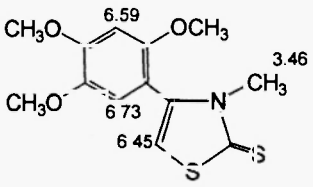
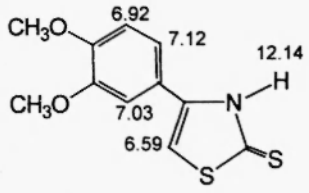


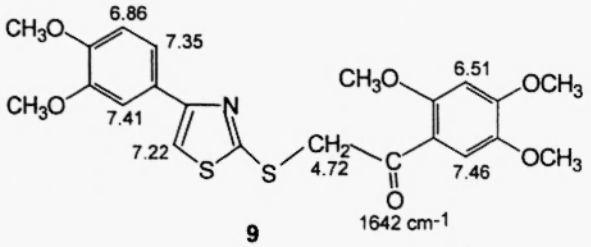
7

When the trimethoxyphenacyl chloride **1** reacted with methylammonium N-methyldithiocarbamate, the intermediate 4-hydroxy-3-methyl-4-(2,4,5-trimethoxyphenyl)-2-thiazolidinethione, **5**, was obtained. This compound presents an IR band at 3257 cm^{-1} (associated OH) (16) and in its mass spectrum the base peak is at m/z 195 (2,4,5-trimethoxybenzoil group), this fragment resulting from the open chain structure **6**. This isomerization occurred in the mass spectrometer, since no carbonyl band is observed in the IR spectrum and the compound gave a negative Janovsky test for α-methylene ketones (17). The ^{1}H-NMR data in formula **5** were obtained in pyridine-d_5 since the spectrum obtained in $CDCl_3$ corresponds to the dehydrated compound, **7**, due to acidity in this solvent. The 2(3*H*)-thiazolethione **7** was obtained by refluxing a solution of **5** in EtOH/HCl. IR 3113 cm^{-1} (C–H in C=CH–S). When its ^{1}H-NMR spectrum was determined in DMSO-d_6, the H-5 signal disappeared upon addition of D_2O. Thus, the compound reacts as an enamine, the deuterium exchange being possible due to the dimethyl sulphoxide polarity that stabilizes a positive N and a carbanion at C-5.

The 4-(3,4-dimethoxyphenyl)-2(3*H*)-thiazolethione, **8**, was obtained from α-bromoacetoveatrone (**18**) and ammonium dithiocarbamate. In this case, N,N-dimethylacetamide as solvent gave a better yield (71%) than pyridine (31%). IR (KBr): 3424 cm^{-1} (thiolactam dimer); disappears in $CHCl_3$ solution. The bromoketone can be obtained with a higher stability by reaction of acetoveratrone with $CuBr_2$ in AcOEt/$CHCl_3$, compare (19), instead of Br_2.

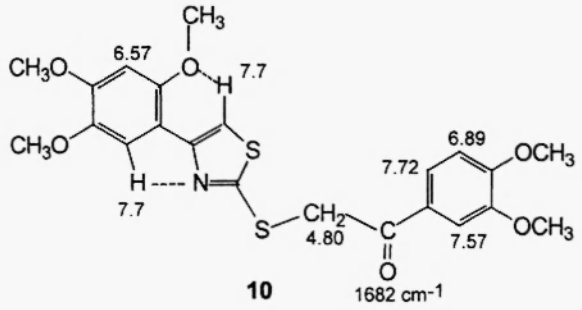


8



9

The 2-(2,4,5-trimethoxyphenacylthio)thiazole derivative **9**, was also obtained. In comparison with **4**, note the different chemical shifts for the thiazolic proton and the benzenic H between the methoxyl and the heterocycle. The absence of a third OMe group in **9** disfavours weak hydrogen bond formation. This was confirmed when the isomeric 2-(3,4-dimethoxyphenacylthio)-4-(2,4,5-trimethoxyphenyl)thiazole, **10**, prepared from compound **3** and α-bromoacetoveratrone, exhibited in its ^{1}H-NMR spectrum low field shifts for the above mentioned protons.



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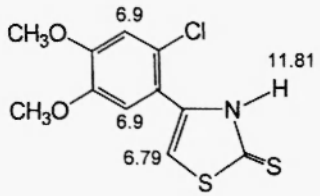
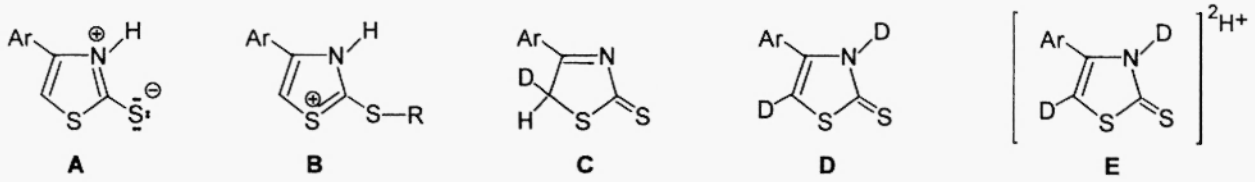


11

The 4-chloroaryl derivative **11** was obtained from α-bromo-6-chloroacetoveratrone (20) and ammonium dithiocarbamate. IR: 3131 (thiazolic CH) and 1462 cm^{-1} (thiolactam).

Finally, some ^{1}H-NMR experiments were carried on using $CDCl_3$/CF_3COOD, CF_3COOD and CF_3COOD/D_2O.

To a $CDCl_3$ solution of compound **3**, a drop of CF_3COOD was added and the spectrum was determined after 15 minutes. Besides the deuterium exchange in the N-H group, a strong decrease of the thiazolic proton signal was observed. This deuterium exchange shows an enamine reactivity, whereas in the alkylation/aromatization reactions leading to compounds **4**, **9** and **10**, the thiazolethiones apparently reacted as thiolactams. However, in the last reactions, a 1,3-dipolar resonance structure, **A**, *must be discarded* since, in the thioxo group, both carbon and sulphur have the same electronegativity, 2.5 in the Pauling scale. The starting is a nucleophilic reaction of the thiazolethione upon the α-haloketone, involving the exocyclic sulphur atom since it is less electronegative than nitrogen (3.0); the resulting carbonium ion at C-2 must be stabilized rather by the endocyclic sulphur atom than by the more electronegative nitrogen atom, structure **B**, derived from the dithiolactone group. Finally, the neutralization and aromatization of the molecule occurs.



On the contrary, in the CF_3COOD experiments , we are dealing with electrophilic reactions. In compound **3**, a deuteron can be fixed in the heteroatoms and in the double bond. In the case of the nitrogen atom there is a rapid neutralization by a proton loss, this not being the case with the sulphur atoms and thus there is not 2-mercaptothiazole formation. Reaction at the double bond gives a methylene imine, **C**, and deuteration ($^2H^+$) at nitrogen restores the enamine structure, **D**. The small signal of the still not exchanged thiazolic proton, mentioned in the $CDCl_3/CF_3COOD$ experiment, presents a 0.33 ppm downfield shift, indicating that we are dealing with a positive charged species, **E**.

In an analogous experiment with the N-CH_3 compound 7, a similar decrease of the H-5 signal was observed, but only after an increase of CF_3COOD (4 drops) and time (45 minutes). In this case a less stable methylene methylimonium ion is formed, instead of the neutral imine intermediate **C**.

The ^{1}H-NMR spectrum of compound 7 in CF_3COOD solution showed a paramagnetic shift of 0.37 ppm for the N-CH_3 signal (quaternary nitrogen) and a very small decrease of the vinylic singlet. A fast acid-base reaction took place; however, the deuterium exchange at C-5 occurred on addition of D_2O; this Lewis base neutralizes the nitrogen atom, thus permitting the enamine reactivity.

As it can be seen, the reactivity of the 2(3*H*)thiazolethiones depends on the involved type of reaction: nucleophilic or electrophilic.

EXPERIMENTAL

The IR spectra were recorded in a Perkin-Elmer FTIR-1600 spectrophotometer, using KBr wafers. The ^{1}H-NMR spectra were obtained in a Varian Inova 300 spectrometer, in $CDCl_3$ solution, except otherwise stated, and TMS as internal standard. The EI-MS data were acquired using a JEOL JMS-SX 102 A double-focusing instrument with electron energy 70 eV.

Only significant data are provided. The methoxyl signals have been obviated.

Bis(2,4,5-trimethoxyphenacyl) disulfide, **2.** To a solution of 2,4,5-trimethoxyphenacyl chloride (0.12 g, 0.5 mmol) in 1,4-dioxane (3 ml) and ethanol (5 ml), at 50°C (oven), ammonium dithiocarbamate (0.15 g, 1.5 mmol) was added in three portions during 2 h. A white solid (60 mg) was filtered, m.p. 193-194°C. IR (KBr) 1638 (CO), 667 (C-S) and 522 cm^{-1} (S-S). ^{1}H-NMR (δ) 4.12 (CH_2), 6.45 (H-3) and 7.45 ppm (H-6). M.W. calc. for $C_{22}H_{26}O_8S_2$, 482. MS (ei): M^{+} 482, 26%; m/z 195, 100% (Ar-CO^+).

4-(2,4,5-Trimethoxyphenyl)-2(3H)-thiazolethione, **3.** To a solution of ammonium dithiocarbamate (0.05 g, 0.5 mmol) in pyridine (1 ml) at room temperature, the phenacyl chloride **1** (0.12 g, 0.5 mmol) was added and the mixture was heated at 40°C for 30 min (stoppered flask). Another equivalent of the ammonium salt was added and heated 1:15 h more. After dilution with water a white solid was obtained (0.13 g, 93%). M.p. 188.5-190°C. IR (KBr) 3126 (C-H in C=CH-S), 3067 (N-H), 1525 (C-N), 1309 (N-H) and 1063 cm^{-1} (C=S). ^{1}H-NMR (δ) 6.60 (vinylic H) and 11.14 ppm (NH). M.W. calc. for $C_{12}H_{13}NO_3S_2$, 283. MS (ei): M^+ 283, 100%; m/z 224, 7.5% (M^+ - H-N=C=S).

2-(2,4,5-Trimethoxyphenacylthio)-4-(2,4,5-trimethoxyphenyl)thiazole, **4**. A mixture of **3** (0.14 g, 0.5 mmol) and **1** (0.12 g, 0.5 mmol) in N,N-dimethylacetamide (1 ml) was refluxed for 1 h. After cooling, water (10 ml) and NH_4OH (5 drops) were added. The solid was filtered and crystallized from CH_2Cl_2-EtOH to give 0.17 g (71%) of greenish small prisms, m.p. 147-149°C. After purification on alumina (1 g) with *Tonsil*® (0.2 g) at the top, or other activated bleaching earth, and eluting with CH_2Cl_2, 0.13 g (54%) of leaflets were obtained. M.p. 151-153°C (CH_2Cl_2-EtOH). IR (KBr) 3137 (C-H in C=CH-S) and 1643 cm^{-1} (CO in S-CH_2-C=O). ^{1}H-NMR (δ) 4.75 (CH_2) and 7.74 ppm (thiazolic H). M.W. calc. for $C_{23}H_{25}NO_7S_2$, 491. MS (ei): $M^{\cdot+}$ 491, 26%; m/z 195, 100% (Ar-CO^+).

4-Hydroxy-3-methyl-4-(2,4,5-trimethoxyphenyl)-2-thiazolidinethione, **5**, was prepared as described for **3**, from methylammonium N-methyldithiocarbamate and 2,4,5-trimethoxyphenacyl chloride. Yield, 90% of white microcrystals, m.p. 188-189°C. IR (KBr) 3257 (OH), 1521 (CN) and 1038 cm^{-1} (C=S). ^{1}H-NMR (pyridine-d_5, δ) 3.52, d, J= 12 Hz and 4.07, d, J= 12 Hz (Hs at C-5). M.W. calc. for $C_{13}H_{17}NO_4S_2$, 315. MS (ci): MH^+ 316, 42%. MS (ei): $M^{\cdot+}$ 315, 8%; m/z 297, 31%; 242, 20%; 195, 100%.

3-Methyl-4-(2,4,5-trimethoxyphenyl)-2(3H)-thiazolethione, **7**. A solution of the hydroxythione **5** (0.18 g, 0.6 mmol) in boiling EtOH (18 ml), and HCl (2 drops), was distilled until crystallization began. Yield, 0.13 g (77%) of white crystals, m.p. 163-164°C. IR (KBr) 3113 cm^{-1} (thiazolic CH). ^{1}H-NMR (δ) 3.46 (N-CH_3) and 6.45 ppm (H-5). M.W. calc. for $C_{13}H_{15}NO_3S_2$, 297. MS (ei): $M^{\cdot+}$ 297, 100%.

4-(3,4-Dimethoxyphenyl)-2(3H)-thiazolethione, **8**, was prepared as described for **3**, using α-bromoacetoveratrone (18) and N,N-dimethylacetamide instead of pyridine. Yield, 71% of small needles (EtOH), m.p. 161-162°C. IR (KBr) 3424 cm^{-1} (thiolactam dimer); disappears in $CHCl_3$ soln. ^{1}H-NMR (δ) 6.59 (thiazolic H) and 12.14 ppm (NH). M.W. calc. for $C_{11}H_{11}NO_2S_2$, 253. MS (ei): $M^{\cdot+}$ 253, 100%.

4-(3,4-Dimethoxyphenyl)-2-(2,4,5-trimethoxyphenacylthio)thiazole, **9**, was prepared as described for **4**, from the thiazolethione **8** and 2,4,5-trimethoxyphenacyl chloride, **1**. Yield, 63% of yellow microcrystalls, m.p. 139-140°C. IR(KBr) 3098 (thiazolic CH) and 1642 cm^{-1} (CO). ^{1}H-NMR (δ) 4.72 (CH_2) and 7.22 ppm (thiazolic H). M.W. calc. for $C_{22}H_{23}NO_6S_2$, 461. MS (ei): $M^{\cdot+}$ 461, 18%; m/z 195, 100% (Ar-CO^+).

2-(3,4-Dimethoxyphenacylthio)-4-(2,4,5-trimethoxyphenyl)thiazole, **10**, was prepared from compound **3** and α-bromoacetoveratrone as described for **4**. Yield, 45% of small white needles, m.p. 148-149°C. IR (KBr) 3154 (thiazolic CH) and 1682 cm^{-1} (CO). ^{1}H-NMR (δ) 4.80 (CH_2) and 7.7 ppm (thiazolic H). M.W. calc. for $C_{22}H_{23}NO_6S_2$, 461. MS (ei): $M^{\cdot+}$ 461, 86%; m/z 165, 100% (Ar-CO^+).

4-(2-Chloro-4,5-dimethoxyphenyl)-2(3H)-thiazolethione, **11**, was prepared as described for **3**, using α-bromo-6-chloroacetoveratrone (0.29 g, 1 mmol), ammonium dithiocarbamate (0.17 g, 1.6 mmoles) and N,N-dimethylacetamide (2.2 ml). The resulting hemiaminal was dehydrated (EtOH, HCl), as compound 7. Yield, 69% of small white needles, m.p. 210-211°C (sealed capillary tube). IR (KBr): 3131 (thiazolic CH) and 1462 cm^{-1} (thiolactam). ^{1}H-NMR (δ) 6.79 (vinylic H) and 11.81 ppm (NH). M.W. calc. for $C_{11}H_{10}ClNO_2S_2$, 287.5. MS (ei): $M_1^{\cdot+}$ 287, 100%; $M_2^{\cdot+}$ 289, 42%.

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