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PREPARATION, STRUCTURE AND MODEL REACTIONS OF THIOAMIDES

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Abstract. The thioamides are not studied in detail yet. They are special group of compounds with variegated chemical reactivity and biological action. This work generalizes most of our investigations on preparation; structure; chemical properties and biological activity of thioamides.

I. Introduction.

The first thioamide was synthesized in 1815 by Gay-Lussak [1]. Later Berzelius (1843) worked on preparation of thioamides too.

The thioamides are analogues of amides in which oxygen is replaced by sulfur.



Scheme 1.

Regardless of the close structural analogy, there is a big difference in the chemical properties of two species [2]. Moreover, the behaviour of the thioamides is a little bit strange. Sulphur has lower electronegativity than oxygen. This means that thioamides should be less polar than amides, with more equable charge density, and less reactive. In fact, thioamides are more polar (and especially more polarizable) compared to respective amides and participate in more reactions.

The chemical versatility of thioamides is a good reason for their study: they are starting materials for the preparation of thiazoles, amidenes, amidrazones and etc. formation; they coordinate strongly metal ions. In addition, the investigations on the thioamides are connected with the expectations for biological activity in view of structural similarity with exceptionally widespread amides. The most important success in this direction is the introduction of *Ethionamide*, a drug with very high antituberculosic activity, in the clinical practice [3]. In the last 15 years tuberculosis has become again a serious health problem worldwide and this turned the preparation and the chemical and microbiological testing of thioamides into a hot issue[4].

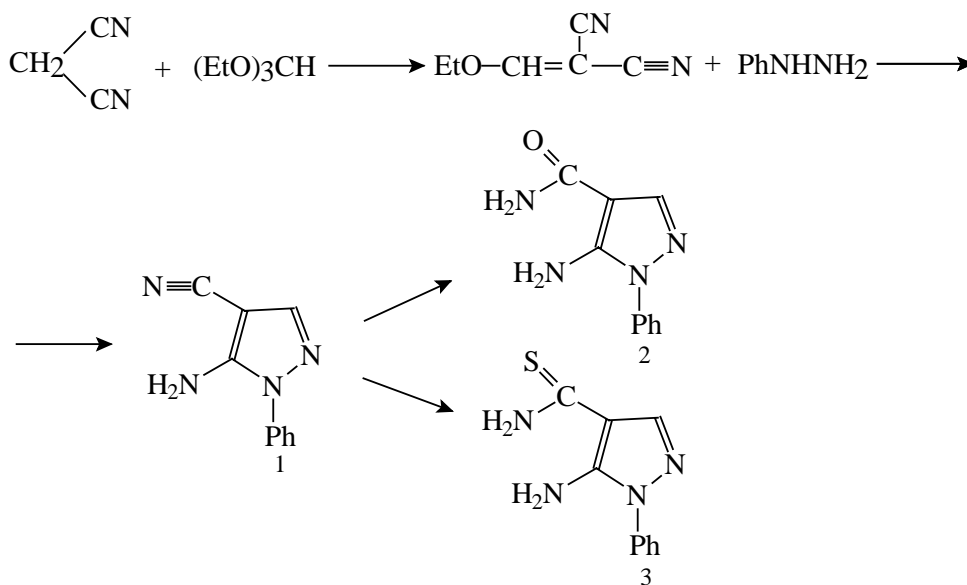
The references in the literature show that thioamides are not studied in detail yet. This work generalizes most of our investigations on preparation; structure; chemical properties and biological activity of thioamides.

II. Preparation and structure of thioamides.

II.1. Preparation of 3-amino-2-phenylpirazo-4-carbothioamide by thiolysis of nitriles and structural investigations [5].

The above thioamide (Scheme 2) was obtained by the Gay-Lussac method [6]. A solution of the corresponding nitrile in EtOH was saturated with H₂S for 3 days in the presence of

base as a catalizator. Water was added and the residue was filtered. In a similar way the nitrile was hydrolysed to amide (Scheme 2, 2). All preparation procedures include 3 steps represented in Scheme 2:



Scheme 2.

Spectral and theoretical methods were applied simultaneously to 2 and 3. The mass spectra (Jeol JMS D100, ionising voltage 70 eV, accelerating voltage 3 kV) of the two compounds confirm expected structure. In the IR spectra (taken on a Perkin-Elmer 983 IR Spectrophotometer in chloroform) the NH_2 -bands for 2 and 3 are very close. The characteristic CO-band at 1646 cm^{-1} for 2 is missing in 3. The CS-band, as usual, is not clearly defined. The structural formulae of 2 and 3 imply tautomerism. The absence of bands typical of the $\text{HN}=\text{C}$ -group in the spectra of 2 and 3, as well as such for the $\text{HO}-\text{C}$ -group in 2 and $\text{HS}-\text{C}$ -group in 3, proves that the presence (if any) of tautomeric forms in this solvent is negligible. UV spectra were taken on a Perkin-Elmer Lambda 17 UV/VIS spectrophotometer in acetonitrile. The absorption maxima of 2 and 3 differ in position and intensity.

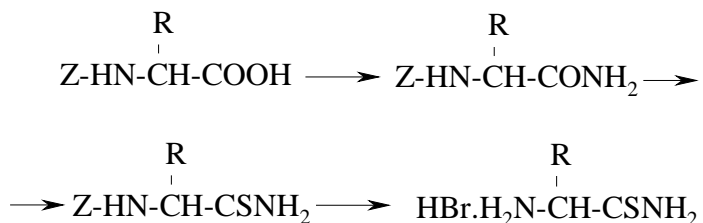
Both compounds were investigated by semi-empirical quantum chemical methods. An all-valence approach (AM1) was used for the geometry optimization. The optimized geometry reveals that both molecules have two practically planar fragments: the benzene ring and the imidazole ring, twisted at about 40° . The amino groups in the two compounds are twisted toward the pyrazole rings (20° in 2 and 10° in 3). There are no specific deviations in the valence angles. The bond lengths are also within the expected values except for the exocyclic CN- and CO- /resp. CS-/ bonds. The former are shorter ($1.35\text{-}1.37\text{ \AA}$) than the typical amino-CN-bonds (1.43 \AA), whereas the latter are longer (1.26 \AA for CO- and 1.63 \AA for CS-) than the carbonyl/thiocarbonyl ($1.22\text{ \AA}/1.61\text{ \AA}$) ones [8, 9]. This is an evidence for a strong conjugation in the amide/thioamide group. This conclusion is supported by the values of the electron atomic charges, which are substantially higher than 1.0 for the O/S-atoms.

The atomic charges were calculated by means of the PPP-method. The most striking difference between 2 and 3 is in the charge at the O/S-atoms. While the net charge at the oxygen atom in 2 is $q_o = -0.36$, and the charges at the neighbouring atoms are slightly reduced, the net charge $q_s = -0.89$ and all neighbouring atoms are characterized by a substantial electron deficiency. This allows the prediction of different chemical behaviour of 2 and 3 and is a good basis for the interpretation of the difference in the chemical and biological behaviour of amides and thioamides in general.

The optimised geometry was used for calculation of the energy and probability of the *singlet-singlet transitions of 2 and 3 using the PPP-CI-method including all mono-excited configurations. Standard parameters [7,8] were employed. The excellent agreement of the calculated values and the UV spectra proves the structure of 3.

II. 2. Preparation of amino acid thioamides [9]

The most effective synthetic method for the preparation of thioamide derivatives of proteinogenic amino acids is the thionation of the corresponding amides with Lawesson reagent (2,4-bis-*p*-methoxyphenyl-1,3,2,4-dithiadiphosphetan-2,4-dithion). The latter substitutes amide oxygen with sulphur selectively in the presence of ester and urethane groups. Amino function should be protected before thionation with this reagent. The obtained derivatives were identified by customary for peptide chemistry analytical methods. The series of thioamides were obtained using Lawesson's Reagent in three steps starting from *Z*- and Boc-protected amino acids as shown in Scheme 3..



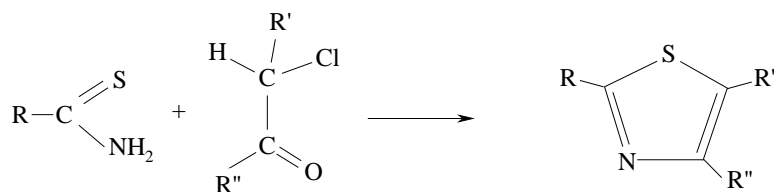
Scheme 3.

III. Properties of thioamides.

III. 1. Reaction with α -halocarbonyls and amines.

The most widely used approach for thioamides reactivity evaluation is their comparison with corresponding amides, usually well known. This modus has been used since the time of the first thioamide synthesis and is based on the structural analogy between the two species. It was demonstrated using quantum-chemical methods that thioamides are more reactive than amides. Moreover, the C=S group is more polarizable than the C=O group on account of the larger kernel of the S atom, which inhibits the formation of double bonds and finally explains the increased nucleophilicity of the sulphur and higher electrophilicity of carbon in thioamides. Very instructive reactions in this aspect are the interactions with α -haloketones and α -haloaldehydes.

The thioamides react with α -halocarbonyls in ethyl alcohol at room temperature for a day.

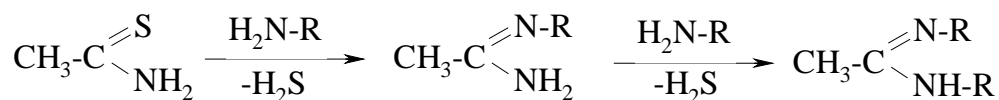


Scheme 4.

For comparison, the interaction between amides and α -halocarbonyls proceeds under remarkably rougher conditions.

The series of the obtained thiazoles were identified unequivocally by elemental analysis and $^1\text{H-NMR}$ spectra [10].

Carbon in thioamide groups is considerably more active electrophilic center than carbon in amides. Amides interact with amides in the presence of PCl_5 to form amidines. It means that they form as intermediate imidoylchloride which react with the amines. Thioacetamide reacts with amines in ethyl alcohol at refluxing temperature to form amidines according to the following scheme (Scheme 5):

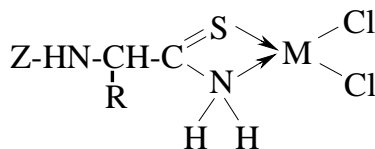


Scheme 5.

III. 2. Coordinating ability of thioamides.

Thioamides form stable complexes on interaction with salts of transition metals. But there are different opinions in the literature on the mechanism and type of coordination. Many authors assume that thioamides are monodentate ligands, and they bind by sulfur atom only to metal ions. Others find spectral proofs for N-M bond and consider thioamides as bidental ligands. There is a third group of investigators who think that thioamides could show bidentality after deprotonation.

Eight new complexes of K_2PtCl_4 and $(\text{NH}_4)_2\text{PdCl}_4$ with the thioamides of Gly and Phe amino acids (as hydrogen bromide salts or Z-protection on α -amino group) were obtained [11]. On the basis of elemental analysis and IR-spectra of the free ligands and the complexes was proposed four-atom helate structure of the prepared compounds.



Scheme 6.

IV. 4. Antibacterial and mutagenic activity of amides and thioamides.

There was a wide spread understanding in the 50s that sulfur atom in organic compound is responsible for their antibacterial activity [12]. This opinion gradually developed to the

conviction that sulfur is included in the intracellular mechanism of antibacterial action. Moreover, there are concepts that thioamides undergo destruction or hydrolysis in the cells. To check the idea for thioamides hydrolysis to corresponding carboxylic acid were made *in vitro* antibacterial experiments for the antibacterial activity determination of thioamides and complexes of thioamides with Pt(II) and Pd(II) [13]. The results confirmed our expectations.

V. Conclusion.

The thioamides are a special group of compounds with variegated chemical reactivity and biological action. In the cases of thiazoles and amidine preparation they could be the best or the only starting material for the synthesis of new compounds in the future. They are promising antibacterial, or more specifically, antituberculous agent. On the other hand, it seems very interesting to find out their intracellular behaviour. These problems could be the subjects of future investigations.

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