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A Conformational Study of Some Secondary 1-Methyl-2-pyrrolecarbothioamides

by T.S. Jagodziński*, T. Dziembowska, E. Jagodzińska and Z. Rozwadowski

Institute of Chemistry and Environmental Protection,
Technical University of Szczecin, Aleja Piastów 42, 71-065 Szczecin, Poland
e-mail: jagszcz@carbon.tuniv.szczecin.pl

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Analysis of the IR, UV and ^{1}H-, ^{13}C-NMR spectra and the dipole moments indicated that the secondary 1-methyl-2-pyrrolecarbothioamides are non-planar and exist in the *trans* (Z)-s-*trans* conformation. The results were compared with those obtained previously for analogous 2-thiophene- and 2-furanecarbothioamides. The influence of the heterocyclic core on the conformation of the secondary carbothioamides was shown.

Key words: 1-methyl-2-pyrrolecarbothioamides synthesis of, IR, UV and NMR-spectra; s-*cis* = s-*trans* conformational equilibrium

The effect of structure on the biological activity of chemical compounds is one of the main topics of the medicinal chemistry, which aims at correlating these properties in a qualitative (SAR) or quantitative (QSAR) manner. However, since a multitude of physical, chemical and biological factors act to control the very complex process of drug interaction with an organism, the correlation attempts usually concern sets of *congener* compounds with rather closely similar physical and chemical properties. Even small structural changes can affect the electron distribution pattern and molecule conformation and, in turn, alter the ionization or solubility abilities. A decrease or an increase of the biological activity or even a change of the activity type may be a consequence of such structural manipulations.

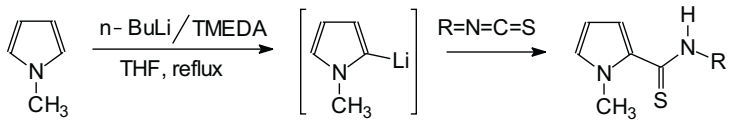
The vast number of biologically active compounds includes also those with a thioamide group [1–4]. As shown earlier, certain thioamides derived from thiophenecarboxylic acids were found to be active as plant growth retardants [3]. A related compound, 5-(*N,N*-diethylaminomethyl)-2-thiophene-*N*-phenylcarbothioamide, has shown a strong anticonvulsive activity [4]. These interesting properties prompted us to study the thioamides derived from different heterocyclic carboxylic acids. Our earlier investigations revealed that the conformation of the secondary thioamides, both in a solution and in the solid state, strongly depends on the nature of the heterocyclic core [5,6,7].

The aim of the present study has been the conformation thioamides derived from 1-methyl-2-pyrrolecarboxylic acid, and to compare the results with those obtained earlier for the analogous thiophene and furane derivatives [5,6].

RESULTS AND DISCUSSION

The secondary thioamides of 1-methyl-2-pyrrolecarboxylic acid (**1a–f**) were obtained in the reaction of the 2-lithiated 1-methylpyrrole with isothiocyanates in the presence of TMEDA in accord with Scheme 1 and method described in experimental part.

Scheme 1



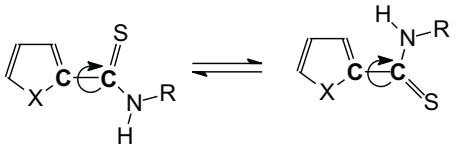
1 a - f

Table 1. Yields and melting points of 1-methyl-2-pyrrolecarbothioamides (**1a**–**f**).

Compound	R	m. p. [°C] (solvent)	Yield [%]
1a	CH_3	74–75 (hexane)	50
1b	cyclo-C_6H_{11}	120–122 (hexane/CCl_4)	61
1c	C_6H_5	100–102 (hexane)	80
1d	4-ClC_6H_4	162–164 (CCl_4)	81
1e	4-$CH_3OC_6H_4$	137–139 (CCl_4)	82
1f	4-$CH_3C_6H_4$	113–114 (hexane)	72

The conformations of the thioamides derived from 2-furane-, 2-thiophene- and 1-methyl-2-pyrrolecarboxylic acids should be regarded as a kind of compromise between coplanarity controlled by possible conjugations (heterocycle-C(S), N-C=S, N-R) on the one hand and certain steric and dipole interactions on the other. Since the N-C=S conjugation makes a major contribution to the molecule stability, the respective fragment of the molecule is planar. The substituent attached to the thiocarbonyl group (the heterocycle) as well as that attached to the thioamide nitrogen atom (NR) may be inclined with respect to this plane [8].

Scheme 2



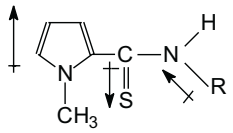
X = O, S, NCH_3

Our earlier studies have shown that in the thioamides, derived from 2-thiophenecarboxylic acid, the thioamide group rotation about the C–C(S) bond is restricted [5]. Hence, they occur as two conformers: *trans*(Z)-s-*trans* and *trans*(Z)-s-*cis* with high dominance of the former.

Its thioamide group is inclined with respect to the thiophene plane at the angle of 10° [9]. On the contrary, the thioamides derived from 2-furanecarboxylic acid in the solid state take the trans(Z)-s-cis conformation [10], while in solution a free rotation of the thioamide group about the C–C(S) bond occurs [6]. As in the thiophene analogs, the thioamide group is *trans*(Z). The secondary thioamides of 2-thiazole- and 2-benzothiazolecarboxylic acids in both solutions and the solid state occur only in the *trans*(Z)-s-*trans* form [7]. This conformation is enforced by a strong intramolecular hydrogen bond, which extends between the thiazole nitrogen atom and thioamide hydrogen atom. Continuing our investigation on the influence of the heterocyclic ring on the conformation of thioamide, we have studied series of the secondary thioamides derived from 1-methyl-2-pyrrolecarboxylic acid (**1a–f**). The X-ray study has revealed that the 2-methylpyrrole N-methylcarbothioamide exists as the *trans*(Z)-s-*trans* conformer. The molecule is non-planar and the thioamide group is inclined with respect to the pyrrole plane at the angle of ≈ 40° [4,9].

*Dipole moment measurements of **1a**.* The dipole moment of **1a** is a result of the dipole moments of the heterocyclic core and the thioamide group (Scheme 3).

Scheme 3



The dielectric polarization of the solute at an infinite dilution P_2 was calculated according to Hedestrand [12]:

$$P = \frac{3M_1}{d_1}\frac{\alpha\varepsilon}{(\varepsilon_1+2)} + \frac{M_2 - M_1\beta}{d_1}\frac{(\varepsilon_1-1)}{(\varepsilon_1+2)}$$

wherein ε, d and M stand for electric permeability, density and molecular mass, respectively, and the 1 and 2 subscripts refer to the solvent and the solute, respectively.

The α and β coefficients are characterized as follows:

$$\alpha = \frac{1}{\varepsilon_1}\frac{(\partial\varepsilon)}{(\partial x_2)} \quad \text{and} \quad \beta = \frac{1}{d_1}\frac{(\partial d)}{(\partial x_2)}$$

wherein x_2 stands for the concentration of **1a**. The values of α and β were used in calculating the dielectric polarizations and dipole moments of **1a** in benzene (Table 2).

Table 2. Dielectric polarization and dipole moments of 1-methyl-2-pyrrole-*N*-methylcarbothioamide (**1a)** in benzene.

$x_2 \times 10^{-3}$	α × ε	β	P_2 [cm^3]	μ [D]
2.2	15.895	0.5227	260.657	3.21
2.5	15.585	0.4522	257.507	3.19
3.3	16.037	0.484	261.907	3.22
3.4	15.766	0.3697	260.827	3.21

The average dipole moment of **1a** in benzene is 3.2 D. A comparison of this value with those calculated for s-*trans* (2.27 D) and s-*cis* (5.64 D), forms by CNDO-2 method [6], indicated that compound exists in s-trans conformation. The value of the α coefficient was found to be roughly concentration independent. This may be considered to be an additional piece of evidence for the less polar s-*trans* conformation of the thioamides.

Infrared spectra. The IR spectra recorded in $CHCl_3$ (Table 3) supplied the preliminary information on the conformation of the thioamide derivatives of 1-methyl-2-pyrrolecarboxylic acid (**1a–f**). As in the *trans(Z)* conformers of the thioamide derivatives of 2-furanecarboxylic acid [6], only one sharp band was observed in the 3420–3385 cm^{-1} range. It was considered to be due to the stretching vibrations of a free NH group. In the thiophene analogs [5], which were equilibrium mixtures of the *trans(Z)-s-trans* and *trans(Z)-s-cis* rotamers, two υNH appeared in the spectra. The amide I, II, and III bands (notation according to Rao [13]) appeared at roughly the same frequencies as in the *trans*(*Z)* conformers of thiophene and furane analogs [5,6]. The IR spectra failed however to answer the question whether **1a**–**f** have a free rotation about the C–C bond or whether they exist in the form of one stable rotamer. In either case only one υNH absorption band has to be expected in the spectrum.

Ultraviolet spectra. Three chromophores, namely the thioamide group, the heterocyclic core, and the phenyl group, give rise to the distinct absorption bands in the UV spectra of **1a**–**f** (Table 4). The π-π* transitions appear in the 282–324 nm range. Moreover, a characteristic low-intensity long wavelength absorption is observed; it shifts to the blue when a polar solvent is substituted for a non-polar one. As in the earlier cases [5,6], the respective band was considered to be due to the n-π* transition in the thioamide group. The replacement of the alkyl radical by an aryl in the thioamides caused a bathochromic shift of the π-π* band. The position of these transitions in *para*-substituted thioanilides **1c–f** does not depend on the substituent. This result shows that the coupling effect is insignificant and the position of the band depends in greater extent on the inductive effect, which suggests the twisting the aromatic ring plane from the plane thioamide group.

Table 3. IR spectra of the thioamides **1a–f**.

Comp.	R	Thioamide bands				Absorption bands of pyrrole ring [14]						
		ν_{NH}	I	II	III	$\nu_{C=C}$	$\nu_{C=C}$	$\nu_{C=C}$	δ_{CH_3}	$\nu_{CN} + \delta_{CH}$	δ_{CH}	δ_{CH}
1a	CH_3	3416	1508	1334	936 (1042)	1536	1476	1416	1378	1324	1096	1060
1b	c-C_6H_{11}	3388	1498	1344	988 (1026)	1532	**	1416	1375sh	1320	1104	1060
1c	C_6H_5	3384	1500	**	980 (1034)	1530	1476	1406	1376	1324	1096	1062
1d	4-ClC_6H_4	3384	1494	**	982 (1034)	1528	**	1412	1376	1320	1094	1062
1f	4-$CH_3OC_6H_4$	3384	1514	**	982 (1030)	1528	1488	1418	1376	1322	1096	1060
1f	4-$CH_3C_6H_4$	3384	1514	**	982 (1034)	1528	1482	1412	1375	1322	1096	1060

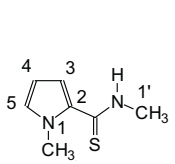
**overlapped.

Table 4. UV spectra of **1a–f**.

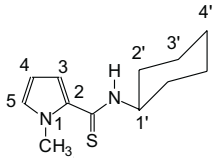
Comp.	R	Methanol			Cyclohexane		
		λ_{max}, nm	lg ε		λ_{max}, nm	lg (ε)	
1a	CH_3	282	4.09	π–π*	286 sh	3.08	π–π*
		307	4.14	π–π*	309	4.11	π–π*
		355	3.00	n–π*	394	2.60	n–π*
1b	cyclo-C_6H_{11}	287	4.14	π–π*	294 sh	4.13	π–π*
		305 sh	4.12	π–π*	308	4.15	π–π*
		360	3.00	n–π	397	2.69	n–π*
1c	C_6H_5	320	4.29	π–π*	320	4.09	π–π*
		391	3.00	n–π	397	2.40	n–π
1d	4-ClC_6H_4	324	4.31	π–π*	325	4.32	π–π*
		391	3.06	n–π	427 sh	2.95	n–π
1e	4-$CH_3OC_6H_4$	320	4.29	π–π*	322	3.98	π–π*
		385	3.23	n–π	422	2.56	n–π
1f	4-$CH_3C_6H_4$	321	4.34	π–π*	322	4.20	π–π*
		391	3.13	n–π	423	3.00	n–π

NMR-spectra. Important information on the electron distribution and conformation of the 2-substituted five-membered heterocyclic compounds is often acquired with the aid of NMR spectroscopy. The chemical shifts of the ^{1}H and ^{13}C nuclei in the investigated thioamides **1a–f** are given in Table 5. The numbering of the atoms is given in Scheme 4.

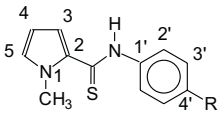
Scheme 4



1a



1b



(**1c**) R = H; (**1d**) R = Cl; (**1e**) R = OCH_3; (**1f**) R = CH_3

It is known that the chemical shifts of protons and carbon atoms at the positions 3 and 5 are particularly sensitive to the nature of the 2-substituents [15]. As far as the position 5 is concerned, the differences between the values Δδ(H5-H4) and Δδ(C5-C4) observed with **1a–f** and those known for the unsubstituted pyrrole may be rationalized by the mesomeric effect of the electron-accepting thioamide group (Table 6). These results show that, in spite of non-planarity of the molecules, an electron conjugation takes place between the pyrrole ring and the thioamide group. On the other hand, the observed differences Δδ(C5-C4) and Δδ(H5-H4) are not affected by the *para*-substituents in the *N*-phenyl ring in a manner, which might be related to their electronic properties. This confirms the non-planarity of the molecule, suggested by the UV-measurements.

The differences in the chemical shifts of proton and carbon atoms at the positions 3 and 4 are greater than in the unsubstituted pyrrole (Table 5). The highest value of Δδ(H3-H4) was observed for the compound with the *N*-(4-methoxyphenyl) substituent. Higher values of the Δδ(C3-C4) differences characterize the aromatically *N*-substituted thioamides but the electronic properties of the substituents in the phenyl ring seem to be of no effect.

Table 5. ^{1}H, ^{13}C chemical shift assignments for compounds **1a–f** in $CDCl_3$.

Comp.	T		Position											Others
			2	3	4	5	C=S	1-Me	NH	1′	2′	3′	4′	
1a	295	H	–	6.40	6.08	6.76	–	4.00	7.47	3.27				
		C	134.06	109.46	107.09	129.35	188.77	37.00	–	32.27				
1b	295	H	–	6.35	6.06	6.75	–	3.98	7.23	4.49	2.13 1.26	1.76 1.46	1.68 1.26	
		C	134.60	109.23	107.02	129.17	186.24	36.91	–	53.04	31.86	24.68	25.52	
1c	295	H	–	6.57	6.12	6.82	–	3.99	8.84	–	7.62	7.40	7.23	
		C	134.88	110.58	107.43	130.28	187.71	37.19	–	138.75	123.86	128.98	126.48	
	250	H	–	6.62	6.16	6.88	–	4.03	8.93	–	7.66	7.45	7.30	
		C	134.60	110.35	107.25	130.62	186.12	37.45	–	138.15	124.11	128.98	126.65	
	230	H	–	6.65	6.18	6.91	–	4.03	8.97	–	7.65	7.47	7.33	
		C	134.33	110.51	107.24	130.77	186.00	37.59	–	137.88	124.14	128.99	126.75	
1d	295	H	–	6.58	6.13	6.84	–	4.00	8.78	–	7.58	7.36	–	
		C	134.70	110.64	107.50	129.05	186.67	37.31	–	137.21	125.22	129.05	131.29	
1e	295	H	–	6.63	6.12	6.81	–	4.00	8.78	–	7.50	6.93	–	3.82
		C	134.71	110.19	107.35	130.10	186.76	37.20	–	131.64	125.93	114.12	157.96	55.47
1f	295	H	–	6.56	6.12	6.81	–	4.00	8.80	–	7.46	7.20	–	2.36
		C	134.77	110.47	107.38	130.16	186.73	37.17	–	136.49	124.05	129.55	136.17	21.44

Table 6. The values of Δδ(H3-H4), Δδ(H5-H4), Δδ(C3-C4), Δδ(C5-C4) [ppm] in the thioamides **1a–f**.

Compound	T(K)	Δδ(H3-H4)	Δδ(H5-H4)	Δδ(C3-C4)	Δδ(C5-C4)
pyrrole [15]	295	0	0.46	0	11
1a	295	0.32	0.68	2.37	22.26
1b	295	0.29	0.69	2.21	23.53
1c	295	0.45	0.70	3.15	22.85
	250	0.46	0.72	3.07	23.34
	230	0.47	0.73	3.27	23.53
1d	295	0.45	0.71	3.14	21.55
1e	295	0.51	0.69	2.84	22.75
1f	295	0.44	0.69	3.09	22.78

The mesomeric effects of the pyrrole ring-attached substituents upon the chemical shifts of the carbon atoms and protons at the positions 3 and 5 should be comparable. Moreover, the chemical shifts of the atoms at the position 3 may be affected by some inductive interactions and by substituent anisotropy. When the Δδ(C3-C4) and Δδ(C5-C4) values of **1a–f** are compared with the corresponding values of the unsubstituted pyrrole, the observed deshielding of the C3 carbon atoms is greater than that which might be expected to be due to the action of the mesomeric effect only. When comparing the corresponding data regarding the C3 atoms, the converse is the case. In the furane-derived thioamides [6], which were considered to have a free rotation about the C–C bond, the Δδ(H3-H4) difference was ~0.9 ppm; it was presumed to be due to the anisotropic effect of the sulfur atom. Much lower values are noted in the **1a**–**f** series presumably because the sulfur atom is sufficiently distant from H3. Minor changes which affected the ^{1}H and ^{13}C chemical shifts while changing temperature suggested some dynamics of the molecules but did not indicate the possibility of any rotation about the C–C bond. Since anisotropy of the phenyl ring had no effect upon H3 it is legitimate to assign the *trans*(*Z)* conformation to **1a**–**f**. This is consistent with the conclusions drawn from the dipole moment measurements. Some deshielding of H3 may be explained in terms of the effect of the nitrogen atom lone pair. The ^{1}H-^{1}H NOESY NMR technique has been recently found to be useful tool for determining the configuration and conformation of 3-acylmethylidene-2,2,3-trisubstituted-2,3-dihydrofurans [16] and 2-acylmethylidene-1,3-thiazolindin-4-ones [17]. In case of the thioamides **1a**–**f**, the ^{1}H-^{1}H NOESY experiments gave no unequivocal proof of the conformation. Nevertheless, analysis of the chemical shifts supports the *trans(Z)-s-cis* conformation of **1a–f**.

Concluding remarks: The dipole moments measurements and the spectroscopic studies of thioamides derived from 1-methyl-2-pyrrolecarboxylic acids show that the molecules are non-planar and exist as the *trans*(Z)-s-*trans* conformers. The results of our present and earlier investigations reveal that the conformation of the secondary thioamides of 2-thiophene-, 2-furane-, and 1-methyl-2-pyrrolecarboxylic acids, both in a solution and in the solid state, strongly depends on the nature of the heterocyclic core; both the electronic and steric effect are of importance.

EXPERIMENTAL

Melting points were determined on a digital apparatus Electrothermal model IA9300 and are uncorrected. The IR spectra were taken with a Specord M-80 instrument in a chloroform solution (0.18 mole/dcm^3). A Specord M-40 ultraviolet spectrophotometer was used for measurements carried out in methanol or cyclohexane (1×10^{-4} mole/cm^3). The ^{1}H- and ^{13}C – NMR spectroscopic measurements were performed on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ with TMS as internal standard. Electric permeability was measured at 2 MHz with a DIPOLMETER DMO1 set working with the sensitivity of $\Delta\varepsilon/\varepsilon = 4\times10^{-5}$. Density was determined pycnometrically at 25±0.05°C with the accuracy of $\pm1\times10^{-4}$ g/cm^3. Benzene was purified by a standard method. Purity and molecular determinations were carried out by gas chromatography-mass spectrometry (GC/MS) on a Hewlett-Packard instrument model HP 6890 equipped with a mass detector HP5973. The results of elemental analyses (C,H,S) data were within ± 0.2% of the calculated values.

1-Methyl-2-pyrrolecarbothioamides (1a–f). General procedure: A solution of 0.82 g (0.87 mL, 0.012 mole) of 1-methylpyrrole and 1.16 g (1.5 mL, 0.01 mole) of TMEDA in 30 mL of dry, freshly distilled (with $LiAlH_4$) THF was placed in a flask equipped with a stirrer, a moisture-protected reflux condenser, a thermometer, and an inert gas inlet. To the solution, slowly bubbled through with dry argon and stirred, a solution of 1.6 M of *n*-butyllithium in hexane (0.012 mole) was added dropwise. The reaction mixture was refluxed for 2 hrs and cooled to 0°C. A solution of 0.01 mole of the appropriate isothiocyanate in 20 mL of dry THF was then added dropwise at 0–5°C. After 30 min, the mixture was treated under vigorous stirring and cooling with a saturated aqueous solution of NH_4Cl. The product was extracted with ethyl acetate, the organic layer was washed with water and dried with $MgSO_4$, and the solvent was removed by distillation under reduced pressure. The crude product was purified by chromatography on silica gel with chloroform as the eluent. The solid left after evaporation of the chloroform was recrystallized from an appropriate solvent. The yields and melting points are collected in Table 1.

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