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^{1}H NMR EVIDENCE OF C–H---O, C–H---N AND C–H---Cl HYDROGEN BONDS IN NEW THIAZOLE DERIVATIVES

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Abstract- A comparative study of the chemical shift differences observed in the ^{1}H NMR spectra of a series of fifteen new polysubstituted 4-aryl- and 2,4-diaryl thiazoles permitted us to establish two groups of rotamers. Some present paramagnetic shifts due to intramolecular weak hydrogen bonding and this was confirmed by experiments "at infinite dilution", single crystal X-Ray studies, NOESY and HMBC experiments.

INTRODUCTION

We have prepared fifteen new polysubstituted 4-arylthiazoles, and established their chemical shifts in their ^{1}H NMR spectra ($CDCl_3$, 300 MHz).[1,2] The assignments were made starting from molecules in which the assignments were unequivocal and then progressed to more complex thiazole derivatives, using this information and the data obtained from model molecules specially prepared for this purpose. These assignments were confirmed by 2D experiments.[1,2]

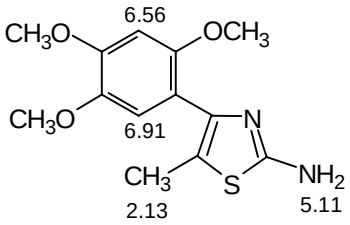
In the progress of this study we observed significant chemical shift differences which could not be attributed to substituents since changes in chemical shifts were observed in distant atoms as we shall see. These effects could be explained by the preference of different rotamers due to intramolecular weak hydrogen-bonding.

These are significant findings since the importance of hydrogen-bonding has been emphasized in a Review and in a book both recently published.[3,4]

RESULTS AND DISCUSSION

In the 2-amino-4-arylthiazole (**1**) the ^{1}H NMR chemical shifts are easily assigned and this allow us to establish the position of the thiazolic hydrogen in compound (**2**) with the aid of model molecule (**3**) for H-3. We have also observed that the signal of the thiazolic proton shows *ringing* at 90 MHz or is

elongated at 300 MHz, this being also the case in the spectrum of **2**. The *ringing* can be accounted for by the presence of a near heteroatom (in this case sulfur in group H–C–S).



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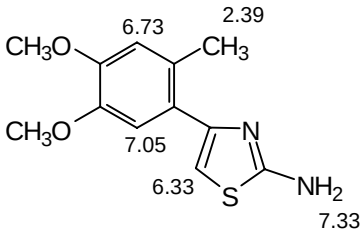

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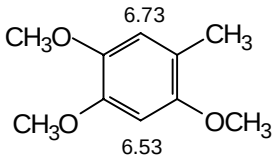

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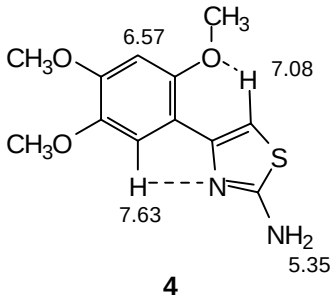
When we prepared 2-amino-4-(2,4,5-trimethoxyphenyl)thiazole (**4**), we observed two significant downfield displacements: to 7.63 for H-6 (benzene ring) and 7.08 ppm for the thiazolic proton (as compared to **1** and **2**). Since both compounds (**1**) and (**4**) have the same trimethoxyphenyl ring, the paramagnetic shifts can be explained by the preference of a different rotamer containing *weak* hydrogen bonds (C–H---N and C–H---O), compare.[5-8] The 0.72 and 0.75 ppm shifts are discreet compared to those observed in strong or classical hydrogen bonds but are adequate for weak or non-classical hydrogen bonds. This was also observed in compound (**5**), in which a chlorine atom replaces a methoxy group, now having a C–H---Cl bond (a similar case is discussed below). For the chemical shift of the proton between methoxy and chlorine, see the model compound (**6**).



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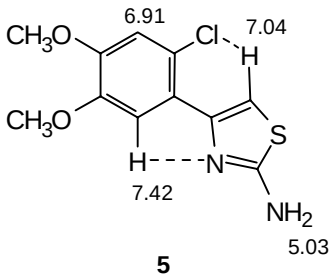

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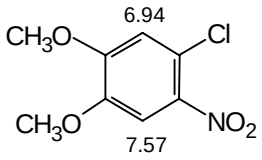

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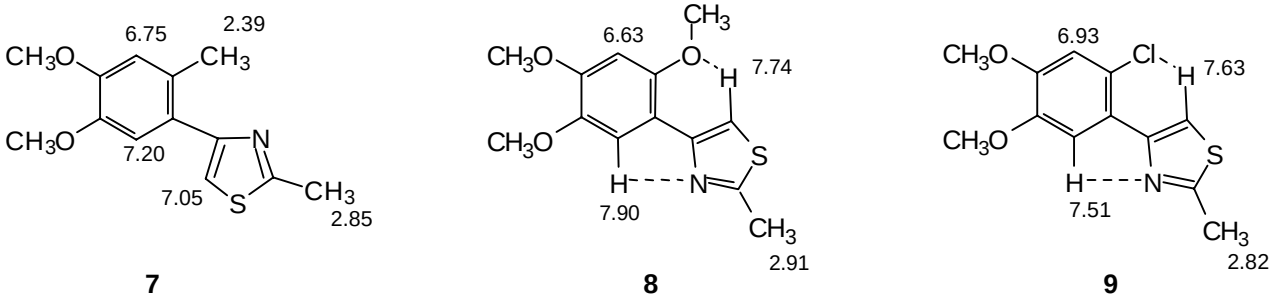
Molecular models of the 5-methylthiazole derivative (**1**) show that there is steric hindrance between the methyl and the methoxy in C-2 in a rotamer of type (**4**), thus favoring rotamer (**1**) and this can not form hydrogen bonds.

The chemical shifts of the thiazolic protons in these 2-aminothiazoles are found upfield due to the mesomeric effect of the amino group at C-5. A comparison can be made with the following 2-methyl compounds.

In addition to the four above mentioned aminothiazoles, we prepared five *2-methyl*-4-arylthiazole derivatives (**7**-**11**). In the ^{1}H NMR spectrum of compound (**7**), the two thiazolic signals show *ringing* at 90 MHz, the methyl group being downfield from the benzenic one due to the mesomeric effect of the imino group. The assignments for the benzene protons were made with the aid of compound (**3**) for H-3.
In the thiazole derivative (**8**), the presence of a third methoxy group favors a different rotamer due to the formation of two weak hydrogen bonds. This accounts for the downfield shifts of 0.7 ppm presented by H-6 and the thiazolic proton (with *ringing*). This effect was also observed in the chloroarylthiazole (**9**). Since in this case the shifts were of smaller magnitude, we determined the single crystal X-Ray structure of **9**. (Figure 1.) This study showed the presence of two hydrogen bonds and gave the *intramolecular contacts for hydrogen bonds*. The bond lengths are 2.47 Å (H---Cl) and 2.36 Å (H---N) and are *shorter* than those described by Cambridge crystallographers in other compounds with similar hydrogen bonds.[5] This study showed also that the molecule is planar. (Figure 2.) The bigger chlorine atom in compound (**9**) does not fit as well as the oxygen atom in thiazole (**8**) and this accounts for smaller paramagnetic shifts in the former. Moreover, the X-Ray structural determination enabled us to establish the preferred rotational isomer in the compounds which present *greater* paramagnetic shifts.



7 **8** **9**

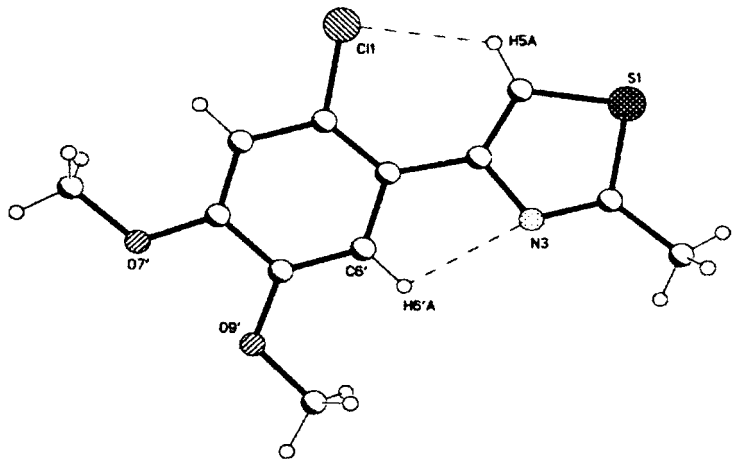


Figure 1. Molecular structure of 2-methyl-4-(2-chloro-4,5-dimethoxyphenyl)thiazole (**9**) obtained by single-crystal X-Ray diffraction and showing two hydrogen bonds.

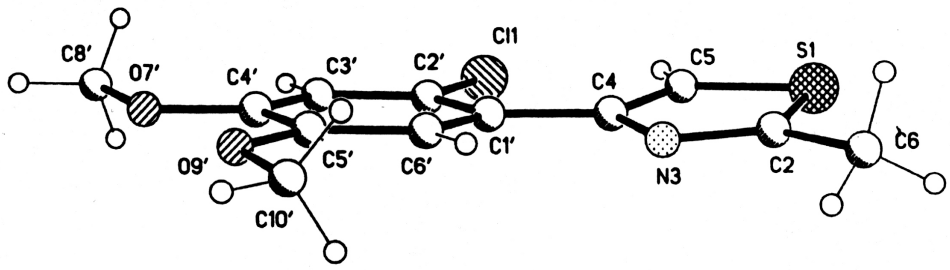
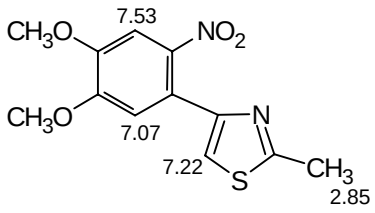


Figure 2. Molecular structure of 2-methyl-4-(2-chloro-4,5-dimethoxyphenyl)thiazole (**9**) obtained by single-crystal X-Ray diffraction and showing the planar structure of the molecule.

When a group at C-2 in the benzene ring can not form a hydrogen-bond, normal shifts for H-6 and the thiazolic proton are observed. This is also the case in the 2-nitroarylthiazoles (**10**) and (**11**). The assignment of the 7.53 ppm singlet in compound (**10**) is in accord with the model molecule (**12**) and the 7.22 ppm signal presents *ringing* at 90 MHz. In the dinitro compound (**11**) we found for H-3 a similar chemical shift as in the cyanonitroveratrole (**13**).



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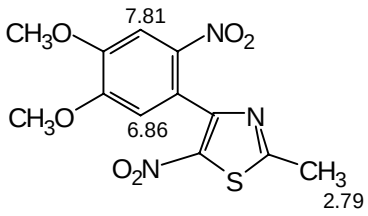

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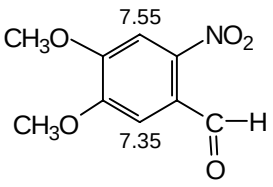

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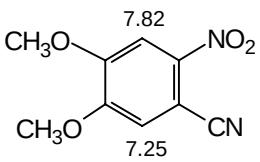

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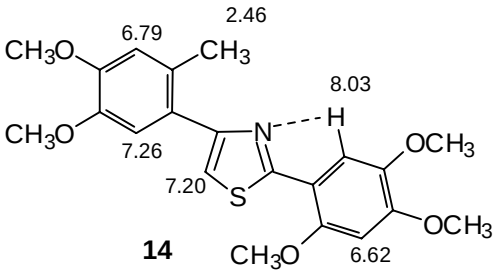
Finally, we prepared six diarylthiazoles (**14**-**19**). The spectra of these compounds present five aromatic singlets. However, we could assign each observed value since we had knowledge of the chemical shifts previously found in the above mentioned 4-arylthiazoles and *only one signal has ringing* at 90 MHz

(thiazole proton). Compound (**14**) presents two close values: 7.20 and 7.26 ppm. However, the first shows *ringing* at 90 MHz. For the chemical shifts in the 4-aryl group compare to compound (**7**). The complete assignations were confirmed by HMBC and NOESY experiments. Observe the downfield shift of 0.61 ppm for H-6 in the 2-aryl group (at 8.03 ppm), compared to the value of 7.42 ppm found in compound (**21**) having a methylketone group in *ortho*. The chemical shifts in the remaining compounds were assigned in similar manner. The number of the thiazole derivative is given and in parentheses the model compounds used: **15**(**8**, **14**); **16**(**9**, **14**); **17**(**10**, **20**); **18**(**8**, **21**). The assignments in the 2-dimethoxyphenylthiazole derivative (**19**) were no problem since this molecule contains a ring which arises an ABX spin system.



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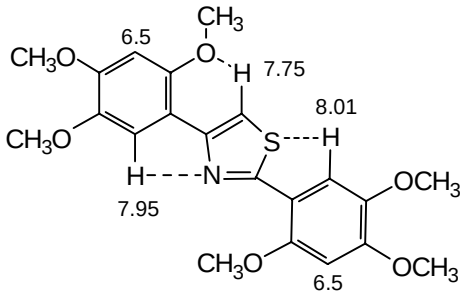

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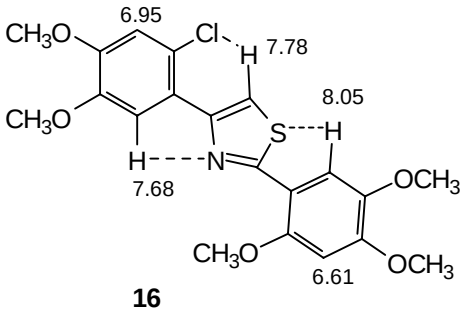

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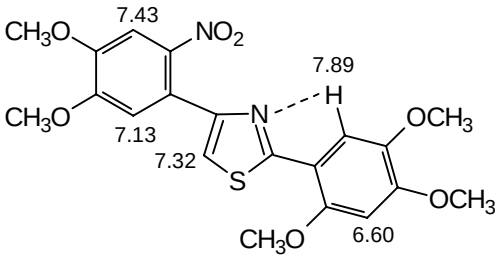

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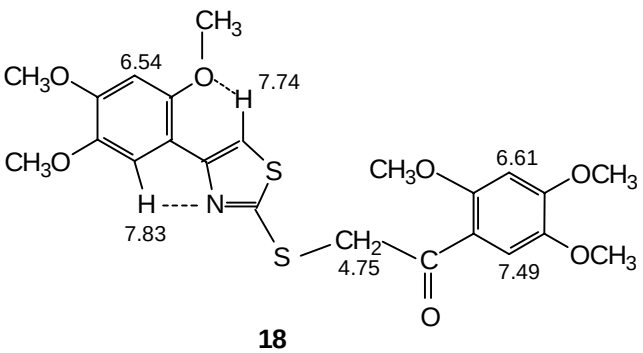

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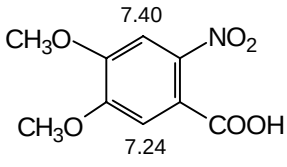

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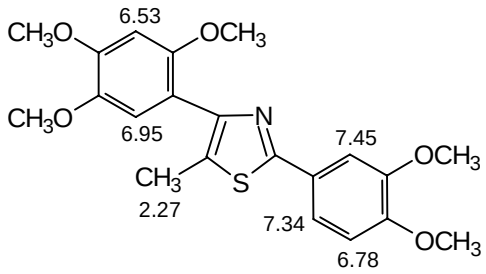

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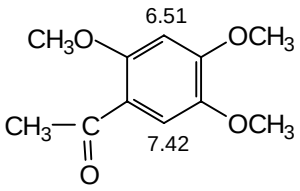

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CONCLUSIONS

The ^{1}H NMR assignments were made starting with small molecules (unequivocal cases) and then progressing to more complex molecules, using model compounds for spectroscopic comparison. Finally, the assignations were confirmed by 2 D experiments.

The significant paramagnetic shifts observed in some of these thiazole derivatives can not be explained only by the ordinary effects of the substituents. For instance, when an additional methoxy group was present at C-2 in the benzene ring (compound **8**) the expected upfield shift of the *ortho* hydrogen was observed, but in addition two paramagnetic shifts were also present: one in *meta* position and the other in the thiazole ring. These two displacements can be accounted for by the preference of a different rotamer involving the formation of two *weak* hydrogen bonds. This was confirmed in eight other compounds which can form also hydrogen bonds. On the other hand, the thiazole derivatives that can not form hydrogen bonds due to steric hindrance (having a thiazolic methyl at C-5), compounds (**1**) and (**19**), or with a methyl or a nitro group at C-2 (benzene ring), instead of a chlorine atom or a methoxy group, present normal chemical shifts in their spectra, compounds (**2**, **7**, **10**, **11**, **14** and **17**).

X-Ray crystallography has proved that *even* the thiazole derivative which showed *lesser* downfield shifts *does form* two hydrogen bonds as found in Figure 1 and in the tables. The pertinent atomic distances are even *shorter* than the previously described ones for C–H---Y bonds.[5] So, there is no problem with the compounds which show *greater* paramagnetic shifts in their spectra. These displacements are of course smaller than those observed in strong or classical hydrogen bonds but we are not dealing with this type of bonds. Finally, variances of the chemical shifts were not observed in experiments “at infinite dilution”, thus proving that the weak hydrogen bonds here involved are *intramolecular*.

On the basis of these results we could assert which rotamer is preferred in each of the fifteen new thiazole derivatives synthesized and studied by us. These novel findings in the recent field of weak hydrogen bonding can be extended to other substituted 2-aryl- and/or 4-arylthiazoles and are summarized in Table 1.

Table 1. Significant chemical shifts in the ^{1}H NMR spectra of the 4-arylthiazoles ($CDCl_3$, 300 MHz).

A) 2-Aminothiazoles *without* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
1	6.91	no H
2	7.05	6.33

B) 2-Aminothiazoles *with* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
4	7.63	7.08
5	7.42	7.04

C) 2-Methylthiazoles *without* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
7	7.20	7.05
10	7.07	7.22
11	6.86	no H

D) 2-Methylthiazoles *with* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
8	7.90	7.74
9	7.51	7.63

E) 2,4-Diarylthiazoles *without* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
14	7.26	7.20
17	7.13	7.32
19	6.95	no H

F) 2,4-Diarylthiazoles *with* weak hydrogen bonds.		
Compound	**H-6**	**Thiazolic proton**
15	7.95	7.75
16	7.68	7.78
18	7.83	7.74

EXPERIMENTAL

Compounds

The thiazole derivatives mentioned in this work were prepared recently in this laboratory[1,2] by known general methods.[9]

The tetrasubstituted benzene derivatives of the veratrole series used for spectroscopic comparison were also prepared by us.[1,2] So there was no need of data from other sources.

2-Amino-4-(2,4,5-trimethoxyphenyl)-5-methylthiazole (**1**), mp 171-172ºC ($CHCl_3$-EtOH); IR (KBr) 3400 and 3295 cm^{-1} (free NH_2) and 3115 cm^{-1} (associated NH_2).

2-Amino-4-(2-methyl-4,5-dimethoxyphenyl)thiazole (**2**), mp 203-204ºC (EtOH); IR (KBr) 3393 (free NH_2) and 3114 cm^{-1} (associated NH_2).

2,4,5-Trimethoxytoluene (**3**), mp 50-50.5ºC (pentane).

2-Amino-4-(2,4,5-trimethoxyphenyl)thiazole (**4**), mp 174.5-176.5ºC (EtOH); IR (KBr) 3428 (NH_2, asym. st.) and 3333 cm^{-1} (NH_2, sym. st.).

2-Amino-4-(2-chloro-4,5dimethoxyphenyl)thiazole (**5**), mp 200-200.5ºC (EtOH); IR (KBr) 3390 (free NH_2) and 3119 cm^{-1} (associated NH_2).

4-Chloro-5-nitroveratrole (**6**), mp 112-113ºC (MeOH); IR (KBr)1524 and 1508 cm^{-1} (NO_2, asym. st.), 1354 and 1334 cm^{-1} (NO_2, sym. st.).

2-Methyl-4-(2-methyl-4,5-dimethoxyphenyl)thiazole (**7**), mp 72-72.5ºC (MeOH-H_2O); IR (KBr) 3140 cm^{-1} (CH in thiazole ring).[10]

2-Methyl-4-(2,4,5-trimethoxyphenyl)thiazole (**8**), mp 113-115ºC (MeOH); IR (KBr) 3160 cm^{-1} (CH in thiazole ring).

2-Methyl-4-(2-chloro-4,5-dimethoxyphenyl)thiazole (**9**), mp 128.5-129.5ºC (MeOH); IR (KBr) 3144 cm^{-1} (CH in thiazole ring).

2-Methyl-4-(2-nitro-4,5-dimethoxyphenyl)thiazole (**10**), mp 106-106.5ºC (hexane); IR (KBr) 3091 cm^{-1} (CH in thiazole ring).

2-Methyl-4-(2-nitro-4,5-dimethoxyphenyl)-5-nitrothiazole (**11**), mp 139.5-140ºC (ether); IR (KBr) 1510 cm^{-1} (NO_2, asym. st.) and 1333 cm^{-1} (NO_2, sym. st.).

6-Nitroveratraldehyde (**12**), mp 133-134ºC (EtOH); IR (KBr) 1675 cm^{-1} (CO).

6-Nitroveratronitrile (**13**), mp 167-167.5ºC (EtOH); IR (KBr) 2228 cm^{-1} (CN).

2-(2,4,5-Trimethoxyphenyl)-4-(2-methyl-4,5-dimethoxyphenyl)thiazole (**14**), mp 144-145ºC (CH_2Cl_2-Et_2O); IR (KBr) 3132 cm^{-1} (CH in thiazole ring).

2,4-Bis(2,4,5-trimethoxyphenyl)thiazole (**15**), mp 175-176ºC (CH_2Cl_2-MeOH); IR (KBr) 3104 cm^{-1} (CH in thiazole ring).

2-(2,4,5-Trimethoxyphenyl)-4-(2chloro-4,5-dimethoxyphenyl)thiazole (**16**), mp 178-179ºC (CH_2Cl_2-MeOH); IR (KBr) 3136 cm^{-1} (CH in thiazole ring).

2-(2,4,5-Trimethoxyphenyl)-4-(2-nitro-4,5-dimethoxyphenyl)thiazole (**17**), mp 199-200ºC (CH_2Cl_2-Et_2O); IR (KBr) 3080 cm^{-1} (CH in thiazole ring).

2-(2,4,5-Trimethoxyphenacylthio)-4-(2,4,5-trimethoxyphenyl)thiazole (**18**), mp 151-153ºC (CH_2Cl_2-EtOH); IR (KBr) 3137 cm^{-1} (CH in C=CH–S group) and 1643 cm^{-1} (CO in $-S-CH_2-C=O$)[11].

2-(3,4-Dimethoxyphenyl)-4-(2,4,5-trimethoxyphenyl)-5-methylthiazole (**19**), mp 137-138ºC (MeOH).

6-Nitroveratric acid (**20**), mp 197-198ºC (EtOH-H_2O).

2,4,5-Trimethoxyacetophenone (**21**), mp 95-96ºC (Et_2O); IR (KBr) 1652 cm^{-1} (CO).

The molecular weights of all compounds were confirmed by Mass Spectrometry. Their fragmentation patterns were published by us.[12]

The single crystal X-Ray diffraction study of 2-methyl-4-(2-chloro-4,5-dimethoxyphenyl)thiazole (**9**), Figures 1 and 2, gave the following data:

Crystal Data: empirical formula, $C_{12}H_{12}NO_2ClS$; color, colorless; habit, irregular; crystal size, 0.8 x 0.4 x 0.1 mm^3; crystal system, monoclinic; space group, $P2_1/c$; unit cell dimensions, a = 7.3379 (9) b = 19.242 (2) c = 8.7798 (8) Å β = 93.738 (9)º; volume, 1237.1 (2) $Å^3$; Z, 4; formula weight, 269.74; density (calc.), 1.448 $g.cm^{-3}$; absorption coefficient, 0.466 mm^{-1}; and *F*(000), 560. *Data Collection*: diffractometer used, Siemens P4/PC; radiation, Mo-K_α(λ = 0.71073 Å); temperature, 298 K; 2θ range, 3-50º; reflections collected, 2900; independent reflections, 2183 (R_{int} = 2.15%); reflections with $F_o>4\sigma(F_o)$, 1701; $<I/\sigma(I)>$(all data), 16.73; absorption correction 12 ψ-scans with χ close to 90º; and transmission factors, min = 0.609, max = 0.719. *Solution and refinement*: extinction correction *x* = 0.012 (2) where $F_c^* = kF_c[1 + 0.001\, xF_c^2\lambda^3/\mathrm{Sin}(2\theta)]^{-1/4}$; hydrogen atoms: riding model, fixed isotropic *U*; final *R* indices ($I>2\sigma(I)$) [(a)], R_1 = 4.01%, wR_2 = 10.46 %; final *R* indices (all data), R_1 = 5.55%, wR_2 = 11.67%; goodness-of-fit, 1.031; largest and mean Δ/σ, 0.000, 0.000; data-to-parameters ratio, 2183/155; largest difference peak, 0.338 $e.Å^{-3}$; and largest difference hole, -0.312 $e.Å^{-3}$.

^{1}H NMR measurements at 90 MHz were carried out at ambient temperature with a Varian 390-90 MHz spectrometer. $CDCl_3$ was used as solvent and TMS as reference. No chemical shifts are given and these spectra were used only to observe the *ringing* of the thiazole signals.

NMR measurements at 300 MHz were carried also at ambient temperature using a Varian Unity Inova 300 pulsed Fourier transform spectrometer operating at 300.2 MHz for ^{1}H. $CDCl_3$ was used as solvent and internal lock. Chemical shifts were referenced to TMS (0.00 ppm).

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