A Quantitative Study of Substituent Effects on Oxidative Cyclization of Some 2-Methylsubstituted Aldehydes. Thiosemicarbazones Induced by Ferric Chloride

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Dedicated to the memory of Professor Nicholas Alexandrou

In order to gain further mechanistical information about the cyclization of thiosemicarbazones and thiosemicarbazone-type substrates induced by metallic salts as oxidizing agents, we performed the synthesis of substrates **1a-s** and a kinetic study of the oxidative cyclization of **1** to 5-imino-Δ^2-1,3,4-thiadiazole **2** and 1,2,4-triazoline-5-thione **3** derivatives induced by methanolic ferric chloride solutions. The results of cyclization were compared to those of corresponding semicarbazones. The kinetic data were analyzed by means of the Hammett's equation and ρ values discussed.

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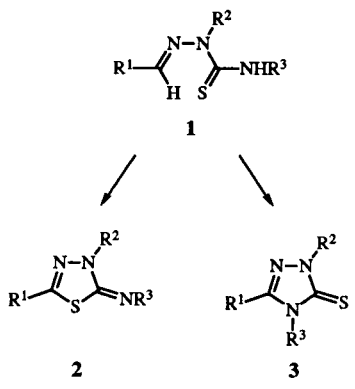
Introduction.

Recently unsymmetrical ureas have been found useful as cholinesterase [1] and as peptidase [2] inhibitors. Also the semi- and thiosemicarbazone fragments, which really have already been considered [3] as peptide isosteres, could be new classes of urea peptide mimetics. The possible biological properties of semi- and thiosemicarbazone derivatives make the study of reactivity of these compounds attractive.

Aldehyde semi- and thiosemicarbazones are well known and useful synthons for the synthesis of five- and six membered heterocyclic compounds [4]. The formation of six-membered rings is, of course, possible only if the aldehydic residue contains a group C=X or a carbon-halogen single bond conjugated with the carbon-nitrogen double bond. The regiochemistry of the above cyclization reaction depends strictly on conditions adopted for the reaction as well as the structure of starting substrate. As far as the former are concerned, it can be remembered, for example, that the 2-methyl-4-phenylthiosemicarbazone of glyoxl methyl ester gave a six membered triazine ring for irradiation [5] and a five membered thiadiazole derivative for oxidation with ferric chloride solutions [4a].

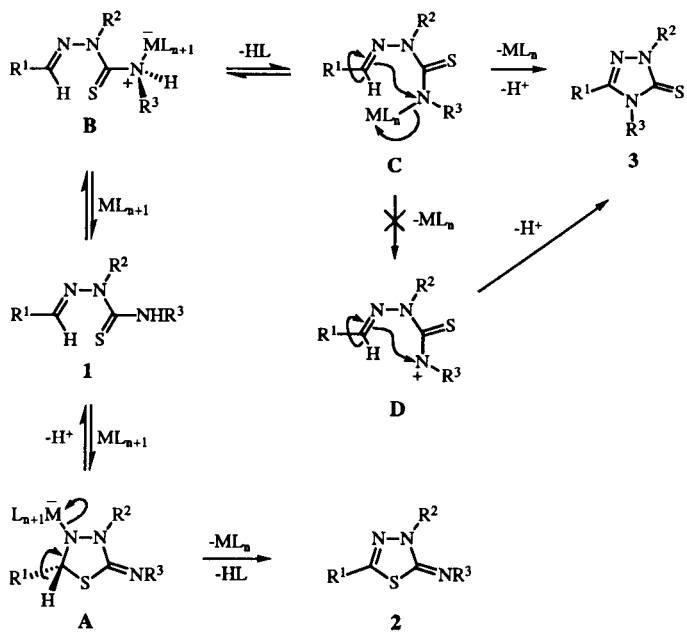
Scheme 1



As far as the structure of starting substrate is concerned, in a previous paper [4a], we have shown as the thiosemicarbazone structure affects the route of cyclization promoted by ethanolic ferric chloride solutions. In fact, from aldehyde thiosemicarbazones **1** (Scheme 1) only 5-imino-Δ^2-1,3,4-thiadiazole **2** derivatives coming from the sulphur intramolecular attack were detected when the nitrogen atom N-2 of the thiosemicarbazone chain was unsubstituted (in **1** R^2 = H) or when the electron density of the carbon-nitrogen double bond was lowered by the effect of a R^1 strong electron-withdrawing group. The nitrogen intramolecular attack, with formation of 1,2,4-triazoline-5-thione **3** derivatives, became competitive with the sulphur one when a substituent was present on N-2 and R^1 was an alkyl or aryl group.

On the grounds of the results obtained we proposed [4a] a mechanism (Scheme 2) for the oxidative cyclization of

Scheme 2



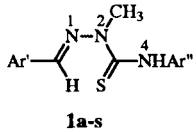
aldehyde thiosemicarbazones.

For thiosemicarbazones bearing a methyl group on the N-2 nitrogen atom two different pathways result in the triazoline and thiadiazoline rings. Formation of triazoline derivatives **3** involves: (i) reversible electrophilic attack of the metal atom on the N(4) nitrogen atom to give the salt **B**; (ii) reversible deprotonation of the species **B**; (iii) concerted rupture of M-N(4) metal-nitrogen bond and electrophilic attack of the nitrogen atom N(4) to the C=N double bond. The latter step is preferible to two consecutive steps consisting in heterolytic rupture of the M-N(4) metal-nitrogen bond of the species **C** with formation of a nitrogen electrophilic cation **D** followed by cyclization due to an electrophilic attack of the nitrogen cation **D** on the carbon-nitrogen double bond. Formation of the thiadiazoline derivatives **2** occurs through the cyclic form **A**. Rupture of both nitrogen-metal and carbon-hydrogen bonds gives thiadiazoline derivatives **2**. Formation of **A** by a reversible nucleophilic intramolecular sulphur attack catalyzed by protic or Lewis acids is a well known process for thiosemicarbazones [4a,6].

In order to gain further information on validity of the mechanism proposed, and to provide deeper insight, we report herein a quantitative study of substituent effect on the oxidative cyclization of substrates **1a-s** induced by alcoholic ferric chloride solutions. Kinetic measurements were carried out at 25°, the reaction advancement was followed by hplc as described in the experimental.

The 2-methyl-4-phenylthiosemicarbazone of benzaldehyde (**1k**) was choosen as the archetype substrate for the present study. Substitution on phenyl bonded to the imino moiety allowed a variation of the carbon-nitrogen double bond order (substrates **1a-k**), whereas substitution on phenyl attached to the N-4 nitrogen atom allowed an electron density variation on the N-4 nitrogen atom (substrates **1k-s**). The substituents used ranged from the strong electron-withdrawing nitro group to the strong electron-donating dimethylamino group.

Scheme 3



1a-s

Compound	Ar'	Ar"
a	*p*-$Me_2NC_6H_4$	C_6H_5
b	*p*-$MeOC_6H_4$	C_6H_5
c	*p*-MeC_6H_4	C_6H_5
d	*p*-ClC_6H_4	C_6H_5
e	*p*-BrC_6H_4	C_6H_5
f	*m*-ClC_6H_4	C_6H_5
g	*m*-BrC_6H_4	C_6H_5
h	*p*-$CF_3C_6H_4$	C_6H_5
i	*p*-CNC_6H_4	C_6H_5
j	*p*-$NO_2C_6H_4$	C_6H_5
k	C_6H_5	C_6H_5
l	C_6H_5	*p*-$MeOC_6H_4$
m	C_6H_5	*p*-MeC_6H_4
n	C_6H_5	*m*-MeC_6H_4
o	C_6H_5	*p*-ClC_6H_4
p	C_6H_5	*p*-BrC_6H_4
q	C_6H_5	*m*-ClC_6H_4
r	C_6H_5	*m*-BrC_6H_4
s	C_6H_5	*p*-$NO_2C_6H_4$

Results and Discussion.

The thiosemicarbazones **1a-s** treated with boiling ethanolic ferric chloride hexahydrate solutions gave the corresponding **2a-s** and **3a-s** derivatives. In Table 1 are reported reaction times and yields in **2a-s** and **3a-s** for the above cyclization.

In Table 2 are reported the second order kinetic constants for disappearance of thiosemicarbazones **1a-g** and **1k-r** together with the kinetic constants for formation of the corresponding triazoline and thiadiazoline derivatives. For compounds **1h-j** and **1s** we were not able to determine kinetic constants because they reacted very slowly. Interconversion between **2** and **3** was not observed under the conditions adopted for the cyclization.

As it can be seen from the data reported in Table 1, the regiochemistry of the reaction studied was not modified by substituents on the phenyl bonded to N-4. In fact, for thiosemicarbazones **1k-s** the nitrogen intramolecular attack always predominated over the sulphur attack. In contrast, substituents on the phenyl bonded to the carbon-nitrogen double bond were able to modify the regiochemistry of the cyclization. In fact, for the thiosemicarbazones **1h-j** with strong electron-withdrawing substituents (trifluoromethyl, cyano and nitro groups) the sulphur

Table 1

Yields for the Reation with $FeCl_3 \cdot 6H_2O$ in Boiling Ethanol [a]

Compound	η_N%	η_S%	time (minutes)
1a	85.5	8.5	5
1b	86.4	7.5	5
1c	78.6	12.7	10
1d	59.2	21.5	20
1e	57.7	37.5	20
1f	55.1	40.3	30
1g	51.9	27.2	30
1h	34.9	50.5	60
1i	—	48 [b]	90
1j	—	54 [c]	180
1k	79.3	17.9	10
1l	74.1	17.0	10
1m	53.2	12.7	10
1n	70.3	20.5	10
1o	64.8	26.8	20
1p	67.0	18.0	20
1q	67.8	26.1	30
1r	63.9	24.1	30
1s	73.6	17.2	60

[a] Data accurate to within a ±5% indetermination. [b] 25% of the starting material was recovered unchanged. [c] 44% of the starting material was recovered unchanged.

intramolecular attack predominated over the nitrogen attack; the opposite behaviour was observed for **1a-g**. These results are in accord with those previously collected by us [4a] and they give a complete picture of the substituent effect on the regiochemistry of the cyclization studied. Moreover, the substituent effect observed seems to exclude the formation of a triazoline ring by a nucleophilic mechanism like that occurring in the semicarbazone derivatives [7]. In our opinion if formation of both thiadiazoline and triazoline derivatives came by nucleophilic attack of the sulphur and nitrogen atoms respectively, a small or even no variation of the relative composition in thiadiazoline and triazoline for the cyclization of thiosemicarbazones **1a-j** should be observed.

The kinetic data were collected (Table 2) in order to allow a deeper insight into the reaction. Although kinetic determinations were carried out under different conditions, *i.e.* methanol at 25° instead of boiling aqueous ethanol, the kinetic data confirmed the results reported in Table 1. Only for **1a** was a meaningful difference found between the results of the two determinations. This difference should be attributed to a particularly strong interaction between the substituent (dimethylamino) in **1a** and the solvent molecules. It is worthwhile to note that the oxidative cyclization of semicarbazones is greatly affected by small amounts of water [8]. As it can be seen from the data reported in Table 2, the reactivity of **1** measured as the disappearance of thiosemicarbazone decreased with decreasing electron-donating or electron-repelling and with increasing electron-withdrawing substituent effect. It is interesting to note that the substituent effect is qualitatively the same independent of which the two phenyl rings bear the substituents. Reactivity variations of the thiosemicarbazones **1a-s** were a consequence of reactivity variations in the same direction of both nitrogen and sulphur intramolecular attack as shown by k_N and k_S values (see Table 2). These stress that the nitrogen intramolecular attack is faster than the sulphur intramolecular attack for thiosemicarbazones **1b-g** and **1k-r**. An opposite trend is observed for **1h-j** considering data reported in Table 1 for compounds **1a-j**. Introduction of an electron-donating (dimethylamino group) or electron-repelling (methyl group) substituent on the phenyl ring bonded to the imino moiety caused as aforesaid an increase in reactivity. For nitrogen attack this effect can be explained as a consequence of both an increase in electron density on the carbon atom of the carbon-nitrogen double bond and a decrease of the carbon-nitrogen bond order [9] as the following resonance structure shows. The increase of electron density should favour electrophilic attack of the N(4) nitrogen atom on the carbon atom of the imino moiety and a decrease in bond order should allow for the nucleophilic and electrophilic centers to reach a better arrangement for a more favourable reactive interaction [10]. The same substituent effect was observed in the oxidation of 2-methyl-4-phenylsemicarbazone of substituted benzaldehydes to the corresponding 1,2,4-triazolin-5-ones [7] and in the cyclization of substituted *N*-benzohydroxamoyl-*N*-methylhydrazones to 3-aryl-1-methyl-5-phenyl-1,2,4-triazoles [12]. For the sulphur attack the above substituent effect could be the result of both a decrease of carbon-nitrogen bond order and an increase in cyclic form **A** of the thiosemicarbazones due to an increase in basicity of N(1) [13] (see above resonance structure) that favours the interaction with a metallic salt. It is worthwhile to emphasize that in acid medium thiosemicarbazones exist prevalently as salt of 2-imino-1,3,4-thiadiazoline [4a,6].

Table 2

Second Order Kinetic Constants for the Reaction with Anhydrous $FeCl_3$ in Methanol at 25°

Compound	k_R [a] x 10^3 ($M^{-1}s^{-1}$)	k_N [b] x 10^3 ($M^{-1}s^{-1}$)	k_S [c] x 10^3 ($M^{-1}s^{-1}$)
1a	118.6	86.5	31.7
1b	63.8	60.7	4.00
1c	25.0	24.0	3.07
1d	5.51	4.41	1.04
1f	3.98	3.15	0.58
1g	3.26	2.86	0.58
1k	20.3	17.3	2.42
1l	29.9	27.4	3.34
1m	27.3	25.1	3.16
1o	12.2	10.2	1.52
1p	9.98	7.83	1.11
1q	8.41	7.37	1.07
1r	8.83	7.66	1.05

[a] Second order kinetic constants for the disappearance of the substrates **1**. Data accurate to within a ±6%. [b] Second order kinetic constants for the formation of the triazolines **3**. Data accurate to within a ±5%. [c] Second order kinetic constants for the formation of the thiadiazolines **2**. Data accurate to within a ±8%.

As aforesaid an increase in reactivity is also observed for the introduction of an electron-donating (methoxyl group) or electron-repelling (methyl group) substituent on the phenyl ring bonded to N(4) nitrogen atom. On the grounds of the mechanism reported in Scheme 2 the increase of electron density on N(4) due to methyl and methoxyl groups should favour steps (i) and (iii) but it should have the opposite effect on step (ii). Experimental data seem to show that steps (i) and (iii) are affected by substituent effect more than step (ii). The increase of electron density on N(4) should also cause an increase in electron density then in the nucleophilicity of the sulphur atom, consequently the formation of thiosemicarbazone cyclic structure **A** should be easier and the oxidation to a thiodiazoline ring faster. In order to quantify the effect of substituents we have attempted to correlate the data reported in Table 2 with σ substituent constants [15] in terms of the Hammett's equation [16] obtaining the following satisfactory correlations:

$\log k_N = -1.80(0.04) - 2.07(0.11)\sigma$ r = 0.992 n = 7 (1)

$\log k_S = -2.86(0.06) - 0.80(0.08)\sigma^+$ r = 0.976 n = 7 (2)

for substitution on the phenyl group bonded to C=N double bond and

$\log k_N = -1.79(0.02) - 0.96(0.10)\sigma$ r = 0.976 n = 7 (3)

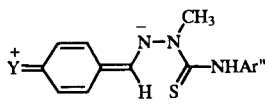
$\log k_S = -2.66(0.03) - 0.87(0.10)\sigma$ r = 0.967 n = 7 (4)

for substitution on the phenyl ring bonded to N(4) nitrogen atom.

The negative values calculated for the susceptibility constant ρ of the above correlations are consistent with the above mentioned substituent effects. It is interesting to note that although $k_N > k_S$ the |ρ| values for the nitrogen intramolecular attack (see eqns 1 and 3) are higher than the corresponding (see eqns 2 and 4) for the sulphur intramolecular attack, *i.e.* the reactivity-selectivity principle [17] is not followed. This seems to confirm that two different mechanisms must be operative for the *N*-attack and *S*-attack. The same result follows by small differences in the values of ρ_N and ρ_S which have been calculated for cyclization of thiosemicarbazones substituted on the phenyl ring bonded to the N(4) nitrogen atom. Indeed a *para* substituent on the phenyl ring of thioamoyl moiety affects the electron density differently on the nitrogen than on the sulphur atoms [18]. So the observed similarity in ρ_N and ρ_S values means that quantitatively similar variations of electron density on the N(4) nitrogen and sulphur atoms have a quantitatively different effect on *N*-attack and *S*-attack. This is possible in the case that two different mechanisms are operative. This hypothesis seems also confirmed by fact that for a simple 5-*endo*-tet [19] nucleophilic cyclization the sulphur atom of the thioamoyl moiety is more reactive than the nitrogen atom [20].

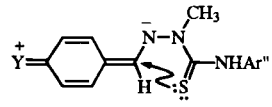
Finally, from the above correlations (eqns 1-4) it follows that the oxidative cyclization is more sensitive to substitution on the phenyl ring bonded to the carbon-nitrogen double bond than to substitution on the other phenyl ring. This conclusion rises from the values -2.07 and -0.96 for the *N*-attack and from the use of σ^+ and σ substituent constants for the S-attack as well. An explanation of the different effect that the substituted phenyl rings in **1a-s** have on the oxidative cyclization could be due to the fact that the reaction studied is a disfavoured 5-*endo*-trig [19] cyclization. Substitution on the phenyl group bonded to N(4) increase or decrease the electrophilic (nitrogen atom) or nucleophilic (sulphur atom) reactivity of cyclizing center but it does not modify the disfavoured character of the reaction. Instead, substitution on the phenyl ring bonded to the carbon atom of the C=N double bond is able to change the reaction type to favoured 5-*exo*-trig cyclization for electron-donating and electron-repelling substituents and reinforces the unfavourable 5-*endo*-trig character of cyclization for electron-withdrawing substituents.

Scheme 4

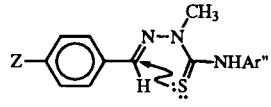


Y = electron-donating substituent

Scheme 5



5-*exo*-trig
Y = electron-donating substituent



5-*endo*-trig
Z = electron-withdrawing substituent

EXPERIMENTAL

Materials.

Anhydrous methanol was prepared by refluxing the commercial product over magnesium for 24 hours and distilling; commercial anhydrous ferric chloride was purified by sublimation just before use (stock solutions of the oxidant about 2*M* and 0.25 *M* were prepared); all other commercial reagents and solvents were used without further purification.

Equipment.

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected; infrared (ir) spectra were all recorded in nujol mulls on a Perkin-Elmer 1310 infrared spectrophotometer; ^{1}H nmr spectra were recorded on a Bruker AC-E series 250 MHz spectrometer; chemical shifts are reported in δ values (ppm) relative to TMS as the internal standard. Analyses by hplc were performed with a Perkin-Elmer LC-10 Series apparatus equipped with a UV-Vis detector.

Thiosemicarbazones **1a-s** were prepared by condensation of the proper benzaldehydes and thiosemicarbazides.

General Procedure for the Synthesis of the Thiosemicarbazides.

The requisite isothiocyanate (10 mmoles) was dissolved in 5 ml (or suspended in 15 ml) of methanol, and the solution/suspension was added dropwise to a stirred solution of 1 ml of methylhydrazine in 5 ml of water at 0°. After mixing, the system was allowed to stir at room temperature for 30 minutes and finally the crude solid product was filtered off (yield 90-95%). In most cases it can be recrystallized from ethanol.

2 -Methyl-4-(*p*-methoxy)phenylthiosemicarbazide.

This compound had mp 163°; ir: ν 3280, 3165 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.71 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 6.91, 7.34 (2d, 4H AB, J = 6.72 Hz, *p*-$MeOC_6H_4$), 9.46 (s, 1H, NH).

Anal. Calcd. for $C_9H_{13}N_3OS$: C, 51.16; H, 6.20; N, 19.89. Found: C, 51.27; H, 6.20; N, 19.97.

2-Methyl-4-(*p*-methyl)phenylthiosemicarbazide.

This compound had mp 160-163°; ir: ν 3270, 3245, 3180 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, *p*-CH_3), 3.70 (s, 5H, NCH_3 overlapped with 2H, NH_2), 7.16, 7.36 (2d, 4H AB, J = 8.3 Hz, *p*-MeC_6H_4), 9.54 (s, 1H, NH).

Anal. Calcd. for $C_9H_{13}N_3S$: C, 55.96; H, 6.71; N, 21.52. Found: C, 56.14; H, 6.84; N, 21.33.

2-Methyl-4-(*m*-methyl)phenylthiosemicarbazide.

This compound had mp 123-127°; ir: ν 3260, 3170 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.34 (s, 3H, m-CH_3), 3.58 (s, 3H, NCH_3), 5.24 (s, 2H, NH_2), 6.97 (d, 1H, J = 8.0 Hz, *m*-MeC_6H_4), 7.23 (t, 1H, J = 8.0 Hz, *m*-MeC_6H_4), 7.42 (d, 1H, J = 8.0 Hz, *m*-MeC_6H_4), 7.43 (s, 1H, *m*-MeC_6H_4), 10.07 (s, 1H, NH).

Anal. Calcd. for $C_9H_{13}N_3S$: C, 55.96; H, 6.71; N, 21.52. Found: C, 56.03; H, 6.68; N, 21.58.

2-Methyl-4-(*p*-chloro)phenylthiosemicarbazide.

This compound had mp 146-151°; ir: ν 3275, 3230 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.59 (s, 3H, NCH_3), 5.27 (s, 2H, NH_2), 7.39, 7.66 (2d, 4H, AB, J = 8.75 Hz, *p*-ClC_6H_4), 10.17 (s, 1H, NH).

Anal. Calcd. for $C_8H_{10}ClN_3S$: C, 44.55; H, 4.67; N, 19.48. Found: C, 44.64; H, 4.48; N, 19.65.

2-Methyl-4-(*p*-bromo)phenylthiosemicarbazide.

This compound had mp 141-146°; ir: ν 3280, 3230 (NH), cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.58 (s, 3H, NCH_3), 5.27 (s, 2H, NH_2), 7.52, 7.61 (2d, 4H AB, J = 6.3 Hz, *p*-BrC_6H_4), 10.15 (s, 1H, NH).

Anal. Calcd. for $C_8H_{10}BrN_3S$: C, 36.94; H, 3.87; N, 16.15. Found: C, 37.15; H, 3.94; N, 16.06.

2-Methyl-4-(*m*-chloro)phenylthiosemicarbazide.

This compound had mp 132-135°; ir: ν 3265, 3245, 3180 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.57 (s, 3H, NCH_3), 5.30 (s, 2H, NH_2), 7.16 (dd, 1H, J1 = 8.25 Hz, J2 = 2.0 Hz, *m*-ClC_6H_4), 7.34 (t, 1H, J = 8.25 Hz, *m*-ClC_6H_4), 7.53 (dd, 1H, J1 = 8.25 Hz, J2 = 2.0 Hz, *m*-ClC_6H_4), 7.91 (t, 1H, J = 2.0 Hz, *m*-ClC_6H_4).

Anal. Calcd. for $C_8H_{10}ClN_3S$: C, 44.55; H, 4.67; N, 19.48. Found: C, 44.41; H, 4.72; N, 19.55.

2-Methyl-4-(*m*-bromo)phenylthiosemicarbazide.

This compound had mp 128-136°; ir: ν 3335, 3245, 3180 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.57 (s, 3H, NCH_3), 5.31 (s, 2H, NH_2), 7.24-7.39 (m, 2H, *m*-BrC_6H_4), 7.55-7.60 (m, 1H, *m*-BrC_6H_4), 8.02-8.03 (m, 1H, *m*-BrC_6H_4), 10.20 (s, 1H, NH).

Anal. Calcd. for $C_8H_{10}BrN_3S$: C, 36.94; H, 3.87; N, 16.15. Found: C, 36.81; H, 3.81; N, 16.01.

2-Methyl-4-(*p*-nitro)phenylthiosemicarbazide.

The crude yellow amorphous product cannot be recrystallized, because it decomposes on heating; it had mp 120-130° dec; ir: ν 3305, 3285, 3220, 3175 (NH) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.61 (s, 3H, NCH_3), 8.11, 8.22 (2d, 4H AB, J = 6.85 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd. for $C_8H_{10}N_4O_2S$: C, 42.47; H, 4.45; N, 24.76. Found: C, 42.49; H, 4.55; N, 24.91.

General Procedure for the Synthesis of Thiosemicarbazones **1a-s**.

The requisite thiosemicarbazide (10 mmoles) was dissolved in 40 ml of hot ethanol, then 10-12 mmoles of aldehyde and 1 ml of acetic acid were added and the mixture was refluxed for about 15 minutes. After cooling overnight, the product, quite pure and crystalline, was filtered off, yield 60-90%. Special procedures were adopted for the synthesis of **1i** and **1s**.

2-Methyl-4-phenylthiosemicarbazone of *p*-Dimethylaminobenzaldehyde (**1a**).

This compound had mp 202-205°; ir: ν 3290 (NH), 1608 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.05 (s, 6H, *p*-$(CH_3)_2N$), 3.96 (s, 3H, NCH_3), 6.76 (d, 2H, J = 8.6 Hz, *p*-$(CH_3)_2NC_6H_4$), 7.21-7.26 (m, 1H, C_6H_5), 7.36-7.43 (m, 2H, C_6H_5), 7.57-7.63 (m, 4H, 2H, C_6H_5 overlapped with 2H *p*-$(CH_3)_2NC_6H_4$), 7.72 (s 1H, CH), 10.28 (s 1H, NH).

Anal. Calcd. for $C_{17}H_{20}N_4S$: C, 65.95; H, 6.45; N, 17.93. Found: C, 65.79; H, 6.31; N, 17.90.

2-Methyl-4-phenylthiosemicarbazone of *p*-Methoxybenzaldehyde (**1b**).

This compound had mp 132-135°; ir: ν 3265 (NH), 1598 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.96 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 6.96, 7.65 (2d, 4H AB, J = 8.7 Hz, *p*-$MeOC_6H_4$), 7.23-7.27 (m, 1H, C_6H_5), 7.36-7.43 (m, 2H, C_6H_5), 7.58-7.62 (m, 2H, C_6H_5), 7.74 (s, 1H, CH), 9.99 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.33; H, 5.61; N, 14.08.

2-Methyl-4-phenylthiosemicarbazone of *p*-Methylbenzaldehyde (**1c**).

This compound had mp 142-146°; ir: ν 3265 (NH), 1588 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, *p*-CH_3), 3.97 (s, 3H, NCH_3), 7.23-7.27 (m, 1H C_6H_5 overlapped with 2H *p*-MeC_6H_4), 7.37-7.44 (m, 2H, C_6H_5), 7.58-7.62 (m, 4H, 2H C_6H_5 overlapped with 2H *p*-MeC_6H_4), 7.75 (s, 1H, CH), 10.01 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83. Found: C, 67.90; H, 6.09; N, 14.99.

2-Methyl-4-phenylthiosemicarbazone of *p*-chlorobenzaldehyde (**1d**).

This compound had mp 158-162°; ir: ν 3270 (NH), 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.22-7.43 (m, 5H, ArH), 7.57-7.65 (m, 4H, ArH), 7.72 (s, 1H, CH), 9.93 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; N, 13.83. Found: C, 59.44; H, 4.55; N, 13.72.

2-Methyl-4-phenylthiosemicarbazone of *p*-Bromobenzaldehyde (**1e**).

This compound had mp 179-182°; ir: ν 3320 (NH), 1600 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.24-7.28 (m, 1H, C_6H_5), 7.37-7.44 (m, 2H, C_6H_5), 7.55-7-60 (m, 6H, 2H C_6H_5 overlapped with 4H *p*-BrC_6H_4), 7.70 (s, 1H, CH) 9.92 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}BrN_3S$: C, 51.73; H, 4.05; N, 12.07. Found: C, 51.66; H, 3.99; N, 12.21.

2-Methyl-4-phenylthiosemicarbazone of *m*-Chlorobenzaldehyde (**1f**).

This compound had mp 177-179°; ir: ν 3300 (NH), 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.24-7.30 (m, 1H, C_6H_5), 7.37-7.45 (m, 4H, 2H C_6H_5 overlapped with 2H *m*-ClC_6H_4) 7.52-7.61 (m, 3H, 2H C_6H_5 overlapped with 1H *m*-ClC_6H_4), 7.70 (s, CH overlapped with 1H

m-ClC_6H_4), 9.92 (s 1H, NH).

Anal. Calcd. for $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; N, 13.83. Found: C, 59.41; H, 4.79; N, 13.91.

2-Methyl-4-phenylthiosemicarbazone of m-Bromobenzaldehyde (**1g**).

This compound had mp 179°; ir: ν 3280 (NH), 1585 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.23-7.34 (m, 2H, 1H C_6H_5 overlapped with 1H *m*-BrC_6H_4), 7.42 (t, 2H, J = 7.4 Hz, C_6H_5), 7.52-7.67 (m, 4H, 2H C_6H_5 overlapped with 2H *m*-BrC_6H_4), 7.68 (s, 1H, CH), 7.85 (s, 1H, *m*-BrC_6H_4), 9.91 (s 1H, NH).

Anal. Calcd. for $C_{15}H_{14}BrN_3S$: C, 51.73; H, 4.05; N, 12.07. Found: C, 51.60; H, 4.00; N, 12.01.

2-Methyl-4-phenylthiosemicarbazone of *p*-Trifluoromethylbenzaldehyde (**1h**).

This compound had mp 179-183°; ir: ν 3330, 3275 (NH), 1595 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.99 (s, 3H, NCH_3), 7.27 (t, 1H, J = 7.25 Hz, C_6H_5), 7.41 (t, 2H, J = 7.25 Hz, C_6H_5), 7.59 (d, 2H, J = 7.25 Hz, C_6H_5), 7.69, 7.80 (2d, 4H AB, J = 8.1 Hz, *p*-$CF_3C_6H_4$), 7.77 (s, 1H, CH), 9.95 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{14}F_3N_3S$: C, 56.96; H, 4.18; N, 12.46. Found: C, 57.01; H, 4.19; N, 12.35.

2-Methyl-4-phenylthiosemicarbazone of *p*-Cyanobenzaldehyde (**1i**).

For the preparation of this compound acetic acid must not be added to the reaction mixture; it had mp 192-195°; ir: ν 3270 (NH), 2220 (C≡N), 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.98 (s, 3H, NCH_3), 7.27 (t, 1H, J = 7.35 Hz, C_6H_5), 7.41 (t, 2H, J = 7.35 Hz, C_6H_5), 7.57 (d, 2H, J = 7.35 Hz, C_6H_5), 7.72, 7.79 (2d, 4H AB, J = 8.2 Hz, *p*-CNC_6H_4), 7.73 (s, 1H, CH), 9.90 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.41; H, 4.88; N, 19.30.

2-Methyl-4-phenylthiosemicarbazone of *p*-Nitrobenzaldehyde (**1j**).

This compound had mp 218°; ir: ν 3330 (NH), 1593 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.01 (s, 3H, NCH_3), 7.28 (t, 1H, J = 7.5 Hz, C_6H_5), 7.43 (t, 2H, J = 7.5 Hz, C_6H_5), 7.58 (d, 2H, J = 7.5 Hz, C_6H_5), 7.78 (s, 1H, CH), 7.86, 8.30 (2d, 4H AB, J = 8.74 Hz, *p*-$NO_2C_6H_4$), 9.91 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.30; H, 4.51; N, 17.88.

2-Methyl-4-(*p*-methoxy)phenylthiosemicarbazone of Benzaldehyde (**1l**).

This compound had mp 120-122°; ir: ν 3270 (NH), 1592 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.83 (s, 3H, OCH_3), 3.98 (s, 3H, NCH_3), 6.93 (d, 2H, J = 8.8 Hz, *p*-$MeOC_6H_4$), 7.33-7.45 (m, 5H, 3H C_6H_5 overlapped with 2H *p*-$MeOC_6H_4$), 7.68-7.73 (m, 2H, C_6H_5), 7.77 (s, 1H, CH), 9.81 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.08; H, 5.76; N, 14.21.

2-Methyl-4-(*p*-methyl)phenylthiosemicarbazone of Benzaldehyde (**1m**).

This compound had mp 144-145°; ir: ν 3270 (NH), 1595 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.37 (s, 3H, *p*-CH_3), 3.98 (s, 3H, NCH_3), 7.10-7.26 (m, 3H, 1H C_6H_5 overlapped with 2H *p*-MeC_6H_4), 7.35-7.46 (m, 4H, 2H C_6H_5 overlapped with 2H *p*-MeC_6H_4), 7.69-7.72 (m, 2H, C_6H_5), 7.77 (s, 1H, CH), 9.90 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83. Found: C, 67.68; H, 5.94; N, 14.72.

2-Methyl-4-(*m*-methyl)phenyl-thiosemicarbazone of Benzaldehyde (**1n**).

This compound had mp 120-122°; ir: ν 3295 (NH), 1600 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, *m*-CH_3), 3.42 (s, 3H, NCH_3), 7.08 (d, 1H, J = 7.5 Hz, *m*-MeC_6H_4), 7.30 (t, 1H, J = 7.5 Hz, *m*-MeC_6H_4), 7.33-7.48 (m, 5H, 3H C_6H_5 overlapped with 2H *m*-MeC_6H_4), 7.68-7.74 (m, 2H C_6H_5), 7.77 (s, 1H, CH), 8.77 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3S$: C, 67.81; H, 6.05; N, 14.83. Found: C, 67.88; H, 6.18; N, 14.89.

2-Methyl-4-(*p*-chloro)phenylthiosemicarbazone of Benzaldehyde (**1o**).

This compound had mp 152-153°; ir: ν 3270 (NH), 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.36, 7.56 (2d, 4H AB, J = 8.6 Hz, *p*-ClC_6H_4), 7.23-7.30 (m, 1H, C_6H_5), 7.42-7.46 (m, 2H, C_6H_5), 7.68-7.72 (m, 2H, C_6H_5), 7.78 (s, 1H, CH), 9.97 (s, 1H, NH).

Anal. $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; N, 13.83. Found: C, 59.22; H, 4.71; N, 13.73.

2-Methyl-4-(*p*-bromo)phenylthiosemicarbazone of Benzaldehyde (**1p**).

This compound had mp 165-166°; ir: ν 3275 (NH), 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.97 (s, 3H, NCH_3), 7.38-7.60 (m, 7H, ArH), 7.70-7.74 (m, 2H, ArH), 7.79 (s, 1H, CH), 9.98 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}BrN_3S$: C, 51.73; H, 4.05; N, 12.07. Found: C, 51.80; H, 4.00; N, 12.17.

2-Methyl-4-(*m*-chloro)phenylthiosemicarbazone of Benzaldehyde (**1q**).

This compound had mp 127°; ir: ν 3290 (NH), 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.19 (br d, 1H, J = 7.96 Hz, *m*-ClC_6H_4), 7.30 (t, 1H, J = 7.96 Hz, *m*-ClC_6H_5), 7.36-7.45 (m, 3H, C_6H_5), 7.53 (br d, 1H, J = 8.04 Hz, m-ClC_6H_5), 7.67-7.70 (m, 3H, 1H *m*-ClC_6H_5 overlapped with 2H C_6H_5), 7.76 (s, 1H, CH), 10.02 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; N, 13.83. Found: C, 59.26; H, 4.55; N, 13.96.

2-Methyl-4-(*m*-bromo)phenylthiosemicarbazone of Benzaldehyde (**1r**).

This compound had mp 120-122°; ir: ν 3285 (NH), 1585 (CN) cm-^{1}; ^1H nmr (deuteriochloroform): δ 3.96 (s, 3H, NCH_3), 7.26 (d, 1H, J = 8.1 Hz, *m*-BrC_6H_5), 7.36 (t, 1H, J = 8.1 Hz, *m*-BrC_6H_5), 7.44-7.51 (m, 3H, C_6H_5), 7.60 (d, 1H, J = 8.1 Hz, *m*-BrC_6H_5), 7.68-7.73 (m, 2H, C_6H_5), 7.78 (s, 1H, CH), 7.82 (s, 1H *m*-BrC_6H_5), 10.01 (s, 1H, NH).

Anal. Calcd. for$C_{15}H_{14}BrN_3S$: C, 51.73; H, 4.05; N, 12.07. Found: C, 51.59; H, 4.11; N, 12.20.

2-Methyl-4-(*p*-nitro)phenylthiosemicarbazone of Benzaldehyde (**1s**).

Because of the thermal decomposition of 2-methyl-4-(*p*-nitro)phenylthiosemicarbazide this compound was prepared as follows: 10 mmoles of the thiosemicarbazide and 10 mmoles of benzaldehyde were dissolved in 5 ml of dimethyl sulphoxide,

two drops of acetic acid were added and the mixture was kept overnight at room temperature, then 25 ml of ethanol were added and the product (which is sufficiently pure) was filtered off (yield about 90%). This compound had mp 213°; ir: ν 3240 (NH), 1595 (CN) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.42 (s, 3H, NCH_3), 7.47-7.49 (m, 3H, C_6H_5), 7.70-7.74 (m, 2H, C_6H_5), 7.83 (s, 1H, CH), 7.99, 8.26 (2d, 4H AB, J = 8.9 Hz, *p*-$NO_2C_6H_4$), 8.77 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.59; H, 4.50; N, 17.88.

General Procedure for the Oxidation of Thiosemicarbazones **1a-s** with Ferric Chloride Hexahydrate in Hot Ethanol.

Thiosemicarbazones **1a-s** (10 mmoles) were dissolved or suspended in 25 ml of boiling ethanol and the oxidant (5.7 g, 21 mmoles) dissolved in 15 ml of ethanol was added. The mixture was refluxed until the reaction was complete - the colour of the solution passes from brown-orange to yellow. After cooling overnight most of the triazoline **3a-s** precipitated and was filtered off; the mother liquors were distilled under vacuum and the residue was extracted with water/chloroform to remove most of the inorganic salts. The organic layer was dried under sodium sulphate and distilled, and the residue was chromatographated on silica (using cyclohexane-ethyl acetate mixtures as eluents) to obtain the pure thiadiazoline **2a-s** and another small amount of triazoline.

2-(*p*-Dimethylamino)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2a**).

This compound had mp 146-147°; ir: ν 1605, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.98 (s, 6H, $(CH_3)_2N$), 3.73 (s, 3H, NCH_3), 6.64, 7.46 (2d, 4H, AB J = 8.85 Hz, *p*-$(CH_3)_2NC_6H_4$), 7.02-7.09 (m, 3H, C_6H_5), 7.30-7.37 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05. Found: C, 65.89; H, 5.81; N, 17.98.

2-(*p*-Methoxy)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2b**).

This compound had mp 102-103°; ir: ν 1605, 1575 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.82 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 6.90, 7.54 (2d, 4H AB, J = 8.78 Hz, *p*-$MeOC_6H_4$), 7.05-7.10 (m, 3H, C_6H_5), 7.32-7.39 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.82; H, 5.21; N, 14.34.

2-(*p*-Methyl)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2c**).

This compound had mp 98-99°; ir: ν 1615, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3), 3.75 (s, 3H, NCH_3), 7.04-7.09 (m, 3H, C_6H_5), 7.18, 7.49 (2d, 4H AB, J = 8.1 Hz,*p*-MeC_6H_4), 7.31-7.38 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93; Found: C, 68.59; H, 5.38; N, 15.02.

2-(*p*-Chloro)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2d**).

This compound had mp 89-90°; ir: ν 1620, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.24-7.30 (m, 6H ArH), 7.49-7.52 (m, 3H, ArH).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.88; H, 3.96; N, 14.11.

2-(*p*-Bromo)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2e**).

This compound had mp 105-107°; ir: ν 1618, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.78 (s, 3H, NCH_3), 7.07-7.14 (m, 3H, C_6H_5), 7.34-7.41 (m, 2H, C_6H_5), 7.48, 7.52 (2d, 4H AB, J = 8.5 Hz, *p*-BrC_6H_4).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 51.94; H, 3.40; N, 11.87.

2-(*m*-Chloro)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2f**).

This compound had mp 107°; ir: ν 1605, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.77 (s, 3H, NCH_3), 7.06-7.12 (m, 3H, C_6H_5), 7.31-7.40 (m, 4H, 2H C_6H_5 overlapped with 2H *m*-ClC_6H_4), 7.43-7.48 (s, 1H, *m*-ClC_6H_4), 7.63-7.65 (s, 1H, *m*-ClC_6H_4).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.98; H, 4.12; N, 13.94.

2-(*m*-Bromo)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2g**).

This compound had mp 111-113°; ir: ν 1605, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.78 (s, 3H, NCH_3), 7.06-7.12 (m, 3H, C_6H_5), 7.22-7.29 (m, 1H, *m*-BrC_6H_5), 7.33-7.40 (m, 2H, C_6H_5), 7.48-7.52 (m, 2H, *m*-BrC_6H_5), 7.79-7.81 (m, 1H, *m*-BrC_6H_4).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 51.89: H, 3.51; N, 12.00.

2-(*p*-Trifluoroethyl)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2h**).

This compound had mp 63-64°; ir: ν 1610, 1583 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.79 (s, 3H, NCH_3), 7.06-7.14 (m, 3H, C_6H_5), 7.64, 7.72 (2d, 4H AB, J = 8.4 Hz, *p*-$CF_3C_6H_4$), 7.34-7.41 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{16}H_{12}F_3N_3S$: C, 57.31; H, 3.61; N, 12.53. Found: C, 57.44; H, 3.68; N, 12.48.

2-(*p*-Cyano)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2i**).

This compound had mp 132-133°; ir ν 2220 (C≡N), 1610, 1580 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.80 (s, 3H, NCH_3), 7.05-7.14 (m, 3H, C_6H_5) 7.37-7.40 (m, 2H, C_6H_5), 7.68, 7.70 (2d, 4H AB, J = 8.5 Hz,*p*-CNC_6H_4).

Anal. Calcd. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.88; H, 4.23; N, 19.20.

2-(*p*-Nitro)phenyl-3-methyl-5-phenylimino-Δ^2-1,3,4-thiadiazoline (**2j**).

This compound had mp 142-143°; ir: ν 1608, 1578 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.06-7.14 (m, 3H) 7.35-7.41 (m, 2H, C_6H_5), 7.76, 8.25 (2d, 4H AB, J = 7.05 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.87; H, 3.79; N, 18.01.

2-Phenyl-3-methyl-5-(*p*-methoxy)phenylimino-Δ^2-1,3,4-thiadiazoline (**2l**).

This compound had mp 117°; ir: ν 1612, 1595 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.75 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.89, 7.01 (2d, 4H AB, J = 8.8 Hz, *p*-$MeOC_6H_4$), 7.36-7.40 (m, 3H, C_6H_5), 7.58-7.62 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13.

Found: C, 64.58, H, 5.10; N, 14.26.

2-Phenyl-3-methyl-5-(*p*-methyl)phenylimino-Δ^2-1,3,4-thiadiazoline (**2m**).

This compound had mp 86-90°; ir: ν 1615, 1595 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.34 (s, 3H, CH_3), 3.76 (s, 3H, NCH_3), 6.98, 7.16 (2d, 4H AB, J = 8.3 Hz, *p*-MeC_6H_4), 7.36-7.63 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.11; H, 5.44; N, 15.02.

2-Phenyl-3-methyl-5-(*m*-methyl)phenylimino-Δ^2-1,3,4-thiadiazoline (**2n**).

This compound had mp 35-40°; ir: ν 1615, 1583 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.37 (s, 3H, CH_3), 3.76 (s, 3H, NCH_3), 6.88-6.91 (m, 3H, *m*-MeC_6H_4) 7.21-7.27 (m, 1H, *m*-MeC_6H_5), 7.36-7.40 (m, 3H, C_6H_5), 7.59-7.83 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.53; H, 5.26; N, 14.82.

2-Phenyl-3-methyl-5-(*p*-chloro)phenylimino-Δ^2-1,3,4-thiadiazoline (**2o**).

This compound had mp 102°; ir: ν 1603, 1588 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.75 (s, 3H, NCH_3), 7.01, 7.30 (2d, 4H AB, J = 8.65 Hz, *p*-ClC_6H_4), 7.37-7.41 (m, 3H, C_6H_5), 7.58-7.63 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.44; H, 4.00; N, 14.02.

2-Phenyl-3-methyl-5-(*p*-bromo)phenylimino-Δ^2-1,3,4-thiadiazoline (**2p**).

This compound had mp 110-111°; ir: ν 1610, 1580 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.75 (s, 3H, NCH_3), 6.96, 7.44 (2d, 4H AB, J = 8.7 Hz, *p*-BrC_6H_4), 7.02-7.09 (m, 3H, C_6H_5), 7.30-7.37 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04; Found: C, 52.29; H, 3.56; N, 12.37.

2-Phenyl-3-methyl-5-(*m*-chloro)phenylimino-Δ^2-1,3,4-thiadiazoline (**2q**).

This compound had mp 57-59°; ir: ν 1613, 1580 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.75 (s, 3H, NCH_3), 6.94-6.99 (m, 1H, *m*-ClC_6H_4), 7.02-7.06 (m, 1H, *m*-ClC_6H_4), 7.09 (t, 1H, J = 1.95 Hz, *m*-ClC_6H_4), 7.26 (t, 1H, J = 7.9 Hz, *m*-ClC_6H_4), 7.38-7.41 (m, 3H, C_6H_5), 7.60-7.64 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.64; H, 3.98; N, 13.82.

2-Phenyl-3-methyl-5-(*m*-bromo)phenylimino-Δ^2-1,3,4-thiadiazoline (**2r**).

This compound was obtained as yellow oil; ir: ν 1608, 1575 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, 3H, NCH_3), 6.99-7.04 (m, 1H, *m*-BrC_6H_4), 7.20-7.27 (m, 3H, *m*-BrC_6H_4), 7.39-7.43 (m, 3H, C_6H_5), 7.61-7.66 (m, 2H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 52.26; H, 3.56; N, 12.08.

2-Phenyl-3-methyl-5-(*p*-nitro)phenylimino-Δ^2-1,3,4-thiadiazoline (**2s**).

This compound had mp 121-131°; ir: ν 1610,1570 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.81 (s, 3H, NCH_3), 7.41-7.45 (m, 3H, C_6H_5), 7.62-7.66 (m, 2H, C_6H_5), 7.88, 8.22 (2d, 4H AB, J = 8.9 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.46; H, 3.90; N, 18.00.

1-Methyl-3-(*p*-dimethylammino)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3a**).

This compound had mp 214-215°; ir: ν 1602 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.95 (s, 6H $(CH_3)_2N$), 3.92 (s, 3H, NCH_3), 6.57, 7.14 (2d, 4H AB, J = 8.95 Hz, *p*-$(CH_3)_2NC_6H_4$), 7.29-7.33 (m, 2H, C_6H_5), 7.46-7.51 (m, 3H, C_6H_5).

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05. Found: C, 65.62; H, 5.88; N, 18.19.

1-Methyl-3-(*p*-methoxy)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3b**).

This compound had mp 175°; ir: ν 1606 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, 3H, OCH_3), 3.93 (s, 3H, NCH_3), 6.78, 7.22 (2d, 4H AB, J = 8.77 Hz, *p*-$MeOC_6H_4$), 7.25-7.31 (m, 2H, C_6H_5) 7.48-7.55 (m, 3H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.88; H, 5.12; N, 14.27.

1-Methyl-3-(*p*-methyl)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3c**).

This compound had mp 199-200°; ir: ν 1595 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.31 (s, 3H, CH_3), 3.94 (s, 3H, NCH_3), 7.08, 7.18 (2d, 4H AB, J = 8.3 Hz, *p*-MeC_6H_4), 7.25-7.31 (m, 2H, C_6H_5), 7.49-7.50 (m, 3H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.41; H, 5.32; N, 15.09.

1-Methyl-3-(*p*-chloro)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3d**).

This compound had mp 239-240°; ir: ν 1595 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.20-7.31 (m, 6H, 4H *p*-ClC_6H_4 overlapped with 2H C_6H_5), 7.49-7.52 (m, 3H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.54; H, 4.08; N, 14.00.

1-Methyl-3-(*p*-bromo)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3e**).

This compound had mp 252-255°; ir: ν 1590 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.93 (s, 3H, NCH_3), 7.17, 7.42 (2d, 4H AB, J = 8.5 Hz, *p*-BrC_6H_4), 7.26-7.33 (m, 2H, C_6H_5), 7.48-7.55 (m, 3H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 51.98; H, 3.58; N, 12.08.

1-Methyl-3-(*m*-chloro)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3f**).

This compound had mp 132-133°; ir: ν 1590 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.09 (dt, 1H, J1 = 7.87 Hz, J2 = 1.14 Hz, *m*-ClC_6H_4), 7.19 (t, 1H, J = 8.10 Hz, *m*-ClC_6H_4), 7.26-7.40 (m, 4H, 2H *m*-ClC_6H_4 overlapped with 2H C_6H_5), 7.49-7.53 (m, 3H, C_6H_5).

Anal. $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.84; H, 3.98; N, 14.05.

1-Methyl-3-(*m*-bromo)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3g**).

This compound had mp 122-128°; ir: ν 1610 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.10-7.15 (m,

2H, *m*-BrC_6H_4), 7.26-7.32 (m, 2H, C_6H_5), 7.48-7.57 (m, 4H, 1H *m*-BrC_6H_4 overlapped with 3H C_6H_5), 7.56 (s, 1H, *m*-BrC_6H_4).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 52.08; H, 3.39; N, 11.95.

1-Methyl-3-(*p*-trifluoromethyl)phenyl-4-phenyl-1,2,4-triazoline-5-thione (**3h**).

This compound had mp 117-120°; ir: ν 1615 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.26-7.32 (m, 2H, C_6H_5), 7.44 (d, 2H, J = 8.05 Hz, *p*-$CF_3C_6H_4$), 7.50-7.80 (m, 3H C_6H_5 overlapped with 2H *p*-$CF_3C_6H_4$).

Anal. Calcd. for $C_{16}H_{12}F_3N_3S$: C, 57.31; H, 3.61; N, 12.53. Found: C, 57.32; H, 3.69; N, 12.41.

1-Methyl-3-phenyl-4-(*p*-methoxy)phenyl-1,2,4-triazoline-5-thione (**3l**).

This compound had mp 147-148°; ir: ν 1608 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.98, 7.21 (2d, 4H AB, J = 8.65 Hz, *p*-$MeOC_6H_4$), 7.26-7.44 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.88; H, 5.00, N, 14.27.

1-Methyl-3-phenyl-4-(*p*-methyl)phenyl-1,2,4-triazoline-5-thione (**3m**).

This compound had mp 171°; ir: ν 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 3.94 (s, 3H, NCH_3), 7.17 (d, 2H, J = 8.3 Hz, *p*-MeC_6H_4), 7.25-7.40 (m, 7H, 5H C_6H_5 overlapped with 2H *p*-MeC_6H_4).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.25; H, 5.42; N, 15.02.

1 -Methyl-3-phenyl-4-(*m*-methyl)phenyl-1,2,4-triazoline-5-thione (**3n**).

This compound had mp 169°; ir: ν 1605 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.37 (s, 3H, CH_3), 3.95 (s, 3H, NCH_3), 7.05-7.12 (m, 2H, ArH), 7.24-7.41 (m, 7H, ArH).

Anal. Calcd. for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.57; H, 5.37; N, 14.82.

1-Methyl-3-phenyl-4-(*p*-chloro)phenyl-1,2,4-triazoline-5-thione (**3o**).

This compound had mp 159°; ir: ν 1595 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.25, 7.46 (2d, 4H AB, J = 8.05 Hz, *p*-ClC_6H_4), 7.31-7.43 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.70; H, 3.97; N, 13.81.

1-Methyl-3-phenyl-4-(*p*-bromo)phenyl-1,2,4-triazoline-5-thione (**3p**).

This compound had mp 182-183°; ir: ν 1590 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.19, 7.62 (2d, 4H AB, J = 8.63 Hz, *p*-BrC_6H_4), 7.26-7.43 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 51.99; H, 3.42; N, 12.28.

1-Methyl-3-phenyl-4-(*m*-chloro)phenyl-1,2,4-triazoline-5-thione (**3q**).

This compound had mp 161°; ir: ν 1582 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.17-7.21 (m, 2H, ArH), 7.26-7.49 (m, 7H, ArH).

Anal. Calcd. for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.46; H, 4.07; N, 13.99.

1-Methyl-3-phenyl-4-(*m*-bromo)phenyl-1,2,4-triazoline-5-thione (**3r**).

This compound had mp 145°; ir: ν 1575 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, NCH_3), 7.22-7.42 (m, 7H, 5H C_6H_5 overlapped with 2H *m*-BrC_6H_4), 7.50 (t, 1H J = 1.9 Hz, *m*-BrC_6H_4) 7.62 (dt, 1H, J1 = 1.9 Hz, J2 = 8.12 Hz, *m*-BrC_6H_4).

Anal. Calcd. for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.04. Found: C, 52.16; H, 3.57; N, 11.83.

1-Methyl-3-phenyl-4-(*p*-nitro)phenyl-1,2,4-triazoline-5-thione (**3s**).

This compound had mp 223°; ir: ν 1595 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, NCH_3), 7.26-7.43 (m, 5H, C_6H_5), 7.53, 8.34 (2d, 4H AB, J = 8.9 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd. for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 58.01; H, 3.94; N, 18.09.

Kinetic Measurements.

Procedure.

The reaction systems were prepared in such a way as to have a twenty times or more excess of the oxidizing agent (pseudo-first order conditions) at a concentration of 10 to 50 m*M*, and were thermostated at 25°. During the kinetic experiment small volumes (0.2-0.4 ml) of the reaction system were taken away time by time and rapidly chromatographated on a silica micro column (4 mm diameter, 6 cm height) eluting with 5 ml of a cyclohexane/ethyl acetate 1:1 mixture in order to remove the excess of inorganic salts; the eluate was concentrated and the residue analysed with an hplc apparatus to evaluate the concentrations of the species in the system. From the relative concentrations of the reactant substrate and of the products the second order kinetic constants were evaluated using standard mathematical methods.

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