STRUCTURE OF ADDUCTS OF 2-ARYLAMINOTHIAZOLINES WITH ISOCYANATES AND ISOTHIOCYANATES§

Martin Avalos, Reyes Babiano, Pedro Cintas, José L. Jiménez, Juan C. Palacios, and Concepción Valencia

Departamento de Química Orgánica, Universidad de Extremadura, E-06071 Badajoz, Spain

Abstract - Extensions of the reaction of 2-chloroethyl isothiocyanate with aliphatic and aromatic amines have been accomplished, and 2-arylamino-2-thiazoline hydrochlorides (**5**) are easily obtained. Structures attributed initially to the products of condensation of **5** with phenyl isocyanate and phenyl isothiocyanate have been corrected and assigned unequivocally by X-ray analysis. By heating, these molecules do not undergo an *endo-N→exo-N'* rearrangement.

The reaction of haloalkyl isothiocyanates with amines constitutes a facile and expeditious access to a large number of thiazoline or thiazine derivatives.[1] It is well-known that compounds containing these structural fragments often exhibit relevant biological properties as potential herbicides and antifungal agents.[2] Interestingly, some of them display also medicinal properties, and thus *N*-phenyl-*N'*-2-thiazolylthiourea (**1**) is an inhibitor of dopamine β-hydroxylase.[3] The influence of dopamine and dopaminergic neurons in various physiological conditions of the central nervous system has stimulated the current search for dopaminergic agonists and antagonists.[4] Despite these promising characteristics, the generality of the synthetic process with respect to the amine has not been systematically investigated and the study has been restricted to arylamines. Finally, the reaction of the resulting aminothiazolines with isocyanates or isothiocyanates yielding attractive dimeric structures, is still an obscure point of this research.

In a recent paper, Outcalt reported[5] that the coupling of amines with 2-chloroethyl isothiocyanate is largely dependent on the electronic nature of the substituents on the amine as well as the solvent and other reaction conditions. The reaction of aromatic amines with 2-chloroethyl isothiocyanate in toluene at reflux provides a mixture of 2-arylamino-2-thiazolines (**2**) and *N*-thiazolinyl-2-iminothiazolidines (**3**). Electron-releasing groups on the aromatic ring result in the preferential formation of **2**, while electron-withdrawing substituents favor compounds (**3**). He also described one experiment in the presence of triethylamine as a proton acceptor, and a dimeric product (**4**) was then obtained. These results are different from those reported previously by our group,[6] in which 2-arylamino-2-thiazolines (**2**) are exclusively formed as hydrochlorides in ether. The structure of reaction products could therefore be controlled by simple choice of the appropriate solvent system. To gain insight into this approach, we have re-examined the condensation of arylamines with 2-chloroethyl isothiocyanate in ether and have extended this procedure to some aliphatic amines.

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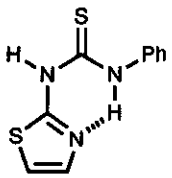
§This paper is dedicated with admiration to Prof. Edward C. Taylor on the occasion of his 70th birthday.



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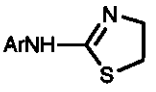

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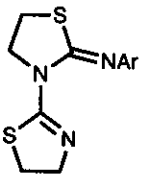

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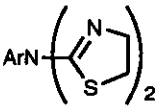

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The substituents on the aromatic ring were varied in the usual range according to σ-values to provide a wide study in electron demand (Table 1). To avoid the uncontrolled exothermic process associated with these reactions, both reagents were mixed slowly at 0 °C and then left at room temperature. Hydrochlorides (**5**) can be easily separated from the reaction mixture as crystalline compounds, with the exception of **5d**, **5k**, and **5l** which were amorphous powders or hygroscopic oils.

Table 1. 2-Alkyl(aryl)iminothiazolidine hydrochlorides (**5**).

Compound	R	σ[a]	Yield (%)
5a	4-$CH_3OC_6H_4$	-0.28	92
5b	2-$CH_3OC_6H_4$		82[b]
5c	4-$CH_3C_6H_4$	-0.14	90[b]
5d	C_6H_5	0.00	89
5e	3-$CH_3OC_6H_4$	0.10	61
5f	4-ClC_6H_4	0.24	60[b]
5g	3,4-$Cl_2C_6H_3$	0.61	75
5h	3-$NO_2C_6H_4$	0.71	66
5i	4-$NO_2C_6H_4$	0.81	0
5j	$(CH_3O)_2CHCH_2$		76
5k	$CH_3CH_2CH_2$		60
5l	$(CH_3CH_2)_2$		78

[a] Hammett values (σ or Σσ) were taken from J. March, *Advanced Organic Chemistry*, 4 th ed.,Wiley, New York, 1992. [b] These compounds were included for comparative purposes from reference 6.

Importantly, yields of monoadducts (**5**) were vastly superior to those reported by Outcalt,[5] and in contrast with his results tlc analysis did not detect any significant formation of bis-adducts in these reactions with the sole exception of 2-aminopyridine. In this case, the only product isolated by crystallization was 2-(2-pyridyl)imino-*N*-(2-thiazolin-2-yl)thiazolidine (**6**) as evidenced by spectroscopic and analytical data (Tables 2 and 3). The yield (27%), however, seems to indicate that half of aminopyridine neutralizes the hydrochloric acid generated owing to its basicity. This explains the formation of bis-adduct (**6**) instead of **5**, by reaction of the free intermediate with more 2-chloroethyl isothiocyanate. It should be pointed out that reaction with 4-nitroaniline was unsuccessful and no product (**5i**) could be isolated, which can be attributed to the strong electron-withdrawing effect of the 4-nitro substituent on the aromatic ring. The desired hydrochloride (**5i**), however, was prepared by the inverse strategy based on the reaction of 4-nitrophenyl isothiocyanate and 2-chloroethylamine in ether.

Table 2. ^{1}H-Nmr data of compounds (**5**, **6**, and **15-16**).

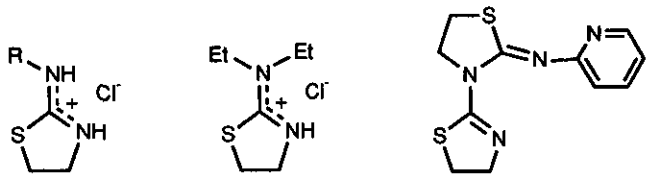
Compd	S-CH_2	N-CH_2	NH	Aryl	Alkyl
5a[a]	3.57t (*J* 7.6)	3.94t (*J* 7.6)	11.23bs	7.29d (*J* 8.9) 7.04d (*J* 8.9)	3.78s
5d[a]	3.56t (*J* 7.6)	3.94t (*J* 7.6)	10.75bs	7.51-7.20m	
5e[a]	3.59t (*J* 7.6)	3.96t (*J* 7.6)	11.50bs	7.43-6.91m	3.78s
5g[a]	3.63t (*J* 7.6)	4.00t (*J* 7.6)		7.77-7.40m	
5h[a]	3.62t (*J* 7.6)	4.00t (*J* 7.6)		8.30-7.72m	
5i[a]	3.66t (*J* 7.7)	4.06t (*J* 7.7)		8.32d (*J* 9.0) 7.71d (*J* 9.0)	
6[a]	3.22t (*J* 7.0) 3.16t (*J* 7.0)	4.17t (*J* 7.0) 3.91t (*J* 7.0)		8.40-7.05m	
15b[b]	3.15t (*J* 7.0)	4.88t (*J* 7.0)	10.91bs	7.58-6.85m	3.81s
16a[b]	3.13t (*J* 7.1)	4.36t (*J* 7.1)	12.00s	7.54-6.99m	
16b[b]	3.23t (*J* 7.1)	4.42t (*J* 7.1)	11.53s	8.24-7.31m	
16c[b]	3.14t (*J* 7.0)	4.35t(*J* 7.0)	12.07s	7.53-6.88m	3.81s

[a] In DMSO-d_6. [b] In $CDCl_3$.

Table 3. ^{13}C-Nmr data of compounds (**5**, **6**, and **15-16**).

Compd	S-CH_2	N-CH_2	C=O	C=N	C=S	Alkyl	Aryl
5a[a]	30.76	49.17		171.17		55.50	158.51, 129.56, 125.71, 114.82
5d[a]	30.89	49.54		170.39			137.01, 129.88, 129.58 127.40, 123.63, 121.59
5e[a]	30.79	49.30		170.55		55.46	159.99, 137.82, 130.63 115.49, 113.19, 109.21
5g[a]	31.00	49.55		170.38			136.71, 131.87, 131.46 129.64, 125.62, 124.01
5h[a]	31.14	49.78		170.39			148.27, 138.02, 131.20 129.97, 121.76, 118.49
5i[a]	31.11	50.03		169.65			144.77, 142.87, 125.14, 122.96
6[a]	33.01 26.53	56.71 50.05		157.15 156.97 156.82			147.03, 138.11, 119.38, 119.28
15b[b]	24.74	54.79		158.91	178.94	55.43	157.13, 141.53, 138.77, 128.69 126.29, 125.00, 122.31, 114.34
15c[b]	24.87	55.23		160.06	178.77		153.80, 144.82, 138.40, 128.78 126.67, 125.18, 125.08, 122.19
16a[b]	25.58	48.82	150.75	158.33			149.07, 138.03, 129.16, 128.85 124.81, 123.58, 121.42, 119.94
16b[b]	25.79	49.24	154.65	159.69			150.14, 144.56, 137.58, 128.93 125.09, 123.98, 122.26, 120.03
16c[b]	25.57	48.76	156.81	158.17		55.40	150.86, 142.37, 138.10, 128.86 123.54, 122.38, 119.91, 114.32

[a] In DMSO-d_6. [b] In $CDCl_3$.



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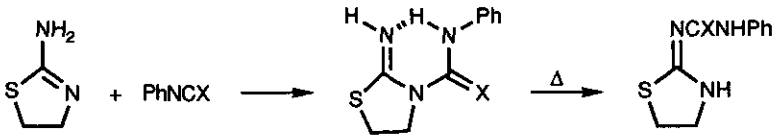
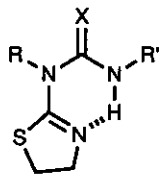
The reactions of 2-amino-2-thiazolines with isocyanates and isothiocyanates have been the subject of an almost detective story with continuous clarifications. As early as 1928, Fromm and Kapeller-Adler reported[7] the reaction of 2-amino-2-thiazoline with phenyl isothiocyanate below 50 °C to afford primarily the imino derivative (**7**) which rearranges by heating to **9**. Klayman *et al.*[8] were unable to reproduce these results and they only obtained the compound (**7**). In a correction, however, Klayman reassigned[9] structure (**9**) for this product which was confirmed by X-ray analysis.[10] Similar reaction with phenyl isocyanate resulted in the formation of the corresponding urea derivative (**10**), by attack of the isocyanate at the exocyclic amino group of the 2-amino-2-thiazoline.



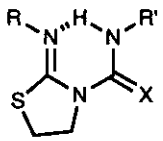
7 X=S
8 X=O

9 X=S
10 X=O

Also, Cherbuliez *et al.* reported[11] that the reaction of 2-aminoethanol esters with alkyl and aryl isothiocyanates gave *N,N'*-dialkyl(aryl)-*N*-(2-thiazolin-2-yl)thioureas (**11**). Yamamoto and coworkers[12] corrected these results and concluded that the compounds isolated in such reactions employing alkyl isothiocyanates had *N*-alkylimino structures (**13**). Thus, reactions of 2-alkylamino-2-thiazolines with methyl or ethyl isothiocyanates yielded compounds having structure (**13**; R = R' = Me or Et). The same authors reported that reaction between 2-amino-2-thiazoline and alkyl isothiocyanates below 50 °C gave mainly compounds (**13**; R = H, R' = alkyl), which isomerized to **11** (R = H, R' = alkyl) under thermal treatment.[13,14] Reactions of 2-amino-2-thiazoline with methyl isocyanate also gave a mixture of **12** and **14** (R = H, R' = Me). In the reaction of 2-methylamino-2-thiazoline with methyl isocyanate compound (**14**; R = R' = Me) was exclusively obtained.[14] It should be noted that Gabriel isolated, by the end of the last century, a by-product in the reaction of 2-bromoethylamine with methyl isothiocyanate and described later as *N,N'*-dimethyl-*N*-(2-thiazolin-2-yl)thiourea (**11**; R = R' = Me).[15]
In an attempt to clarify this puzzling situation, Rasmussen and his associates reinvestigated in detail the reaction of 2-amino-2-thiazoline with phenyl isothiocyanate.[16] They obtained exclusively compound (**7**) at low temperature which is only relatively stable in low temperature (below -5 °C). Compound (**7**) dissociates to release starting materials, so phenyl isothiocyanate or its reaction products are unavoidable by-products. Even at -30 °C transformation into **9** was observed after 1 month, and by heating **7** rearranges completely to **9**.



11 X=S
12 X=O



13 X=S
14 X=O

Similarly, reaction with phenyl isocyanate gave **8** with a minor amount of **10**. At ambient temperature **8** rearranges to **10** and this compound is quantitatively obtained by heating. Structures of **7** and **8** were elucidated by X-ray crystallography. The authors concluded that addition of isocyanates and isothiocyanates must occur at endocyclic nitrogen, and the resulting substances might undergo rearrangement providing more stable compounds (**9**) and (**10**).

In view of these assumptions, we proposed structures of thioureas and ureas (**11**, **12**) for the products of condensation at room temperature of 2-arylamino-2-thiazolines with isocyanates and isothiocyanates, ruling out structures (**13**) and (**14**).[6] Nevertheless, these isomeric structures could not be discriminated on the basis of spectroscopic data. Some aryl and glycosyl isothiocyanates[6,17-19] were reacted with 2-chloroethylamine in pyridine at room temperature to give products for which structures (**11**) were previously assigned.[6] The compound derived from the reaction with phenyl isothiocyanate was studied by X-ray crystallography. The data were consistent with a structure of 2-imino-*N*,*N'*-bis(phenyl)-*N*-thiazolidinecarbothioamide (**13**, R = R' = Ph), obtained by regioselective attack at the endocyclic nitrogen, opposite to our previous statements. Also, this substance was indefinitely stable in the solid state. A perspective view of the molecule showing bond connections and the atomic numbering scheme, is given in figure 1.[20]

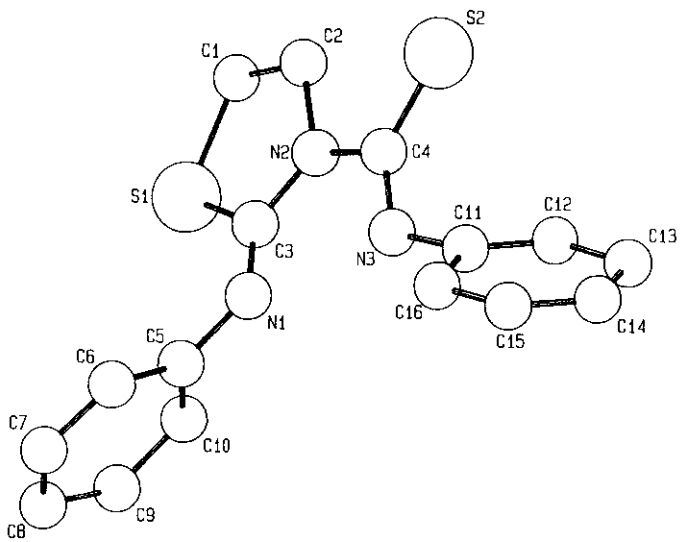


Figure 1

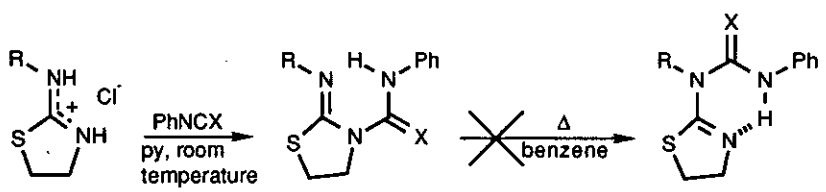
Some striking points, however, remain unsolved. It is not clear whether the reaction at the *endo* nitrogen is due to its higher reactivity compared to that of an *exo* nitrogen, or because only one tautomer exists at ambient temperature. On the other hand, the influence of substituents on this thermal rearrangement has not been discussed in detail, and thus aromatic groups on the *exo-N* have not been studied.

Table 4. Preparation of compounds (**15-16**).

Compound	R	R'	X	Yield (%)
15a	C_6H_5	C_6H_5	S	80[a]
15b	4-$CH_3OC_6H_4$	C_6H_5	S	49
15c	4-$NO_2C_6H_4$	C_6H_5	S	36[b]
16a	C_6H_5	C_6H_5	O	67
16b	4-$NO_2C_6H_4$	C_6H_5	O	74
16c	4-$CH_3OC_6H_4$	C_6H_5	O	79

[a] Ref 6. [b] Ref 11a.

Additionally, several 2-alkyl- and 2-arylamino-2-thiazoline hydrochlorides reacted with both phenyl isothiocyanate and phenyl isocyanate in pyridine to afford analogous mixed thioureas or ureas, respectively (Table 4). All compounds were then subjected to thermal rearrangement conditions (Scheme 1). Compound (**15a**; R = phenyl) was heated, neat or in solution, in order to cause conversion to **17a**. After prolonged reaction time (~16 h) and even until melting of the solid, no rearrangement was detected. The product isolated showed ^{1}H-, ^{13}C-nmr, and ir spectra and tlc behavior identical with **15a**. Similarly, other *N*-thiazolidinecarbothioamides or carboxamides (**15** and **16**) having aryl substituents on the exocyclic 2-imino group were unaffected by thermic treatment. These results contrast clearly with those of Rasmussen *et al.*[16] who postulated an intramolecular rearrangement and/or dissociation to starting materials and further recombination at the *exo*-nitrogen with unsubstituted (R =H) derivatives. An evidence for this surmise arises from the presence of phenyl isothiocyanate and a dimeric adduct derived from it, during the decomposition of compound **7**.

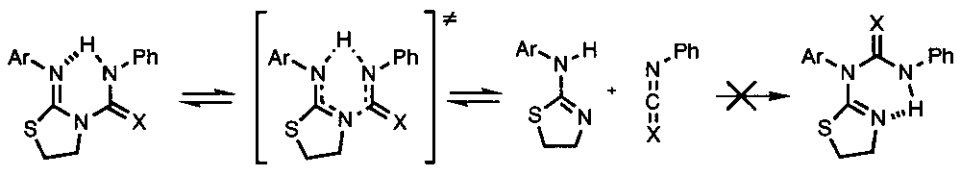


5 **15** X=S, **16** X=O **17** X=S, **18** X=O

Scheme 1

We have also found some evidences supporting a dissociation pathway. Thermal treatment of carboxamide (**16a**) (R_f 0.82) in benzene for 16 h gave no evidence of rearranged products, but a significant amount (~9 %) of crystalline *N,N'*-diphenylurea (R_f 0.36) was obtained directly from the reaction mixture. Its formation occurred presumably by reaction of phenyl isocyanate with traces of water or ambient moisture. Additional water was

added (1 drop), then refluxed for 24 h to trap the isocyanate released, and more *N,N'*-diphenylurea was observed by tlc analysis. Furthermore, carboxamide (**16a**) was suspended in ethanol and the reaction mixture was refluxed (~16 h). Nmr analysis of the crude product showed the almost complete disappearance of the starting material and the formation of ethyl phenylcarbamate and 2-phenylamino-2-thiazoline (ratio ~1:1). In view of these results, it is plausible to conclude that a reversible fragmentation to aryl isocyanate or aryl isothiocyanate and 2-arylamino-2-thiazoline and further recombination take place. This process might occur by a pericyclic mechanism *via* a cyclic six electron transition state (Scheme 2). In the case of **15c**, in which recombination is not favored, the prolonged heating gives rise to a mixture of phenyl isothiocyanate and 4-nitrophenylamino-2-thiazoline. Reactions of 2-arylamino-2-thiazolines (or their iminothiazolidine tautomers) with aryl isocyanates or aryl isothiocyanates occur therefore regiospecifically at the endocyclic nitrogen to afford the kinetically controlled products (**15** or **16**). Since dissociation and furher recombination at the endocyclic nitrogen give the same compounds, these should also be the thermodynamically controlled products. This may be attributed to the stability increased by conjugation of the aromatic ring with the exocyclic double bond. As pointed out in our previous report,[6] thiazolidine-carbothioamides or carboxamides display a chelated structure evidenced by a strong intramolecular hydrogen bond.



Scheme 2

Conclusions.

Some salient conclusions emerge from these experimental results. a) In general, reactions of arylamines with 2-chloroethyl isothiocyanate produce aryliminothiazolidine hydrochlorides in good to high yield, with the exception of strong electron-withdrawing substituents. b) Bis-adducts originated by condensation of these hydrochlorides with aryl isocyanates or aryl isothiocyanates have *N*-arylimino structures, as demonstrated by X-ray analysis. c) These molecules remain unaffected by thermal treatment. The only exception occurs with an hydrogen as substituent at the exocyclic nitrogen, and compounds with this structural feature always rearrange to the more stable ureas or thioureas.[13,14,16] Therefore, the structures assigned previously in the literature[6,17-19] should be corrected.

EXPERIMENTAL

Melting points were determined on an Electrothermal digital apparatus and are uncorrected. Ir spectra (KBr discs, unless otherwise specified) were recorded on a Perkin-Elmer 399 spectrophotometer, and nmr spectra ($CDCl_3$ or DMSO-d_6) on a Bruker AC 200-E spectrometer operating at 200 MHz (for ^1H) or 50.3 MHz (for ^{13}C) using TMS as internal reference. Chemical shifts are quoted in ppm and coupling constants in Hz. Assignments were confirmed by homo- and heteronuclear double-resonance, and DEPT experiments. Spectroscopic data are collected in Tables 2 and 3. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. X-Ray crystallographic analysis was carried out using a CAD4 Enraf-Nonius automatic diffractometer. All reactions were monitored by tlc on silica gel 60 F_{254} (Merck) using benzene-methanol (9:1, v/v) or chloroform as eluents.

2-Chloroethyl isothiocyanate was synthesized from 2-chloroethylamine hydrochloride and thiophosgene according to the literature procedure.[21] All other reagents of this study were commercially available (Aldrich or Merck) and used as received.

2-Alkyl(aryl)iminothiazolidine hydrochlorides (**5**). These compounds were prepared as earlier described,[6] from 2-chloroethyl isothiocyanate and the corresponding alkyl(aryl)amine, with a slight modification. 2-Chloroethyl isothiocyanate (0.96 ml, 10.0 mmol) in ether (10 ml) was added dropwise to a cold solution (0 °C) of alkyl(aryl)amine (10.0 mmol) in ether (10 ml). The reaction mixture was allowed to warm up to room temperature, and then the solid was filtered, washed with cold ether, and recrystallized from ethanol.

2-(4-Methoxyphenyl)iminothiazolidine hydrochloride (**5a**). From 4-methoxyaniline, yield: 92%; mp 188-190 °C (from ethanol); ir (ν_{max} cm^{-1}) 3200-2400 (NH^+), 1640 (C=N), 1530 (NH), 1595, 1510, 840 (aromatic), 1235 (C-O-C). Anal. Calcd for $C_{10}H_{13}N_2OClS$: C, 49.08; H, 5.35; N, 11.45. Found: C, 48.90; H, 5.36; N, 11.42.

2-Phenyliminothiazolidine hydrochloride (**5d**). From aniline, yield: 89% (amorphous powder); ir (ν_{max} cm^{-1}) 3600-2200 (NH^+), 1630 (C=N), 1575 (NH), 1490, 770, 690 (aromatic). Satisfactory analysis could not be obtained for this compound. It was also characterized as the derivative (**16a**).

2-(3-Methoxyphenyl)iminothiazolidine hydrochloride (**5e**). From 3-methoxyaniline, yield: 61%; mp 124-126 °C (from ethanol); ir (ν_{max} cm^{-1}) 3200-2400 (NH^+), 1630 (C=N), 1555 (NH), 1590, 1490, 795, 675 (aromatic), 1230 (C-O-C). Anal. Calcd for $C_{10}H_{13}N_2OClS$: C, 49.08; H, 5.35; N, 11.45. Found: C, 49.20; H, 5.56; N, 11.39.

2-(3,4-Dichlorophenyl)iminothiazolidine hydrochloride (**5g**). From 3,4-dichloroaniline, yield: 75%; mp 209-211 °C (from ethanol); ir (ν_{max} cm^{-1}) 3200-2500 (NH^+), 1640 (C=N), 1550 (NH), 1590, 1480, 860, 830 (aromatic). Anal. Calcd for $C_9H_9N_2Cl_3S$: C, 38.12; H, 3.20; N, 9.88. Found: C, 38.27; H, 3.30; N, 9.85.

2-(3-Nitrophenyl)iminothiazolidine hydrochloride (**5h**). From 3-nitroaniline, yield: 66%; mp 174-176 °C (from ethanol); ir (ν_{max} cm^{-1}) 3100-2300 (NH^+), 1640 (C=N), 1525 (NH), 1560, 1350 (NO_2), 1610, 1600, 1450, 740, 670 (aromatic). Anal. Calcd for $C_9H_{10}N_3O_2ClS$: C, 42.11; H, 3.88; N, 16.18. Found: C, 41.76; H, 4.13; N, 16.28.

2-(4-Nitrophenyl)iminothiazolidine hydrochloride (**5i**). Reaction from 4-nitroaniline failed (0% yield). To a solution of 2-chloroethylamine hydrochloride (1.7 g, 15 mmol) in water (10 ml) were added ether (30 ml) and *N* sodium hydroxide (30 ml) with stirring. The organic layer was separated and the aqueous phase was extracted with more ether (3x30 ml). The organic extracts were combined, dried ($MgSO_4$), and evaporated to ~30 ml. Then, 4-nitrophenyl isothiocyanate (1.12 g, 5.9 mmol) was added with vigorous stirring. The resulting yellow solid was filtered and washed with cold ether (1.0 g, 66%). Recrystallized from ethanol had mp 208-210 °C; ir (ν_{max} cm^{-1}) 3100-2500 (NH^+), 1630 (C=N), 1510 (NH), 1590, 1440, 850 (aromatic), 1335 (NO_2). Anal. Calcd for $C_9H_{10}N_3O_2ClS$: C, 42.11; H, 3.88; N, 16.18. Found: C, 42.23; H, 4.02; N, 16.44.

2-(2,2-Dimethoxyethyl)iminothiazolidine hydrochloride (**5j**). From (2,2-dimethoxyethyl)amine, yield: 76%; mp 118-119 °C (from ethanol); ir (ν_{max} cm^{-1}) 3600-2600 (NH^+), 1655 (C=N), 1565 (NH), 1140, 1080 (C-O-C). Anal. Calcd for $C_7H_{15}N_2O_2ClS$: C, 37.08; H, 6.67; N, 12.36. Found: C, 37.10; H, 6.86; N, 12.32.

2-(1-Propyl)iminothiazolidine hydrochloride (**5k**). From 1-propylamine, yield: 60% (hygroscopic solid); ir (ν_{max} cm^{-1}) 3600-2500 (NH^+), 1650 (C=N), 1555 (NH).

2-Diethyliminothiazolidine hydrochloride (**5l**). From diethylamine, yield: 78% (hygroscopic oil); ir (ν_{max} cm^{-1}, neat) 3600-2600 (NH^+, water), 1640 (C=N). Satisfactory analysis was not obtained. ^1H- and ^{13}C-nmr data are

given in Tables 2 and 3.

2-(2-Pyridyl)imino-N-(2-thiazolin-2-yl)thiazolidine (**6**). From 2-aminopyridine, yield: 27%; mp 105-107 °C (from ethanol); ir (ν_{max} cm^{-1}) 3065-2850 (CH), 1600, 1595 (C=N), 1580, 1550, 1465, 780 (pyridine ring). Anal. Calcd for $C_{11}H_{12}N_4S_2$: C, 49.98; H, 4.58; N, 21.19. Found: C, 49.93; H, 4.65; N, 21.50.

*2-Imino-N-aryl(alkyl)-N'-phenyl-N-thiazolidinecarboxamide or carbothioamide (**15** or **16**). General procedure.* To a solution of 2-alkyl(aryl)iminothiazolidine hydrochloride (**5**, 1.0 mmol) in pyridine (2 ml) was added phenyl isocyanate (0.11 ml, 1.0 mmol) or phenyl isothiocyanate (0.12 ml, 1.0 mmol), and the mixture was left at room temperature for 24 h, then poured into ice-water. The white solid was filtered and recrystallized from ethanol.

2-Imino-N-(4-methoxyphenyl)-N'-phenyl-N-thiazolidinecarbothioamide (**15b**). Yield: 49%; mp 117-118 °C (from ethanol); ir (ν_{max} cm^{-1}) 3100-2850 (NH, CH), 1600 (C=N), 1550 (NH), 1600, 1510, 830 (aromatic), 1245, 1230 (C-O-C). Anal. Calcd for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.91; N, 12.23. Found: C, 59.20; H, 5.17; N, 12.22.

2-Imino-N,N'-bis(phenyl)-N-thiazolidinecarboxamide (**16a**). Yield: 67%; mp 141-142 °C (from ethanol); ir (ν_{max} cm^{-1}) 3100-2850 (NH, CH), 1700 (amide), 1630 (C=N), 1570 (NH), 1600, 1490, 760, 710 (aromatic). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.20; H, 5.08; N, 14.03.

2-Imino-N-(4-nitrophenyl)-N'-phenyl-N-thiazolidinecarboxamide (**16b**). Yield: 74% ; mp 171-173 °C (from ethanol); ir (ν_{max} cm^{-1}) 3200-2950 (NH, CH), 1700 (amide), 1630 (C=N), 1560 (NH, NO_2), 1350 (NO_2), 1590, 1510, 855, 750, 695 (aromatic). Anal. Calcd for $C_{16}H_{14}N_4O_3S$: C, 56.13; H, 4.10; N, 16.36. Found: C, 55.97; H, 4.15; N, 16.36.

2-Imino-N-(4-methoxyphenyl)-N'-phenyl-N-thiazolidinecarboxamide (**16c**). Yield: 79%; mp 135-136 °C (from ethanol); ir (ν_{max} cm^{-1}) 3100-2900 (NH, CH), 1700 (amide), 1620 (C=N), 1565 (NH), 1600, 1510, 835, 750, 695 (aromatic), 1235 (C-O-C). Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 61.93; H, 5.28; N, 12.75.

Attempts of Rearrangement to N-alkyl(aryl)-N'-phenyl-N-(2-thiazolin-2-yl)thiourea (**17**) *or urea* (**18**). a) In solution: compounds **15** or **16** (3.0 mmol) were dissolved in benzene (16 ml) and refluxed for 16 h. After cooling, the solvent was evaporated and the crude mixture analyzed by ^1H- and ^{13}C-nmr. b) In solid state: compounds **15** or **16** (0.06 mmol) were melted. After cooling to room temperature the resulting solid was analyzed by nmr spectroscopy.

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REFERENCES

1. For a recent review on haloalkyl isothiocyanates in heterocyclic chemistry: M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, and J. C. Palacios, *Heterocycles*, **1992**, *33*, 973.
2. See for instance a) O. Behner and W. Stendel, Ger. Offen. 2,015,675, 1971 (*Chem. Abstr.*, **1972**, *76*, 46195q); b) Sumitomo Chemical Co. Ltd., Japan Kokai Tokkyo Koho JP 82,106,674, 1982 (*Chem. Abstr.*, **1982**, *97*, 182402r); c) Sumitomo Chemical Co. Ltd., Japan Kokai, Tokkyo Koho JP 82,144,205, 1982 (*Chem. Abstr.*, **1983**, *98*, 12930q).

3. a) G. A. Johnson, S. J. Boukma, and E. G. Kim, *J. Pharmacol. Exp. Ther.*, **1970**, *171*, 80; b) P. F. von Voigtlander and K. E. Moore, *Proc. Soc. Exp. Biol. Med.*, **1970**, *133*, 817.
4. a) O. Hornykiewicz in, Biogenic Amines and Physiological Membranes in Drug Therapy, *Medicinal Chemistry Research Series*, ed. by J. H. Biel and L. G. Abood, New York, 1971, No. 5, Part B, pp 173-258; b) D. D. Miller and N. J. Uretsky, Dopaminergic Agonists and CNS Receptors, in *Advances in CNS Drug-Receptor Interactions*, ed. by J. G. Cannon, JAI Press, Greenwich, CT, 1991.
5. R. J. Outcalt, *J. Heterocycl. Chem.*, **1987**, *24*, 1425.
6. M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, and J. C. Palacios, *Heterocycles*, **1990**, *30*, 463.
7. E. Fromm and R. Kapeller-Adler, *Ann. Chem.*, **1928**, *467*, 240.
8. D. L. Klayman, J. J. Maul, and G. W. A. Milne, *Tetrahedron Lett.*, **1967**, 281.
9. D. L. Klayman, J. J. Maul, and G. W. A. Milne, *J. Heterocycl. Chem.*, **1968**, *5*, 517.
10. J. L. Flippen and I. L. Karle, *J. Phys.Chem.*, **1970**, *74*, 769.
11. a) E. Cherbuliez, B. Baehler, S. Jaccard, H. Jindra, G. Weber, G. Wyss, and J. Rabinowitz, *Helv. Chim. Acta*, **1966**, *49*, 807; b) E. Cherbuliez, B. Baehler, O. Espejo, S. Jaccard, H. Jindra, and J. Rabinowitz, *Helv. Chim. Acta*, **1966**, *49*, 2408; c) J. Rabinowitz, *Helv. Chim. Acta*, **1969**, *52*, 255.
12. Y. Yamamoto, R. Yoda, and M. Matsumura, *Chem. Pharm. Bull.*, **1975**, *23*, 2134.
13. Y. Yamamoto and R. Yoda, *Bull. Kyoritsu Pharm. College*, **1973**, *18*, 53.
14. Y. Yamamoto, R. Yoda, and K. Sekine, *Kyoritsu Yakka Daigaku Kenkyu Nenpo*, **1976**, *21*, 48 (*Chem. Abstr.*, **1977**, *87*, 135171y).
15. S. Gabriel, *Ber.*, **1889**, *20*, 1150. See also *Beilstein Handbuch der Organische Chemie*, Band III, *27*, 361.
16. C. R. Rasmussen, F. J. Villani, Jr., M. S. Mutter, and E. A. Griffin, *J. Org. Chem.*, **1986**, *51*, 1910, and references cited therein.
17. a) M. Avalos, R. Babiano, P. Cintas, J. Fuentes, J. L. Jiménez, and J. C. Palacios, *Heterocycles*, **1989**, *29*, 1; b) M. Avalos, R. Babiano, P. Cintas, J. Fuentes, J. L. Jiménez, and J. C. Palacios, *Nucleosides & Nucleotides*, **1990**, *9*, 137; c) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, and J. C. Palacios. *Carbohydr. Res.*, **1990**, *198*, 247.
18. H. Ogura, K. Takeda, and H. Takayanagi, *Heterocycles*, **1989**, *29*, 1171.
19. J. Fuentes, W. Moreda, C. Ortiz, I. Robina, and C. Welsh, *Tetrahedron*, **1992**, *48*, 6413.
20. Crystallographic parameters will be reported elsewhere: M. J. Dianez, M. D. Estrada, A. López-Castro, and S. Pérez, unpublished results.
21. H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Ber.*, **1949**, *82*, 389.

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