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Cyclization of Isothiosemicarbazones. III.[1] Formation of Thiazolines and Thiazoles through Potential Sulfonium Salts from *N,S*-Disubstituted Isothiosemicarbazones

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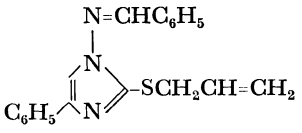
The reaction of 3,4-disubstituted isothiosemicarbazones with α-bromo ketones led to the formation of 4-thiazoline derivatives, the substituents on the sulfur atom being cleaved as bromides. They are identical with the compounds obtained by the condensation of the corresponding thiosemicarbazones, having significantly lower *E*/*Z* ratios in certain products than in those from thiosemicarbazones. The yields of 4-thiazolines widely vary with the substituents on the N-4 and the sulfur atom in the isothiosemicarbazones and also with halo ketones. A mechanism has been suggested which deals with a sulfonium-formation and dissociation process at the apparently less nucleophilic sulfur atom of isothiosemicarbazone. The mechanism might explain the effect of changes in the substituents on the sulfur atom upon the yield of 4-thiazolines, the higher contents of (*Z*)-4-thiazoline from (*E*,*E*)-2,6-dichlorobenzaldehyde 3-allyl-4-methylisothiosemicarbazone, and the inertness or less reactivity of anisaldehyde 2,3-dimethylisothiosemicarbazone and salicylaldehyde 3-allyl-4-phenylisothiosemicarbazone. Differentiation between isomeric thiazole and 4-thiazoline compounds was also described.

Cyclocondensation of a number of isothiosemicarbazones with α-halo carbonyl compounds leads to the formation of 2-mercapto-1*H*-imidazole derivatives and other nitrogen-containing heterocycles.[1,2] In an attempt to improve the yield of imidazoles, an equimolar mixture of benzaldehyde *S*-allylisothiosemicarbazone (**3r**) and phenacyl bromide (**4b**) was heated in toluene at a bath temperature of 130 °C. An appreciable amount of compound was detected with a characteristic resonance at δ 6.80 ppm in chloroform-*d* together with the major product of 1-benzylideneamino-2-allylthio-4-phenyl-1*H*-imidazole (**1**). On the basis of spectral



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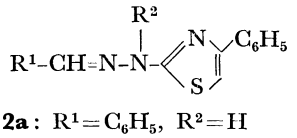


2a: $R^1=C_6H_5$, $R^2=H$
2b: $R^1=p$-$CH_3OC_6H_4$, $R^2=CH_3$

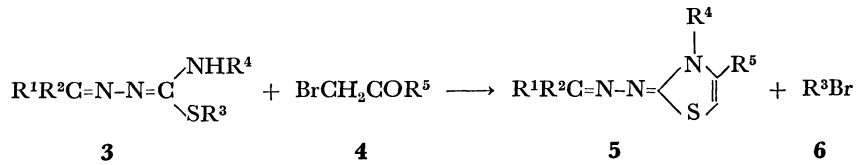
data and elemental analysis, the compound has been identified as benzaldehyde 4-phenyl-2-thiazolylhydrazone (**2a**). The formation of **2a** is of particular interest because it apparently involves an allyl-phenacyl exchange reaction on the much less nucleophilic sulfur atom of the isothiosemi-carbazone than that of alkyl sulfides,[3] probably through a sulfonium formation and dissociation process.[4] In the present work, some isothiosemicarbazones in which the N-2 or N-4 was blocked by certain substituents to prevent the imidazole formation were reacted with α-bromo ketones and the effects of substituent on the formation of sulfur-containing five-membered ring were examined in order to elucidate the reaction pathway.

Results and Discussion

An equimolar mixture of **3n** and **4b** was heated in toluene at a bath temperature of 130 °C for 90 min. A product with a characteristic resonance at δ 6.10 ppm in chloroform-*d*, having a molecular formula $C_{23}H_{19}N_3OS$ (M^+, 385) and showing no NH stretching band in the IR spectrum, was obtained by column-chromatographic separation on silica gel. It was found to be identical with a compound prepared by the condensation of anisaldehyde 4-phenylthiosemicarbazone with **4b** according to methods[5] for the preparation of 2-[alkylidene(or arylmethylene)hydrazono]-4-thiazolines and consequently assigned a structure of 2-(*p*-methoxyphenylmethylenehydrazono)-3,4-diphenyl-4-thiazoline (**5k**).

The NMR spectrum of a low-boiling portion distilled from the reaction mixture of **3o** and **4b** in toluene was found to be indentical with that of 3-bromopropene in this solvent, providing evidence for the formation of **6c** in the reaction. Similarly, a volatile compound formed by the reaction between **3b** and **4b** was identified as 1-bromopropane (**6b**). The expected high-boiling **6d** was detected by direct NMR measurement at intervals of the reaction mixture of **3p** and **4b** in toluene-d_8. No bromomethane (**6a**), which would be formed from the reaction of **3n**, was collected. The equation of the present reactions between 3,4-disubstituted isothiosemicarbazones (**3**) and α-bromo ketones (**4**) can thus be written as in Scheme 1.

The conditions for obtaining **5k** in the preliminary work can successfully be applied to the reactions of other isothiosemicarbazones, representing a general procedure[6] for carrying out the present reactions. The formation of **5** from 3,4-disubstituted isothiosemicarbazones showed considerable solvent-dependence (Table 1). Little or no formation of **5** was noted in acetic acid, 1-butanol, and dimethyl sulfoxide (DMSO),[8] a complex mixture being produced from which no identifiable materials were isolated. A polar solvent might promote the sulfonium formation, since the transition state for the reaction is more polar than the starting materials.[9] On the other hand, the starting isothiosemicarbazones and bromo ketones are not very stable in polar solvents, particularly in those having solvolytic action on the bromo ketone to generate hydrogen bromide which might destroy the starting materials or facilitate side reactions at elevated temperatures. Less polar solvents such as toluene and chlorobenzene seem to be more suitable for the 4-



3 4 5 6

4a: $R^5=CH_3$
4b: $R^5=C_6H_5$

6a: $R^3=CH_3$
6b: $R^3=CH_2CH_2CH_3$
6c: $R^3=CH_2CH=CH_2$
6d: $R^3=CH_2C_6H_5$

	R^1	R^2	R^3	R^4
3a:	C_6H_5	H	CH_3	$CH_2CH=CH_2$
3b:	C_6H_5	H	$CH_2CH_2CH_3$	C_6H_5
3c:	C_6H_5	H	$CH_2CH=CH_2$	C_6H_5
3d:	C_6H_5	CH_3	$CH_2CH=CH_2$	CH_3
3e:	C_6H_5	C_6H_5	$CH_2CH=CH_2$	CH_3
3f:	*o*-HOC_6H_4	H	CH_3	C_6H_5
3g:	*o*-HOC_6H_4	H	$CH_2CH=CH_2$	C_6H_5
3h:	*o*-$CH_3OC_6H_4$	H	$CH_2CH=CH_2$	C_6H_5
3i:	*p*-$CH_3OC_6H_4$	H	CH_3	CH_3
3j:	*p*-$CH_3OC_6H_4$	H	$CH_2CH=CH_2$	CH_3
3k:	*p*-$CH_3OC_6H_4$	H	$CH_2C_6H_5$	CH_3
3m:	*p*-$CH_3OC_6H_4$	H	$CH_2CH=CH_2$	$CH(CH_3)_2$
3n:	*p*-$CH_3OC_6H_4$	H	CH_3	C_6H_5
3o:	*p*-$CH_3OC_6H_4$	H	$CH_2CH=CH_2$	C_6H_5
3p:	*p*-$CH_3OC_6H_4$	H	$CH_2C_6H_5$	C_6H_5
3q:	2,6-$Cl_2C_6H_3$	H	$CH_2CH=CH_2$	CH_3
3r:	C_6H_5	H	$CH_2CH=CH_2$	H

Scheme 1. The reaction of 3,4-disubstituted isothiosemicarbazones with α-bromo ketones.

TABLE 1. YIELD/%[7] OF **5** IN DIFFERENT SOLVENTS

Compd[a]/Solv.	Toluene	*N*,*N*-Dimethyl-formamide	2-Methoxy-ethanol	Chloro-benzene	Dioxane
5h	47	54	43	—	30
5k	70—68	16	13	62	44

a) From the corresponding *S*-allylisothiosemicarbazones, **3j** and **3o**, at a bath temperature of 130 °C for 20 min.

thiazoline or thiazole formation rather than highly polar ones.

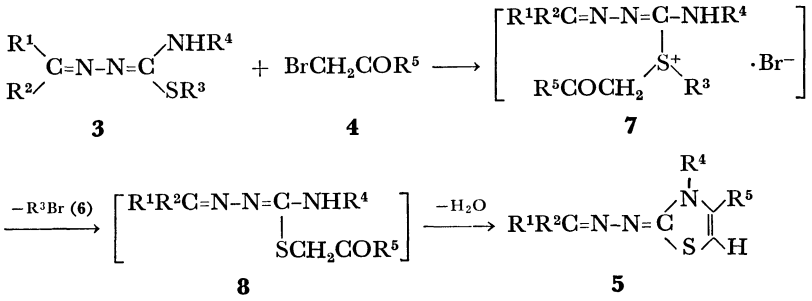
When **3n** was allowed to react with **4b** in acetonitrile or ethanol at the reflux temperature, 3-(*p*-methoxyphenyl)-4-phenyl-5-methylthio-4*H*-1,2,4-triazole was the only product which could be isolated and identified,[10] its yield amounting to 30% in the latter solvent. The triazole may be formed through electrocyclic reaction[11] of the starting isothiosemicarbazone followed by autoxidation of the intermedially formed 3-methylthio-4-phenyl-5-(*p*-methoxyphenyl)-1,5-dihydro-1,2,4-triazole by analogy with oxidative cyclization of thiosemicarbazones.[12]

Since the ring closure of 3,4-disubstituted isothiosemicarbazone with loss of **6** involves displacement of R^3 by a phenacyl group, the reaction might depend primarily upon the nature of substituent on the sulfur atom. An equimolar mixture of **3i**, **3j**, **3k**, and **4b** in toluene was heated at a bath temperature of 130 °C for 15 min. **4b** disappeared and the approximate molar ratio of the remaining isothiosemicarbazones, estimated on the basis of the NMR spectrum, was found to be 1:18:30 for allyl, benzyl, and methyl compounds, respectively. Although the ratio may represent the relative reactivity of the three isothiosemicarbazones, the yield of **5h** in this reaction was only as little as 42% based on the consumed isothiosemicarbazones due to undetermined side reactions. The above order of reactivities of isothiosemicarbazones, however, is reflected in the actual yields of **5** obtained by the reaction of anisaldehyde 4-methyl- and 4-phenylisothiosemicarbazones bearing allyl, benzyl, or methyl group on the sulfur atom with **4b** in toluene (Table 2). This is in line with the order of stability of the carbocations corresponding to these substituents, the order not being affected by the nature of R^4. The higher yields of **5** from 3-allyl- and 3-benzylisothiosemicarbazones can be rationalized as a result of easy ionization of these groups by S_N1 type pathway from the positively charged

TABLE 2. YIELDS[a] OF 2-(*p*-METHOXYBENZYLIDENEHYDRAZONO)-4-THIAZOLINES FROM 3,4-DISUBSTITUTED ISOTHIOSEMICARBAZONES BEARING VARIOUS SUBSTITUENTS ON THE SULFUR ATOM

	R^3		
	CH_3[b]	$CH_2C_6H_5$	$CH_2CH=CH_2$
5h	9—11	38	47
5k	26	57	70

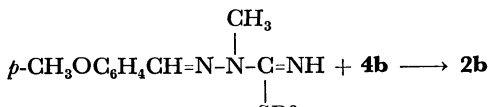
a) Obtained by heating an equimolar mixture of **3** and **4b** in toluene at a bath temperature of 130 °C for 20 min and isolating **5** by means of column chromatography. b) Heated for 90 min.



Scheme 2. Mechanism of 4-thiazoline formation.

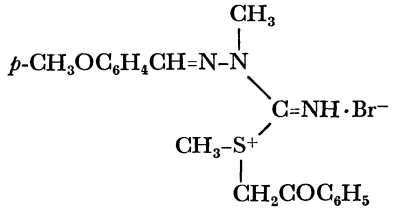
sulfur atom of potential sulfonium salt (**7**). On the other hand, the reaction of **3b** with **4b** gave **5b** (10% yield) and **6b**, but no 2-bromopropane which would be formed if the 3-propyl group is dissociated as a free carbocation from the sulfur atom. Thus 3-propyl- and probably also 3-methylisothiosemicarbazones should react with **4b** to yield the corresponding **5** through S_N2 type dissociation of the sulfonium salt (**7**) into **6b** or **6a** and *S*-phenacylisothiosemicarbazone ($R^5=C_6H_5$) (**8**). In either case, **8** may rapidly cyclize to **5** and can be considered a common intermediate through which the same 4-thiazoline was produced from the corresponding thiosemicarbazone. A tentative mechanism for the 4-thiazoline formation is shown in Scheme 2. The reaction should involve, as the first step, nucleophilic attack of the α-carbon of the halo ketone by sulfur atom as in the simple alkylation reaction of alkyl sulfides.[4] However, the nucleophilicity of the sulfur atom of isothiosemicarbazones seems to be much lower than that of alkyl sulfides, since one of the α-carbons becomes attached to electron-withdrawing groups and the lone electron pairs on the sulfur conjugate to the 2,3-diaza-1,3-butadiene system which may further extend to R^1. Thus the thiazoline formation from isothiosemicarbazones can occur with acetonyl and phenacyl bromides (**4a** and **4b**), but not with the corresponding less reactive chlorides even under drastic conditions.

Under general reaction conditions, **9a** was unreactive and gave no expected thiazole (**2b**) upon heating with **4b** in toluene. In contrast to the inertness of 2,3-dimethyl compound (**9a**), 2-methyl-3-allylisothiosemicarbazone (**9b**) and 2-methylthiosemicarbazone (**9c**) gave **2b** in 64 and 81% yields, respectively. The



9a: $R^3=CH_3$
9b: $R^3=CH_2CH=CH_2$
9c: $R^3=H$

methyl group at the 2-position is by no means obstructive to the ring closure of the probable *S*-phenacylisothiosemicarbazone. The extremely diminished reactivity of **9a** may be explained in terms of the restraint of S_N2-type attack of the bromide ion on the methyl carbon in the sulfonium salt (**10**), presumably due to the free rotation about the N^2–C bond, which gives **10** a less rigid, fluttering structure, the methyl moiety



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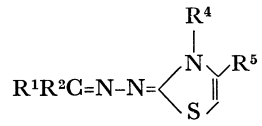
responsible for this reaction thus being a more elusive target for bromide ion. On the other hand, **9b** can produce *S*-phenacylisothiosemicarbazone and **6c** through S_N1 pathway from the sulfonium salt, leading to the formation of the corresponding thiazole. *o*-Hydroxybenzylidene compound (**3g**) required much longer reaction periods (5 h or more) than did the *o*-methoxy analog (**3h**) to give **5e** in comparable yields, although salicylaldehyde 4-phenylthiosemicarbazone gave **5e** in almost quantitative yield upon brief heating with **4b**. Since **3h** gave **5f** in 55% yield within 20 min, the strong intramolecular hydrogen bonding associated with the phenolic hydrogen and the N-1 atom (νOH 3060 cm^{-1} at 2×10^{-3} mol dm^{-3} in carbon tetrachloride) should account for the lower reactivity of **3g** by withdrawing electrons through 2,3-diaza-1,3-butadiene system from the sulfur atom. The unexpectedly high yield of **5d** from **3e** may be interpreted as a result of the exclusion of possible side reactions involving the azomethine double bond by virtue of the two bulky phenyl groups attached.

With bromoacetone (**4a**), major portions of the starting isothiosemicarbazones (**3j** and **3o**) remained unreacted under the general reaction conditions, **5g** and **5i** being obtained in 17 and 5% yields, respectively. Prolonged periods of time caused darkening of the reaction mixture, giving no improvement in the yield of **5**. 2-Arylmethylenehydrazono-3,4-disubstituted 4-thiazolines obtained are given in Table 3.

Compound **5m** formed through the allyl-phenacyl exchange reaction from (*E*,*E*)-**3q**[13] consists of two isomers, *E* and *Z* forms, and has higher content of *Z* (38%) than that produced by the reaction between (*E*)-2,6-dichlorobenzaldehyde 4-methylthiosemicarbazone (**11**) and **4b**, the latter route giving a mixture of *E* (91%) and *Z* (9%) forms. The higher content of *Z* compound was not the result of simple thermal isomerization of initially formed *E* isomer to *Z* form, since the pure (*E*)-**5m** isomerized to only 8% to *Z* upon heating in toluene at 130 °C for the same period of time as that for the reaction of **3q** with **4b**. Di-

TABLE 3. 2-ARYLMETHYLENEHYDRAZONO-3,4-DISUBSTITUTED 4-THIAZOLINES



Compd No.	R^1	R^2	R^4	R^5	Yield/%[a]	Mp/°C	Formula	Found(%) C	H	N	Calcd(%) C	H	N	PMR[b] H-5
5a	C_6H_5	H	$CH_2CH=CH_2$	C_6H_5	22[c]	139.5—140.5	$C_{19}H_{17}N_3S$	71.73	5.40	13.41	71.45	5.37	13.16	5.96
5b	C_6H_5	H	C_6H_5	C_6H_5	59	189.5—190.5	$C_{22}H_{17}N_3S$	74.25	4.83	11.80	74.35	4.82	11.84	6.15
5c	C_6H_5	CH_3	CH_3	C_6H_5	55	102—104	$C_{18}H_{17}N_3S$	70.38	5.58	13.83	70.34	5.58	13.67	5.92
5d	C_6H_5	C_6H_5	CH_3	C_6H_5	98	168—169	$C_{23}H_{19}N_3S$	74.68	5.06	11.25	74.77	5.18	11.37	5.93
5e	*o*-HOC_6H_4	H	C_6H_5	C_6H_5	62	206	$C_{22}H_{17}N_3OS$	70.86	4.51	11.24	71.15	4.61	11.32	6.17
5f	*o*-$CH_3OC_6H_4$	H	C_6H_5	C_6H_5	55	178—180	$C_{23}H_{19}N_3OS$	71.63	5.01	10.94	71.67	4.97	10.90	6.08
5g	*p*-$CH_3OC_6H_4$	H	CH_3	CH_3	17	222—222.5[e]	$C_{13}H_{16}BrN_3OS$	45.53	4.74	12.34	45.62	4.71	12.28	5.65[d]
5h	*p*-$CH_3OC_6H_4$	H	CH_3	C_6H_5	47	124—125.5	$C_{18}H_{17}N_3OS$	67.16	5.33	12.99	66.86	5.30	13.00	5.95
5i	*p*-$CH_3OC_6H_4$	H	C_6H_5	CH_3	5	189—190[e]	$C_{18}H_{18}BrN_3OS$	53.54	4.36	10.32	53.47	4.49	10.39	5.65[d]
5j	*p*-$CH_3OC_6H_4$	H	$CH(CH_3)_2$	C_6H_5	57	141.5	$C_{20}H_{21}N_3OS$	68.57	6.01	12.12	68.36	6.02	11.96	5.79
5k	*p*-$CH_3OC_6H_4$	H	C_6H_5	C_6H_5	70	163—166	$C_{23}H_{19}N_3OS$	71.53	4.94	10.89	71.67	4.97	10.90	6.10
5m	2,6-$Cl_2C_6H_3$	H	CH_3	C_6H_5	58[f]	149.5—150[g]	$C_{17}H_{13}Cl_2N_3S$	56.09	3.52	11.69	56.36	3.62	11.60	5.98
						96—97.5[h]	$C_{17}H_{13}Cl_2N_3S$	56.44	3.56	11.46	56.36	3.62	11.60	5.97

a) Obtained from *S*-allylisothiosemicarbazones unless otherwise indicated. b) All the values are for free bases in deuteriochloroform. c) Obtained from *S*-methylisothiosemicarbazone. d) A poorly resolved quartet, $J=ca.$ 1.2 Hz. e) Hydrobromide salt. f) Consisting of two isomers, 62% *E* and 38% *Z*. g) *Z* form. h) *E* form.

TABLE 4. CHEMICAL SHIFTS[a] OF THIAZOLE(**2b**) AND 4-THIAZOLINE(**5h**)

	NCH_3	C_6H_5	CH=N	H-5
2b	3.69	$H^{m,p}$ 7.32	7.56	6.88
		H^{o} 7.89		
5h	3.34	7.40	8.32	5.95

a) δ ppm from internal TMS in $CDCl_3$.

minished bond order of the $CH=N^1$ bond in the intermediate species bearing positive charge on the sulfur atom might be responsible for the promoted isomerization. These isomers could be differentiated on the basis of the NMR spectrum in which the azomethine proton ($CH=N^1$) of *E* form resonated at δ 8.61 and that of *Z* form at δ 7.65 ppm in chloroform-*d*. In view of the greater difference (0.96 ppm) between the chemical shifts of the azomethine protons of these two isomers and a smaller difference (0.26 ppm) between the resonances of N-methyl protons and the substantially equivalent value for the H-5 proton on the thiazoline ring (Table 3), the isomerism should be about the $C=N^1$ bond rather than $N^2=C$ bond.[14] The proximity of aldehydic proton to the electron pair of nitrogen in *Z* aldoxime caused upfield shift of that proton relative to the corresponding *E* aldoxime.[15] Thus the predominant isomer exhibiting downfield resonance should be of *E*-configuration. A trace of *Z* compound was also detected in the reaction of **3d** with **4b**, being easily removed by means of column chromatography. Recently, assignment of isomeric hydrazones of 2,6-dichlorobenzaldehyde on the basis of NOE observation[16] has been proposed and the conclusions may similarly apply to the present compounds.

A predominant tautomer has been determined by means of UV spectroscopy[17] in the 2-hydrazino-4-phenylthiazole and 2-hydrazono-4-phenyl-4-thiazoline system. An isomeric pair of thiazole (**2b**) and 4-thiazoline (**5h**) showed certain spectral differences sufficient to distinguish them from each other. In the mass spectrometry, the primary fragmentation of **5h** occurred at the $N^2=C$ bond to produce a fragment ion, *m/e* 176, representing the base peak, whereas that of **2b** took place at the N–N bond giving an ion, *m/e* 134 (100%) (*p*-$CH_3OC_6H_4$–$C\equiv\overset{+}{N}H$). The former ion may be produced by hydrogen transfer from the azomethine carbon to the sulfur of thiazoline ring, probably through a six-membered transition state. This was confirmed by the spectrum of 2-(α-deuteriobenzylidenehydrazono)-3,4-diphenyl-4-thiazoline which showed a fragment ion, *m/e* 239, as compared with the value *m/e* 238 for that of the corresponding protium compound (**5b**). Further differentiation could be made on the basis of NMR spectra of **2b** and **5h** (Table 4). The resonance of H-5 proton on the heterocyclic ring seems to be of particular diagnostic value for this purpose.

Experimental

General. Melting points were determined in an open glass capillary and are uncorrected. ^1H NMR spectra, obtained with a Hitachi R-24 spectrometer (60 MHz) in chloroform-*d*, are given in δ ppm downfield from internal tetramethylsilane unless otherwise stated. IR spectra were obtained on a Hitachi EPI-G2 or 260-30 grating spectrophotometer and mass spectra (75 eV) on a Japan Electron Optics JMS-D100 mass spectrometer. Wakogel C-300 was used for column chromatography. Commercial phenacyl bromide (**4b**) was recrystallized from ethanol to give colorless prisms, mp 50 °C (lit,[18] mp 50 °C).

Thiosemicarbazones. All the thiosemicarbazones, $R^1R^2C=NNHCSNHR^4$, were prepared by the conventional method.[19] New ones are (R^1, R^2, R^4, % yield, mp °C, and elemental analyses given): C_6H_5, CH_3, CH_3, 78, 134.5—136. Found: C, 57.83; H, 6.39; N, 20.57%. Calcd for $C_{10}H_{13}$-

N_3S: C, 57.96; H, 6.32; N, 20.28%. *o*-$CH_3OC_6H_4$, H, C_6H_5, 87, 150—151. Found: C, 63.07; H, 5.28: N, 14.82%. Calcd for $C_{15}H_{15}N_3OS$: C, 63.15; H, 5.30; N, 14.73%. *p*-$CH_3OC_6H_4$, H, $CH(CH_3)_2$, 81, 192—193.5. Found: C, 57.26; H, 6.91; N, 16.69%. Calcd for $C_{12}H_{17}N_3OS$: C, 57.35; H, 6.82; N, 16.72%. 2,6-$Cl_2C_6H_3$, H, CH_3, 89, 190—191. Found: C, 41.11; H, 3.39; N, 16.27%. Calcd for $C_9H_9Cl_2N_3S$: C, 41.23; H, 3.46; N, 16.03%.

Isothiosemicarbazones. The compounds **3a**—**3r** were prepared according to the procedure reported previously[20] with some appropriate modifications. New ones are: **3a** (HBr salt): yellow prisms (from EtOH), mp 163—164 °C, yield 89%. Found: C, 45.99; H, 5.09; N, 13.63%. Calcd for $C_{12}H_{16}BrN_3S$: C, 45.86; H, 5.13; N, 13.37%. **3b**: colorless prisms (from hexane), mp 58—59 °C, yield 31%. Found: C, 68.55; H, 6.45; N, 13.90%. Calcd for $C_{17}H_{19}N_3S$: C, 68.66; H, 6.44; N, 14.13%. **3c** (HBr salt): pale yellow prisms (from EtOH), mp 161—162.5 °C, yield 93%. Found: C, 54.24; H, 4.80; N, 11.32%. Calcd for $C_{17}H_{18}BrN_3S$: C, 54.26; H, 4.82; N, 11.17%. **3d** (HBr salt): colorless needles (from EtOH), mp 156—157 °C, yield 87%. Found: C, 47.44; H, 5.53; N, 12.80%. Calcd for $C_{13}H_{18}BrN_3S$: C, 47.56; H, 5.53; N, 12.80%. **3e** (HCl salt): faintly yellowish needles (from aqueous *i*-PrOH), mp 128—129 °C, yield 61%. Found: C, 70.07; H, 6.15; N, 13.63%. Calcd for $C_{18}H_{19}N_3S$ (free base): C, 69.88; H, 6.19; N, 13.58%. **3f**: yellow prisms (from benzene–*i*-PrOH, 1:1 by volume), mp 137—138 °C, yield 89%. Found: C, 63.10; H, 5.29; N, 14.83%. Calcd for $C_{15}H_{15}N_3OS$: C, 63.15; H, 5.30; N, 14.73%. **3g**: pale yellow needles (from *i*-PrOH), 78—78.5 °C, yield 77%. Found: C, 65.50; H, 5.44; N, 13.56%. Calcd for $C_{17}H_{17}N_3OS$: C, 65.58; H, 5.50; N, 13.50%. **3h** (HBr salt): pale yellow fine needles (from EtOH), mp 157—158 °C, yield 88%. Found: C, 52.99; H, 4.93; N, 10.30%. Calcd for $C_{18}H_{20}BrN_3OS$: C, 53.21; H, 4.96; N, 10.34%. **3j** (HBr salt hemihydrate): yellow needles (from MeOH), mp 116.5—117 °C, yield 83%. Found: C, 44.06; H, 5.45; N, 11.72%. Calcd for $C_{13}H_{18}BrN_3OS \cdot 1/2H_2O$: C, 44.20; H, 5.42; N, 11.89%. **3k**: pale yellow fine needles (from *i*-Pr_2O), mp 55—56 °C, yield 96%. Found: C, 64.88; H, 6.00; N, 13.42%. Calcd for $C_{17}H_{19}N_3OS$: C, 65.16; H, 6.11; N, 13.41%. **3m** (HBr salt hemihydrate): pale yellow prisms (from EtOH), mp 98—99 °C, yield 92%. Found: C, 47.28; H, 6.13; N, 10.99%. Calcd for $C_{15}H_{22}BrN_3OS \cdot 1/2H_2O$: C, 47.25; H, 6.08; N, 11.02%. **3n**: pale yellow needles (from EtOH), mp 112 °C, yield 89%. Found: C, 64.15; H, 5.78; N, 14.13%. Calcd for $C_{16}H_{17}N_3OS$: C, 64.20; H, 5.72; N, 14.04%. **3o** (HBr salt): pale yellow needles (from EtOH), mp 157—158 °C, yield 89%. Found: C, 53.01; H, 4.91; N, 10.41%. Calcd for $C_{18}H_{20}BrN_3OS$: C, 53.21; H, 4.96; N, 10.34%. **3p**: faintly yellowish needles (from benzene–*i*-PrOH, 1:3 by volume), mp 138—138.5 °C, yield 87%. Found: C, 70.61; H, 5.52; N, 11.05%. Calcd for $C_{22}H_{21}N_3OS$: C, 70.38; H, 5.64; N. 11.19%. **3q** (HBr salt): pale yellow prisms (from EtOH), mp 167.5—168.5 °C, yield 62%. Found: C, 37.62; H, 3.65; N, 11.18%. Calcd for $C_{12}H_{14}BrCl_2N_3S$: C, 37.62; H, 3.68; N, 10.97%. **3r**: colorless needles (from hexane), mp 41—41.5 °C, yield 80%. Found: C, 60.52; H, 5.86; N, 19.28%. Calcd for $C_{11}H_{13}N_3S$: C, 60.26; H, 5.98; N, 19.15%. **9b** (HBr salt): pale yellow needles (from MeOH), 175—175.5 °C, yield 54%. Found: C, 45.46; H, 5.22; N, 12.30%. Calcd for $C_{13}H_{18}BrN_3OS$: C, 45.35; H, 5.27; N, 12.21%.

*The Reaction of Benzaldehyde 3-Allylisothiosemicarbazone (**3r**) with Phenacyl Bromide (**4b**).* A solution of **3r** (0.22 g, 1 mmol) and **4b** (0.20 g, 1 mmol) in toluene (1 ml) was heated under reflux in an oil bath at 130 °C for 20 min and then the solvent was evaporated under reduced pressure. The residue was partitioned between chloroform and a 10% aqueous sodium carbonate solution. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The remaining viscous liquid (0.31 g) was subjected to column-chromatographic separation on silica gel (20 g) using a benzene–ethanol mixture (98:2 by volume). Two fractions, imidazole (0.11 g) and thiazole (0.02 g), each consisting a substantially pure compound, were obtained. Recrystallization of the former twice from ethanol gave **1** as pale yellow needles (0.02 g), mp 101—102 °C. IR (KBr): 3140 cm^{-1} (νC–H of imidazole ring[21]); NMR: 3.95 (2H, dt, J=7 Hz and *ca.* 1 Hz, SCH_2), 5.03—6.43 (3H, m, CH_2=CH), 7.36 (6H, m, $H^{m,p}$ of two phenyls), 7.69 (1H, s, H-5 of imidazole ring), 7.78 (4H, m, H^o of two phenyls), 8.25 (1H, s, CH=N); MS (75 eV), *m/e* (rel intensity), 319(100) (M^+), 277(29), 220(97), 215(93), 173(34), 117(51), 104(31), 103(69), 77(45), 41(22). Found: C, 71.26; H, 5.33; N, 13.05%. Calcd for $C_{19}H_{17}N_3S$: C, 71.45; H, 5.37; N, 13.16%; M, 319. This was identical with a compound obtained by the standard method.[2] The thiazole **2a** exhibited IR and NMR spectra identical with those of an authentic sample (mp 191—192 °C; Found: C, 69.03; H, 4.63; N, 14.82%; M^+, 279. Calcd for $C_{16}H_{13}N_3S$: C, 68.80; H, 4.69; N, 15.05%; M, 279) which was prepared by heating an equimolar mixture of benzaldehyde thiosemicarbazone and **4b** in 80% aqueous ethanol and neutralizing the hydrobromide formed with aqueous sodium carbonate. The hydrobromide conventionally prepared from the thiazole fraction showed no depression in melting point on mixing with the authentic sample (223 °C).

*The Reaction of Benzaldehyde 3-Allyl-4-phenylisothiosemicarbazone (**3c**) with **4b** (a Typical Example).* A mixture of **3c** (0.3 g, 1 mmol), **4b** (0.2 g, 1 mmol), and toluene (2 ml) was heated in an oil bath at 130 °C for 20 min with occasional agitating and then the solvent was removed under reduced pressure. The residue was partitioned between chloroform and a 10% aqueous sodium carbonate solution. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The remaining crystalline solid (0.38 g) was subjected to column chromatography on silica gel (30 g) eluting with benzene containing 1% by volume of ethanol. A homogeneous fraction (140 ml) gave **5b** as yellow crystals (0.21 g, 59%), mp 189—190 °C. Recrystallization from an acetone–benzene mixture (1:1 by volume) gave yellow prisms, mp 189.5—190.5 °C. NMR: 6.15 (1H, s, H-5 of 4-thiazoline ring), 7.15 (5H, s, phenyl), 7.27 (5H, s, phenyl), 7.32 (3H, m, $H^{m,p}$ of benzylidene group), 7.73 (2H, m, H^o of benzylidene group), 8.22 (1H, s, CH=N); MS, *m/e* (rel intensity), 355(100) (M^+), 326(25), 238(86), 133(22), 91(15), 77(48). Under similar conditions except for a heating period of 2.5 h, **3b** gave **5b** in 10% yield. The same compound was also obtained by refluxing benzaldehyde 4-phenylthiosemicarbazone (mp 189—191 °C, lit,[19a] mp 189 °C) with **4b** in 95% ethanol for 1 h and by recrystallization of the product, after being converted into the free base by an aqueous sodium carbonate solution, from an acetone–benzene mixture, mp 190—191.5 °C. Mixed melting point with **5b** showed no depression. Similarly benzaldehyde-α-*d* 4-phenylthiosemicarbazone (C_6H_5CD=N–NHCSNHC_6H_5) afforded the corresponding monodeuteriothiazoline, mp 190.5—191.5 °C; IR (KBr): νC–D 2200 cm^{-1}; MS, *m/e* (rel intensity) 356(100) (M^+), 327(25), 239(70), 133(16), 91(18), 77(32).

*The Reaction of 2,6-Dichlorobenzaldehyde 3-Allyl-4-methylisothiosemicarbazone (**3q**) with **4b**.* A mixture of **3q** (0.3

g, 1 mmol), **4b** (0.2 g, 1 mmol), and toluene (1 ml) was heated under reflux for 2.5 h and then evaporated under reduced pressure. Work-up of the residue in the same way as described in the reaction of **3c** with **4b** gave a thiazoline fraction (0.21 g, 58%) consisting of 62% *E* and 38% *Z* forms. This fraction was further subjected to column chromatography on silica gel (20 g) with benzene as an eluent giving a *Z* fraction (0.045 g) which preceded an *E* fraction (0.07 g). The *Z* compound, (*Z*)-**5m**, crystallized from ethanol as yellow plates (0.04 g), mp 149.5—150 °C. NMR: 3.12 (3H, s, NCH_3), 5.98 (1H, s, H-5 of 4-thiazoline ring), 7.27 (3H, s, 2,6-dichlorophenyl), 7.38 (5H, s, phenyl), 7.65 (1H, s, CH=N); MS, *m/e* (rel intensity), 363(30), 361(41) (M^+), 326(100), 176(29), 134(7), 123(17), 102(45), 91(13), 77(10). The *E* compound, (*E*)-**5m**, was obtained as a yellow oil which gradually solidified upon standing. Recrystallization of the solid from ethanol gave fine yellow needles, mp 96—97.5 °C. NMR: 3.38 (3H, s, NCH_3), 5.97 (1H, s, H-5 of 4-thiazoline ring), 7.20 (3H, m, 2,6-dichlorophenyl), 7.35 (5H, s, phenyl), 8.61 (1H, s, CH=N); MS, *m/e* (rel intensity), 363(25), 361(35) (M^+), 326(100), 176(36), 134(32), 123(27), 102(72), 91(17), 77(18). When **5m** containing *Z* isomer was converted into the hydrobromide and the salt recrystallized from ethanol, pure (*E*)-**5m** hydrobromide was obtained as pale yellow prisms solvated with one molecule of ethanol, mp 213.5—214 °C not depressed by the authentic sample prepared by the reaction of 2,6-dichlorobenzaldehyde 4-methylthiosemicarbazone with **4b**. NMR: 1.20 (3H, t, J=7 Hz, CCH_3), 3.72 (2H, q, J=7 Hz, CCH_2), 4.01 (3H, s, NCH_3), 6.81 (1H, s, H-5 of 4-thiazoline ring), 7.35 (3H, s, 2,6-dichlorophenyl), 7.51 (5H, m, phenyl), 9.70 (1H, s, CH=N), broadly dispersed signal centered at about 14.1 ($\overset{+}{N}H$ and OH). Found: C, 46.72; H, 3.95; N, 8.70%. Calcd for $C_{19}H_{20}BrCl_2N_3OS$: C, 46,64; H, 4.12; N, 8.59%.

*The Reaction of Anisaldehyde 2-Methyl-3-allylisothiosemicarbazone (**9b**) with **4b**.* A mixture of **9b** (0.09 g, 0.34 mmol), **4b** (0.07 g, 0.35 mmol), and toluene (0.5 ml) was refluxed for 2 h and evaporated under reduced pressure. The residue was worked up by the same procedure as described for the reaction of **3c** with **4b** to give anisaldehyde 1-methyl-1-(4-phenyl-2-thiazolyl)hydrazone (**2b**) (0.07 g, 64%) as yellow plates, mp 178—180 °C. Recrystallization from an *i*-Pr_2O–AcMe mixture (1:1 by volume) raised the melting point to 186.5—187 °C. NMR: 3.69 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 6.88 (1H, s, H-5 of thiazole ring), 6.92 (2H, d, J=9.0 Hz, *p*-methoxyphenyl), 7.32 (3H, m, $H^{m,p}$ of phenyl), 7.56 (1H, s, CH=N), 7.63 (2H, d, J=9.0 Hz, *p*-methoxyphenyl), 7.89 (2H, m, H^o of phenyl). Found: C, 66.79; H, 5.29; N, 12.86%; M^+, 323. Calcd for $C_{18}H_{17}N_3OS$: C, 66.86; H, 5.30; N, 13.00%; M, 323. The same compound was obtained by refluxing anisaldehyde 2-methylthiosemicarbazone (0.22 g, 1 mmol; mp 191 °C, lit,[21] mp 192 °C) and **4b** (0.20 g, 1 mmol) in ethanol (5 ml) for 1 h and neutralizing the hydrobromide with aqueous sodium carbonate as pale yellow plates (0.26 g, 81%), mp 185—187 °C, not depressed by admixture with the compound prepared as above.

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