Ring Transformation of 5-Aroyl-3(2*H*)-isothiazolones to 1,2,5-Oxathiazole and 1,2,3-Thiadiazole Derivatives [1]

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Reaction of 2-substituted-5-aroyl-3(2*H*)-isothiazolones **2** with hydroxylamine and phenylhydrazine was found to give (*N*-substituted-carboxamido)methylene derivatives of 1,2,5-oxathiazole and 1,2,3-thiadiazole, **5** and **7**, respectively. The formation of these heterocycles was ascribed to a mononuclear heterocyclic rearrangement of the initially formed ketone derivatives, oximes and hydrazones, through a nucleophilic attack of the =N-OH and =N-NH- groups on the S-N bond of the isothiazolone ring. In a similar manner, reaction of isothiazolones **2** with hydrazine was found to give 4-aryl-5-(*N*-substituted-carboxamido)methyl-1,2,3-thiadiazoles **17**.

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We have recently reported [2] that reaction of open chain γ-keto amides of the general formula **1** with excess thionyl chloride at room temperature results in the formation of 2-substituted-5-aroyl-3(2*H*)-isothiazolones **2**. This new and simple synthesis of isothiazolones **2** was since described also by Beer and Wright [3]. Reactions of nucleophilic cleavage of the S-N bond of 2-substituted-3(2*H*)-isothiazolones have been investigated by Crow, *et al.* [4]. A similar cleavage was observed in 2-substituted-5-aroyl-3(2*H*)-isothiazolones, since the dimerization products **3** of 2-substituted-3(2*H*)-isothiazolones [4] were also obtained by treatment of **2** with bases [2]. We now report a new ring transformation of compounds **2** to the heterocyclic compounds **5** and **7**, resulting again from a nucleophilic cleavage of the S-N bond.

The rearrangement reaction of **2** to **5** and **7** was discovered in an attempt to prepare ketone derivatives of the aroyl group of **2**, oximes **4** and hydrazones **6**, respectively.

When the *N*-benzylisothiazolone **2a** was treated with hydroxylamine hydrochloride in the presence of sodium acetate, a compound was obtained whose spectroscopic data were not consistent with the expected oxime structure **4a**. The proton nmr spectrum of the new compound lacked the typical singlet for the *N*-benzyl methylene protons of the parent isothiazolone **2a** (see Table 1) and revealed instead, beyond a vinyl proton singlet at δ 6.31 ppm, a two-protons doublet (δ 4.51 ppm, J = 5.6 Hz) and an one-proton broad triplet (δ 8.40 ppm, J = 5.6 Hz). These two signals could only be assigned to an *N*-benzylcarboxamido group, -CONHCH$_2$C$_6$H$_5$, and possibly to a β,β-disubstitu-

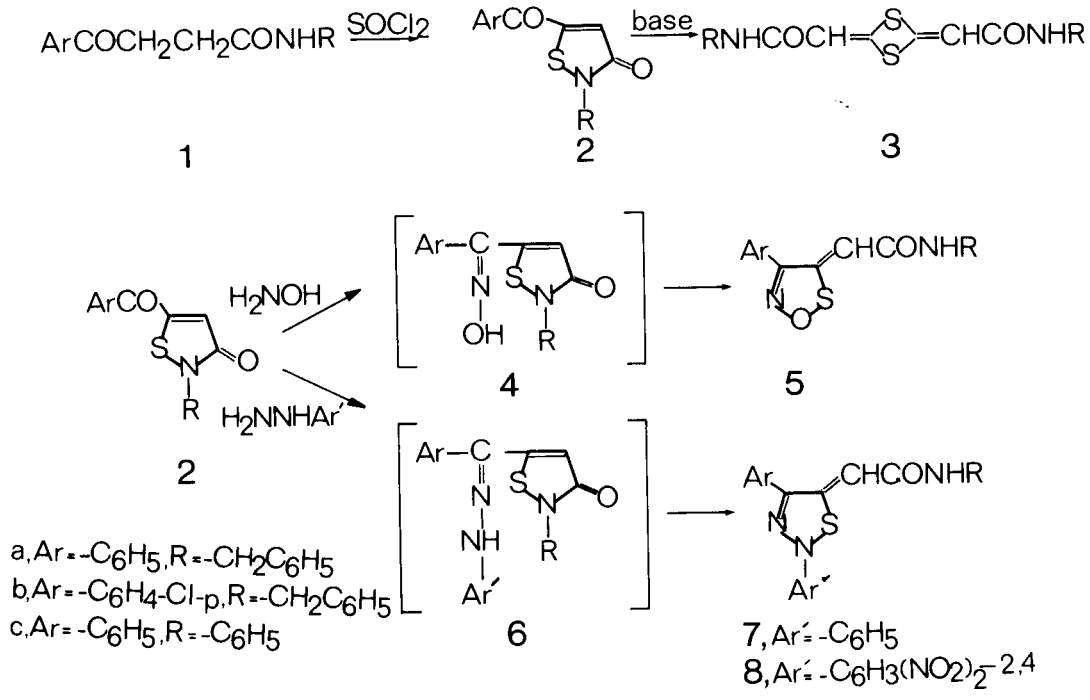


Table 1

PMR Spectra [a]

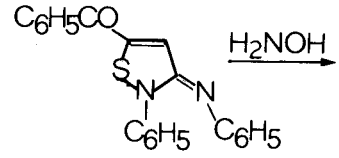
Compound (solvent) [b]	*N*-Benzyl methylene [c]	=CH-CON< or -CH_2-CON<	-CONH-	Aromatic protons
2a (A) [d]	4.97, s, 2H	6.72, s, 1H	——	7.20-7.95, m, 10H [e]
2b (A)	4.95, s, 2H	6.70, s, 1H	——	7.33, s, 5H, R 7.43 and 7.80, dd (8.5), 4H, Ar
5a (C)	4.51, d (5.6), 2H	6.31, s, 1H	8.40, br t (5.6), 1H	7.36, s, 5H, R 7.45-7.86, m, 5H, Ar
5b (A)	4.51, d (5.6), 2H	5.96, s [f]	5.88, br m [f]	7.25, s, 5H, R 7.46, apparent d, 4H, Ar
5c (C)	——	6.41, s, 1H	10.13, br s, 1H	6.96-7.83, m, 10H
7a (A)	4.56, d (5.6), 2H	6.00, s, 1H	5.73, br t (5.6), 1H	7.10-7.93, m, 15H [g]
(C)	4.46, d (5.6), 2H	6.30, s, 1H	8.50, br t (5.6), 1H	6.96-7.96, m, 15H [g]
7b (A)	4.53, d (5.6), 2H	5.95, s, 1H	5.80, br t (5.6), 1H	7.01-7.78, m, 14H [h]
8a (B)	4.36, br d (5.6), 2H	6.41, s, 1H	8.85, br t (5.6), 1H	7.20, s, 5H, R 7.50, br s, 5H, Ar 7.55-8.60, m, 3H, Ar' [i]
8c (B)	——	6.56, s, 1H	10.60, br s, 1H	6.96-8.70, m, 13H [j]
10 (A)	——	6.90, s, 1H [k]	6.63, br s, 1H [l]	7.06-7.93, m, 15H
11 (A) [m]	4.95, s, 2H	6.23, s, 1H	——	7.33 and 7.45, two s, 10H
17a (A)	4.38, d (5.6), 2H	3.98, s, 2H	6.88, br m, 1H	7.28, s, 5H, R 7.48, br s, 5H, Ar
(B)	4.37, d (5.6) [n]	4.27, s [n]	8.91, br t (5.6), 1H	7.33, s, 5H, R 7.48-7.96, m, 5H, Ar
17b [o]	4.43, d (5.6), 2H	4.08, s, 2H	8.41, br m, 1H	7.35, s, 5H, R 7.50 and 7.55, dd (8.5), 4H, Ar

[a] Chemical shifts are given in δ values (ppm) relative to TMS (internal standard) and coupling constants (Hz) are given in parentheses. [b] Solvents: A, deuteriochloroform, B, DMSO-d_6; C, deuteriochloroform/DMSO-d_6 1:1. [c] The *N*-benzyl methylene doublet collapses to a singlet when irradiating the -CONH- signal. [d] *Cf.* ref [2]. [e] The multiplet includes a two-proton signal at 7.70-7.95 ppm, characteristic of the *ortho* protons in the benzoyl group. [f] The signals at 5.96 and 5.88 ppm integrate for two protons. [g] The multiplet includes a sharp singlet at 7.34 ppm (R) and a rather broad singlet at 7.52 ppm (Ar). [h] The multiplet includes a sharp singlet at 7.33 ppm (R). [i] The multiplet includes the characteristic signals of the Ar'=-$C_6H_3(NO_2)_2$-2,4 protons: 7.65, d (9.5), 1H, H_6; 8.21 and 8.36, dd (9.5 and 2.5), 1H, H_5; 8.53, d(2.5), 1H, H_3. [j] The multiplet includes the characteristic signals of the Ar' protons as for compound **8a**. [k] Vinylic proton of compound **10**. [l] NH proton of compound **10**. [m] The signal for the N-OCH_3 protons appears at 4.10 ppm, s, 3H. [n] The signals at 4.37 and 4.27 ppm integrate for four protons. [o] The sample was dissolved in deuteriochloroform containing three drops of DMSO-d_6.

ted acrylamide group, >C=CHCONHCH$_2$C$_6$H$_5$, if one includes the vinylic proton singlet. Since this group could be formed from a fission of the S-N bond of the normally expected oxime **4a**, structure **5a** was assigned to the isomeric compound actually obtained.

A similar pattern was observed in the pmr spectrum (see Table 1) of the compound obtained from the reaction of the isothiazolone **2a** with phenylhydrazine in ethanol at room temperature. Accordingly, the rearranged structure **7a** was assigned to the new compound.

Other examples of compounds **5**, **7** and **8**, derived from the isothiazolones **2a-c** on reaction with hydroxylamine, phenylhydrazine and 2,4-dinitrophenylhydrazine, respectively, are given in the Experimental and their pmr spectra are reported in Table 1. A significant downfield shift of the -CONH- proton signal can be observed in compounds **5**, **7** and **8** in DMSO-d_6 when compared to deuteriochloroform solutions, as a consequence of a strong hydrogen bond to the more polar solvent.



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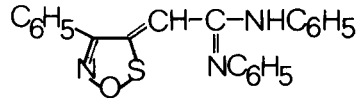

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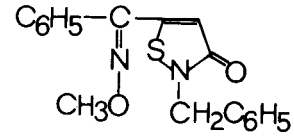

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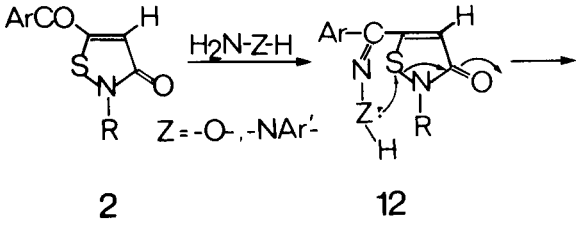
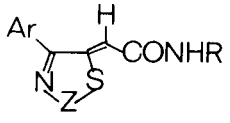
Even compound **9**, the intensely coloured phenylimine of the parent isothiazolone **2c** [3], afforded the rearranged oxathiazole derivative **10** on reaction with hydroxylamine. On the other hand, reaction of the isothiazolone **2a** with *O*-methylhydroxylamine hydrochloride, under the same

conditions as for the reaction with hydroxylamine hydrochloride, yielded the unrearranged *O*-methyloxime **11**. Accordingly, the transformation of isothiazolones **2** to **5** and **7** on reaction with the bifunctional nucleophiles H_2N-OH and H_2N-NHAr′ would proceed through initial formation of the normal ketone derivatives **12**, which would then rearrange to the isomeric compounds **13** through a nucleophilic attack of the =N-OH and =N-NH- groups on the S-N bond of the isothiazolone nucleus. This rearrangement should be compared to the well known monocyclic rearrangement of substituted azoles, **14** → **15** [5], which has already been extensively illustrated [6].



2 **12**



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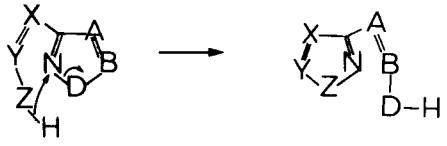


14 **15**

The rearrangement **12** → **13** should be a facile reaction, since the corresponding ketone derivatives **4** and **6** could not be isolated. Moreover, the reactions of the isothiazolones **2** with H_2N-NHAr′ were found to proceed faster and in excellent yields in the presence of acids (see Experimental Section, reaction with phenylhydrazine in the presence of acetic acid and reaction with 2,4-dinitrophenylhydrazine in the presence of concentrated sulfuric acid).

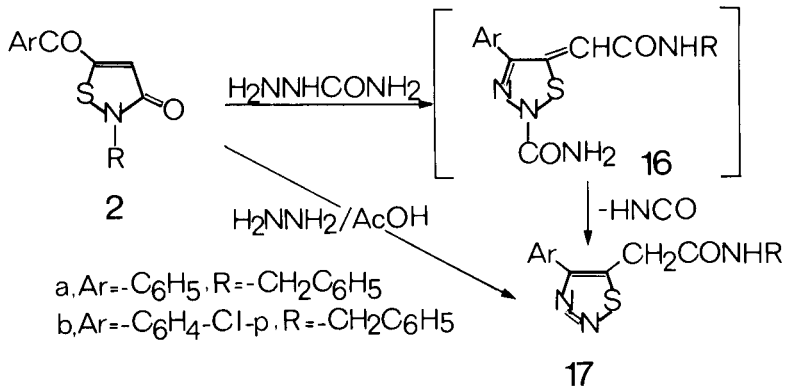
In agreement with the investigations of Crow, *et al.* [7] on the mechanism of the nucleophilic cleavage of the S-N bond in 3-hydroxyisothiazole, the conjugate acid of **12** should be subjected to a much faster attack.

There is no direct experimental evidence on the configuration of the exocyclic double bond in compounds **5, 7** and **8**. However, the appearance of a single set of signals for the (*N*-substituted-carboxamido)methylene group in their pmr spectra (see Table 1) is consistent with the formation of a single isomer in all cases. Since the geometry of the trisubstituted double bond is not involved in the mononuclear rearrangement **12** → **13**, the configuration of compounds **5, 7** and **8** is tentatively assigned as Z (*cf.* **13**), which would be considered as the more stable isomer on stereochemical considerations.

A rearrangement reaction similar to the sequence **2** → **12** → **13** was observed in the reaction of isothiazolones **2** with semicarbazide hydrochloride, though the expected carboxamidomethylene derivatives **16** could not be isolated. The products actually obtained lacked the elements of isocyanic acid and their structure was unambiguously assigned as **17** on the basis of their spectral data (*cf.* Table 1). Compounds **17** would be expected to derive directly from the reaction if isothiazolones **2** with hydrazine. An attempted reaction of the isothiazolone **2a** with hydrazine hydrate in ethanol was shown to yield a resinous material, but an excellent yield of compound **17a** was obtained from the same reaction in the presence of acetic acid. The rearrangement reaction should thus be useful for the synthesis of 4-aryl-5-carboxamidomethyl-1,2,3-thiadiazoles **17**.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 267 spectrometer as nujol mulls; absorption bands, in reciprocal centimeters, are characterized as of strong (s) or medium (m) intensity and as broad (br) or sharp (sh). The pmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and are accurate to ± 0.02 ppm. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).



2

a, Ar=-C_6H_5, R=-$CH_2C_6H_5$
b, Ar=-C_6H_4-Cl-p, R=-$CH_2C_6H_5$

17

2-Substituted-5-aroyl-3(2*H*)-isothiazolones **2**.

The preparation of the isothiazolones **2a** and **2c** by reaction of the corresponding γ-keto amides **1** with thionyl chloride has already been reported [2].

The same experimental procedure was used for the preparation of the isothiazolone **2b**: *N*-benzyl-3-(*p*-chlorobenzoyl)propionamide [8] (5 g) was stirred at room temperature with thionyl chloride (50 ml) for 90 minutes, when a dark green mixture was obtained. The excess thionyl chloride was removed *in vacuo* and the solid residue was recrystallized from ethanol to give compound **2b** (2.5 g, 45%) as an analytically pure yellow product, mp 153-154°; ir: sharp bands at 1663 (s), 1650 (s) and 1596 (m) cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; Cl, 10.75; N, 4.24; S, 9.72. Found: C, 61.97; H, 3.44; Cl, 10.75; N, 4.23; S, 9.51.

Reaction of Isothiazolones **2** With Hydroxylamine.

Isothiazolone **2** (3.5 mmoles) and hydroxylamine hydrochloride (7-10 mmoles) were added to a solution of sodium acetate (7 mmoles) in 2 ml of water and 25 ml of ethanol. The mixture was refluxed for one hour and was then filtered while still warm. Compounds **5** usually crystallized after cooling the alcoholic solution.

Compound **5a** was obtained in 78% yield as a pale yellow product, mp 158-160°. A recrystallization from ethanol gave an analytically pure sample, mp 161-162°; ir: sharp and strong bands at 3320, 1610, 1594 and 1560 cm^{-1}.

Anal. Calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.54; N, 9.03; S, 10.33. Found: C, 66.23; H, 4.60; N, 8.70; S, 10.32.

Compound **5b** was obtained after evaporation of the alcoholic solution under vacuum; the resinous residue was treated with ether and the solid formed was washed with water and recrystallized from benzene to give a product of mp 134-135°; ir: strong and sharp bands at 3410, 1612 and 1562 cm^{-1}.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2S$: C, 59.21; H, 3.80; Cl, 10.28; N, 8.12; S, 9.29. Found: C, 59.35; H, 3.76; Cl, 10.18; N, 7.88; S, 9.24.

Compound **5c** was obtained, after recrystallization from ethanol, as a pale yellow solid, mp 170-171°; ir: strong and sharp bands at 3390, 3350, 1612, 1600 and 1560 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O_2S$: C, 64.84; H, 4.08; N, 9.45; S, 10.81. Found: C, 64.54; H, 3.93; N, 9.37; S, 10.81.

Reaction of Isothiazolones **2** With Phenylhydrazine.

A mixture of isothiazolone **2a** (0.75 g, 2.5 mmoles) and phenylhydrazine (0.3 ml, 3 mmoles) in 10 ml of ethanol was stirred at room temperature for 17 hours. The precipitate which was formed was filtered and washed with ether to give 0.7 g (72%) of compound **7a** as a yellow solid, mp 135-136°. A recrystallization from ethanol gave an analytically pure product, mp 138-139°; ir: 3300 (br, m), 1620 (sh, m), 1600 (sh, s), 1565 (br, s) and 1520 cm^{-1} (m).

Anal. Calcd. for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.96; N, 10.90. Found: C, 71.79; H, 5.09; N, 10.99.

A similar mixture of isothiazolone **2b** and phenylhydrazine was stirred at room temperature for three days. The precipitate formed was filtered and washed with ethanol to give compound **7b**, in 75% yield, as a yellow solid, mp 154-155°. A recrystallization from ethanol gave an analytically pure product, mp 157-159°; ir: 3290 (br, m), 1620 (sh, m), 1600 (sh, s), 1570 (br, s) and 1525 cm^{-1} (m).

Anal. Calcd. for $C_{23}H_{18}ClN_3OS$: C, 65.78; H, 4.32; Cl, 8.44; N, 10.00. Found: C, 65.69; H, 4.29; Cl, 8.61; N, 9.98.

Compounds **7a** and **7b** were obtained in considerably better yields by the following procedure: A mixture of isothiazolone **2** (1.8 mmoles) and phenylhydrazine (2 mmoles) in 10 ml of ethanol containing 1 ml of acetic acid was refluxed for 20 minutes. After cooling the reaction mixture, compound **7** was filtered and washed with ethanol. Compound **7a**, mp 137-138°, was obtained in 94% yield, and compound **7b**, mp 154-156°, in 92% yield.

Reaction of Isothiazolones **2** With 2,4-Dinitrophenylhydrazine.

A warm solution of isothiazolone **2** (1.7 mmoles) in 10 ml of methanol was added to a warm solution of 2,4-dinitrophenylhydrazine (1.7 mmoles) in 18 ml of methanol containing 0.7 ml of concentrated sulfuric acid and the mixture was refluxed for 5 minutes. The intensely red coloured precipitate which was formed was filtered and washed with ether.

Compound **8a**, mp 185-188°, was obtained in 62% yield. A recrystallization from methanol gave an analytically pure product, mp 219-220°; ir: bands at 3400, 3340, 1587 and 1538 cm^{-1}.

Anal. Calcd. for $C_{23}H_{17}N_5O_5S$: C, 58.09; H, 3.60; N, 14.73; S, 6.74. Found: C, 58.34; H, 3.49; N, 14.80; S, 6.71.

Compound **8c**, mp 253-255°, was obtained in 90% yield. A recrystallization from ethanol gave an analytically pure product, mp 263-264°.

Anal. Calcd. for $C_{22}H_{15}N_5O_5S$: C, 56.50; H, 3.21; N, 14.82; S, 7.08. Found: C, 56.60; H, 3.19; N, 14.84; S, 6.82.

Reaction of Phenylimine **9** With Hydroxylamine.

The phenylimine **9** [3] (0.5 g, 1.4 mmoles) and hydroxylamine hydrochloride (0.25 g, 3.6 mmoles) were added to a solution of sodium acetate (0.2 g, 2.4 mmoles) in 1 ml of water and 25 ml of ethanol. The mixture was stirred at room temperature for 30 minutes - the deep red colour of the phenylimine **9** disappeared after 5 minutes of stirring. The precipitate formed was filtered and washed with ethanol to give 0.36 g (52%) of compound **10**, mp 188-190°. An analytical sample, obtained after recrystallization from ethanol, had the same mp; ir: 3390 (sh, m), 1595 (sh, s) and 1570 cm^{-1} (br, s).

Anal. Calcd. for $C_{22}H_{17}N_3OS$: C, 71.13; H, 4.61; N, 11.31; S, 8.63. Found: C, 70.95; H, 4.69; N, 11.39; S, 8.67.

Reaction of Isothiazolone **2a** With *O*-Methylhydroxylamine.

The isothiazolone **2a** (1 g, 3.4 mmoles) and *O*-methylhydroxylamine hydrochloride (0.83 g, 9.9 mmoles) were added to a solution of sodium acetate (0.5 g, 6.9 mmoles) in 2 ml of water and 25 ml of ethanol. The mixture was refluxed for one hour and was then filtered while still warm. The filtrate was concentrated under vacuum, the semi-solid residue was dissolved in ether and the ether solution was washed successively with water, a 10% solution of sodium hydrogen carbonate and water. After evaporation of the solvent, the solid residue was recrystallized from ether to give 0.55 g (50%) of compound **11** as a colourless solid, mp 90-92°; ir: strong and broad band at 1645 cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.63; S, 9.88. Found: C, 67.04; H, 4.88; N, 8.60; S, 9.93.

Anal. Calcd. for $C_{23}H_{18}ClN_3OS$: C, 65.78; H, 4.32; Cl, 8.44; N, 10.00.

Found: C, 65.69; H, 4.29; Cl, 8.61; N, 9.98.

Reaction of Isothiazolones **2** With Semicarbazide.

Semicarbazide hydrochloride (0.45 g, 4 mmoles) was added to a suspension of isothiazolone **2a** (1 g, 3.4 mmoles) in 15 ml of ethanol and the mixture was stirred at room temperature for 4 days. The resulting solution was then concentrated *in vacuo* and the solid residue was recrystallized from ethanol to give 0.93 g (89%) of compound **17a** as a colourless solid, mp 112-114°; ir: sharp bands at 3280 (m), 1670 (s) and 1570 cm^{-1} (m).

Anal. Calcd. for $C_{17}H_{15}N_3OS$: C, 65.99; H, 4.88; N, 13.58. Found: C, 65.93; H, 4.90; N, 13.82.

A similar mixture of semicarbazide hydrochloride and isothiazolone **2b** was stirred at room temperature for 6 days. The precipitate formed was filtered and washed with ethanol to give compound **17b** in 91% yield, mp 157-159°. An analytical sample, obtained after recrystallization from ethanol, had the same mp; ir: sharp bands at 3320 (s), 1640 (s) and 1565 cm^{-1} (m).

Anal. Calcd. for $C_{17}H_{14}ClN_3OS$: C, 59.38; H, 4.10; Cl, 10.31; N, 12.22; S, 9.32. Found: C, 59.50; H, 4.09; Cl, 10.35; N, 12.26; S, 9.01.

Compound **17a** was also obtained by the following procedure: A mixture of isothiazolone **2a** (1 g, 3.4 mmoles) and semicarbazide hydrochloride (0.39 g, 3.4 mmoles) in 10 ml of ethanol containing 1 ml of acetic acid was refluxed for 30 minutes. After cooling, compound **17a** crystallized as a colourless solid, 0.8 g (76%), mp 112-114°.

Reaction of Isothiazolone **2a** With Hydrazine.

Hydrazine hydrate (0.2 ml, 4.1 mmoles) and acetic acid (0.4 ml, 7 mmoles) were added to a suspension of isothiazolone **2a** (1 g, 3.4 mmoles) in 10 ml of ethanol and the mixture was stirred at room temperature. After 30 minutes a clear solution was obtained and after 6 hours a colourless crystalline precipitate was formed. This was filtered, after cooling the reaction mixture, and washed with ethanol to give 0.9 g (86%) of compound **17a**, mp 112-114°, identical (mixed mp and spectra) to the product obtained from the reaction of the isothiazolone **2a** with semicarbazide hydrochloride.

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