

Preparation and Properties of 2-Dialkylamino-5-haloacetyl-thiazoles and 4-(2-Dialkylamino-5-thiazolyl)-thiazoles ¹⁾**Cornelia Mokry**

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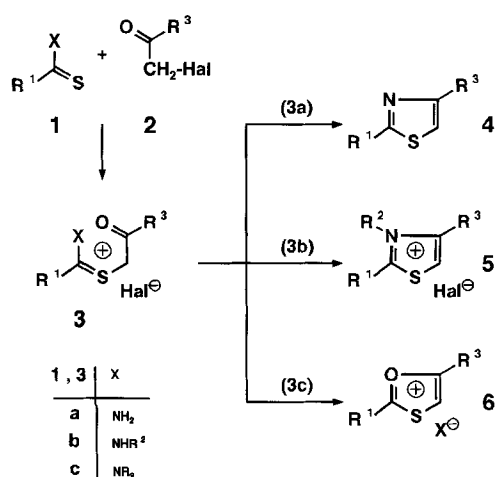
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Abstract. By the reaction of *N*-acylthioureas **7** with 1,3-dichloroacetone **9** 2-dialkylamino-5-chloroacetyl-thiazoles **11** are available. These compounds react with thioureas or arylthioamides under heterocyclisation to give bis-(2-dialkylamino-5-thiazolyl)-ketones **13**, 2-aryl-4-(2-dialkylamino-5-thiazolyl)-thiazoles **14**, or 2-dialkylamino-4-(2-dialkylamino-5-thiazolyl)-

thiazoles **15**, resp., from which the last-mentioned compound exhibit a high reactivity towards several electrophilic reagents. Thus, deeply colored cyanovinylyl, arylazo, and arylmethine substituted bisthiazole dyes **17**, **18**, and **19**, resp., have been formed.

Halomethyl ketones **2** are versatile educts for preparing sulfur-containing heterocycles, such as thiazoles and related compounds. Thus, by their reaction with *N*-unsubstituted or *N*-monosubstituted thioamides **1a** or **1b** the thiazoles **4** [1] or thiazolium salts **5** [2], resp., are obtained. By starting with *N*-disubstituted thioamides **1c** 1,3-oxa-thiolium salts **6** are formed [3]. All the reactions run, in general, on intermediate *S*-ketomethylene-thioamidinium salts **3** and yield the corresponding heterocycles in satisfactory yields mostly.

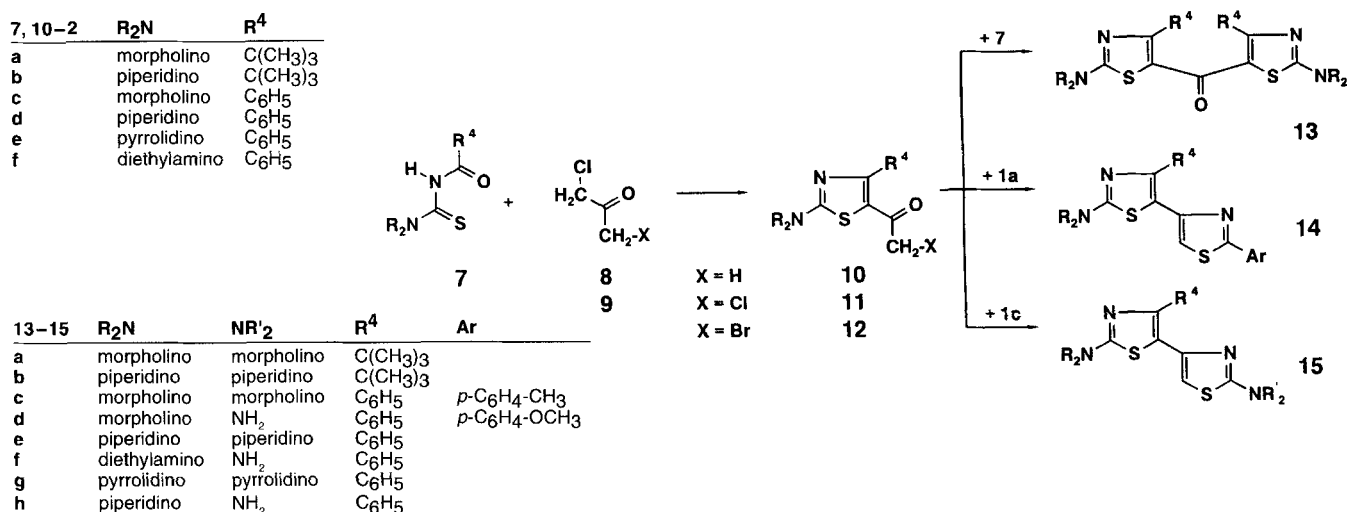
**Scheme 1**

A different result is obtained, however, if halomethyl ketones **2** are allowed to react with *N*-acylthioamides which can be considered as a special type of *N*-monosubstituted thioamides. *E.g.*, by starting with *N*-acylthioureas **7** [4] (or their imidoyl analogs [5]) and monochloroacetone **8** the 5-acetylthiazoles **10** are obtained [6]. In this case, contrary to the simple *N*-monosubstituted thioamides **1b**, only one of the carbon atom of the halomethylketone educt **8** is incorporated in the heterocyclis formed.

This heterocyclization reaction is extensible, as we found, to 1,3-dichloroacetone **9** also. Thus, 5-chloroacetyl-thiazoles **11** can be prepared in satisfactory yields if the necessary *N*-acylthioureas **7** are allowed to react with the dichloro ketone **9** in a stoichiometric ratio. Otherwise, *e.g.*, if the same educts are applied in a 1:2 ratio, or if special substituted *N*-acylthioureas **7** are used, the bis-5-thiazolyl-ketones **13** are formed in rather high yields.

Because the prepared thiazoles **11** contain an α -halomethyl ketone moiety they can be used as educts for preparing thiazolyl-substituted thiazoles by using one of the before-mentioned heterocyclizations. The same is valid for the 5-bromoacetyl-thiazoles **12** which can be prepared from 5-acetylthiazoles **10** by their reaction with elemental bromine in acetic acid. Thus, by the reaction of the 5-haloacetyl-thiazoles **11** or **12** with

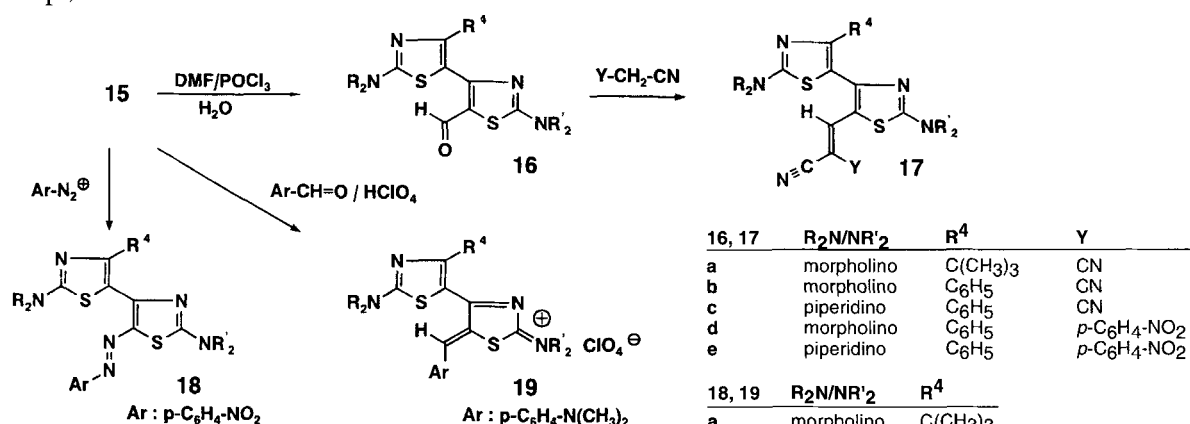
¹⁾ Presented in part at the third conference on iminium salts, Stimpfach-Rechenberg (Germany), September 17–19, 1997



Scheme 2

N-unsubstituted thioamides **1a**, such as arylthiocarbamides (R¹ = Aryl in **1a**), the 2-aryl-substituted 4-(2-dialkylamino-5-thiazolyl)-thiazoles **14** are obtained. Furthermore, by starting with *N,N*-disubstituted thioureas **1a** (R¹ = NR'₂) or with *N*-acylthioureas **7** the 2-dialkylamino-4-(2-dialkylamino-5-thiazolyl)-thiazoles **15** or the bis-(2-dialkylamino-5-thiazolyl)-ketones **13**, resp., are obtained.

azo-substituted bithiazoles **18** and 5-arylmethylene-substituted 4-(2-dialkylamino-5-thiazolyl)-2,5-dihydrothiazole-2-iminium salts **19**, respectively. Whereas the formation of the 5-arylamino-substituted bithiazoles **18** occurs in weakly acidic or neutral medium only, the formation of the 5-arylmethylene-substituted 4-(2-dialkylamino-5-thiazolyl)-2,5-dihydro-2-thiazoliniminium salts



Scheme 3

In contrast to the 2-aryl-4-(2-dialkylamino-5-thiazolyl)-thiazoles **14** the 2-dialkylamino-4-(2-dialkylamino-5-thiazolyl)-thiazoles **15** are highly reactive against electrophilic reagents. Thus, with the Vilsmeier reagent and subsequent hydrolysis of the iminium salt intermediates the 2-dialkylamino-4-(2-dialkylamino-5-thiazolyl)-5-formyl-thiazoles **16** are obtained. These compounds are able to condense with active methylene compounds, such as malononitrile or 4-nitrobenzylcyanide, to give the 5-cyanvinyl-substituted bithiazoles **17**. Furthermore, the 2-dialkylamino-4-(2-dialkylamino-5-thiazolyl)-thiazoles **15** react with aryldiazonium salts, such as *p*-nitrophenyl diazonium salts, or dialkylamino-substituted benzaldehydes to give deeply colored 5-aryl-

19 occurs only if strong mineralic acids, such as perchloric acid, are added to the reaction mixture.

The structures of the new thiazole and bithiazole derivatives prepared have been elucidated by elemental analytical and spectroscopic methods unambiguously. Thus, both 5-haloacetyl-thiazoles **11** and **12** exhibit in their ¹H NMR spectra characteristic signals at about 4.00 ppm which can be attributed to their thiazole-linked methylene group. Furthermore, these compounds exhibit, analogously to the bithiazolyl ketones **13**, in their IR spectra intense absorption bands at about 1600 cm⁻¹ which can be attributed to their carbonyl moiety.

The 5*H*-substituted bis-thiazoles **14** and **15** exhibit

in their ^1H NMR spectra characteristic signals at about 6.0 to 7.0 ppm which can be attributed to the H atoms at their C-5 position. The 5-formyl-substituted bisthiazoles **16** exhibit signals at about 9.5 ppm which can be attributed unambiguously to the H-atoms at their formyl groups. Similar signals at relative low-fields at about 7.5 ppm are observed in compounds **19** for their methine protons.

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Experimental

Melting points were determined by means of a Boëtius heating-block microscope and are corrected. The i.r. spectra were recorded in potassium bromide pellets with a Philips FTIR spectrometer PU 9624, the visible spectra (in methylene-chloride) with a Shimadzu spectrometer UV 3101, and the n.m.r. spectra with a Varian 300 MHz Gemini 300 spectrometer or with a JEOL 200 MHz JNM FX 200 spectrometer. The elemental analytical data are estimated by means of a LECO analyser CHNS 932.

Preparation of 4-Substituted 5-Acetyl-2-dialkylamino-thiazoles (10) and 2-Dialkylamino-5-chloroacetyl-thiazoles (11) (General Procedure)

A *N,N*-disubstituted *N*-acylthiourea **7** (0.06 mol) [4] and 1-chloroacetone **8** (0.06 mol, 5.6 g) or 1,3-dichloroacetone **9** (0.06 mol, 7.6 g), solved in acetonitrile (100 ml), are refluxed for 1 h. After cooling at room temperature triethylamine (0.06 mol, 6.0 g) is added and the mixture is further refluxed for 45 min. After cooling at room temperature the product formed crystallises and can be isolated by filtration.

5-Acetyl-4-*tert*-butyl-2-(4-morpholino)-thiazole (10a)

This compound was obtained from 4-(*N*-pivaloyl-thiocarb-amido)-morpholine (**7a**) and chloroacetone (**8**) as colorless crystals (ethanol) in a yield of 47%, *m.p.* 108–109 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1633\text{ cm}^{-1}$. – ^1H NMR (deuterio-chloroform) $\delta/\text{ppm} = 1.33$ (s, 9H, CH_3), 2.53 (s, 3H, CH_3), 3.50 (t, 4H, NCH_2), 3.75 (t, 4H, OCH_2).

$\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ Calcd.: C 58.17 H 7.51 N 10.44 S 11.95 (268.4) Found: C 58.16 H 7.08 N 10.34 S 12.16.

5-Chloroacetyl-2-(4-morpholino)-4-phenyl-thiazole (11c)

This compound was obtained from 4-(*N*-benzoyl-thiocarb-amido)-morpholine (**7c**) and 1,3-chloroacetone (**9**) as yellow crystals (acetonitrile) in a yield of 59%, *m.p.* 221–223 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1645\text{ cm}^{-1}$. – ^1H NMR (deuterio-chloroform) $\delta/\text{ppm} = 3.61$ (t, 4H, NCH_2), 3.79 (t, 4H, OCH_2), 3.92 (s, 2H, COCH_2), 3.48 (m, 5H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$ Calcd.: C 55.81 H 4.68 N 8.68 S 10.17 (322.8) Found: C 55.81 H 4.94 N 8.88 S 10.17.

5-Chloroacetyl-2-(1-piperidino)-4-phenyl-thiazole (11d)

This compound was obtained from 4-(*N*-benzoyl-thiocarb-

amido)-piperidine (**7d**) and 1,3-chloroacetone (**9**) as yellow crystals (ethanol) in a yield of 52%, *m.p.* 138 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 16551\text{ cm}^{-1}$. – ^1H NMR (deuterio-chloroform) $\delta/\text{ppm} = 1.67$ (m, 6H, CH_2), 3.60 (t, 4H, NCH_2), 3.91 (s, 2H, COCH_2), 7.89 (m, 5H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{OS}$ Calcd.: C 59.90 H 5.34 N 8.73 S 10.00 (320.8) Found: C 59.82 H 5.09 N 8.80 S 10.38.

5-Bromoacetyl-2-(4-morpholino)-4-*tert*-butyl-thiazole (12a)

To 5-acetyl-4-*tert*-butyl-2-(4-morpholino)-thiazole (**10a**, 0.037 mol, 10.0 g) solved in acetic acid (20 ml) bromine (0.037 mol, 5.95 g) is added dropwise under stirring at 10 °C. After 2 h the mixture is poured on ice and the product which precipitates as oil is extracted by diethyl ether from which the product is isolated by evaporating to give 6.0 g (47%) of 5-bromoacetyl-2-(4-morpholino)-4-*tert*-butyl-thiazole, *m.p.* 108–109 °C (ethanol/water 1:4). – IR (potassium bromide): $\nu_{\text{CO}} = 1633\text{ cm}^{-1}$. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.93$ (s, 9H, CH_3), 3.56 (t, 4H, NCH_2), 3.79 (t, 4H, OCH_2), 4.11 (s, 2H, COCH_2).

$\text{C}_{13}\text{H}_{19}\text{BrN}_2\text{O}_2\text{S}$ Calcd.: C 44.96 H 5.51 N 8.07 S 9.23 (347.3) Found: C 45.05 H 5.19 N 8.45 S 9.60.

Preparation of Bis-(2-dialkylamino-5-thiazolyl)-ketones (13) (General Procedure)

A *N,N*-disubstituted *N*-acylthiourea **7** (0.06 mol) and 1,3-dichloroacetone **9** (0.03 mol, 3.8 g) solved in 100 ml acetonitrile, are refluxed for 1 h. After cooling at room temperature triethylamine (0.06 mol, 6.0 g) are added, and the mixture is further refluxed for 45 min. After cooling, the reaction mixture is diluted with water (500 ml) and the product which precipitates as oil is extracted by diethyl ether. After evaporation the product crystallizes and can be isolated by filtration.

Bis-[[4-*tert*-butyl-2-(4-morpholino)]-5-thiazolyl]-ketone (13a)

This compound was obtained from 4-(*N*-pivaloyl-thiocarb-amido)-morpholine (**7a**) and 1,3-dichloroacetone (**9**) as yellow crystals (ethanol) in a yield of 34%, *m.p.* 206–207 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1608\text{ cm}^{-1}$. – ^1H NMR (deuterio-chloroform) $\delta/\text{ppm} = 1.34$ (s, 18H, CH_3), 3.45 (t, 8H, NCH_2), 3.76 (t, 8H, OCH_2).

$\text{C}_{23}\text{H}_{34}\text{N}_4\text{O}_3\text{S}_2$ Calcd.: C 57.70 H 7.16 N 11.70 S 13.40 (478.7) Found: C 58.04 H 6.73 N 11.69 S 13.66.

Bis-[[4-*tert*-butyl-2-(1-piperidino)]-5-thiazolyl]-ketone (13b)

This compound was obtained from 4-(*N*-pivaloyl-thiocarb-amido)-piperidine (**7b**) and 1,3-dichloroacetone (**9**) as yellow crystals (ethanol) in a yield of 45%, *m.p.* 182–183 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1614\text{ cm}^{-1}$. – ^1H NMR (deuterio-chloroform) $\delta/\text{ppm} = 1.34$ (s, 18H, CH_3), 1.62 (m, 12H, CH_2), 3.43 (t, 8H, NCH_2).

$\text{C}_{25}\text{H}_{38}\text{N}_4\text{OS}_2$ Calcd.: C 63.25 H 8.07 N 11.80 S 13.51 (474.7) Found: C 63.40 H 7.75 N 11.69 S 13.47.

Bis-[(2-diethylamino-4-phenyl)-5-thiazolyl]-ketone (13f)

This compound was obtained from 1-benzoyl-3-diethyl-thiourea (**7f**) and 1,3-dichloroacetone (**9**) as yellow crystals (ethanol)

in a yield of 63%, *m.p.* 158–159 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1585 \text{ cm}^{-1}$. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.17$ (t, 12H, CH_3), 3.41 (q, 8H, NCH_2), 7.17 (m, 10H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_2\text{S}_2$ Calcd.: C 66.08 H 6.16 N 11.42 S 13.07 (490.7) Found: C 65.75 H 5.72 N 11.42 S 13.08.

Bis-[[2-(1-pyrrolidino)-4-phenyl]-5-thiazolyl]-ketone (13g)

This compound was obtained from 4-(*N*-benzoyl-thiocarbamido)-pyrrolidine (7e) and 1,3-dichloroacetone (9) as yellow crystals (ethanol) in a yield of 59%, *m.p.* 142 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1545 \text{ cm}^{-1}$. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 2.00$ (t, 8H, CH_2), 3.41 (t, 8H, NCH_2), 7.17 (m, 6H, $\text{CH}_{\text{phenyl}}$), 7.23 (d, 4H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{27}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$ Calcd.: C 66.64 N 5.39 S 13.18 (486.6) Found: C 66.20 H 5.68 N 11.21 S 13.12.

Preparation of 5-(4-Thiazolyl)-2-(4-morpholino)-4-phenyl-thiazoles (14) and 4-Substituted 2-Dialkylamino-5-(2-dialkylamino-4-thiazolyl)-thiazoles (15) (General Procedure)

A mixture of a 5-chloroacetyl- or 5-bromoacetyl-2-dialkylamino-4-phenyl-thiazole **11** or **12** (0.05 mol), resp., and an arylthioamide or a *N,N*-disubstituted thiourea (0.05 mol) in ethanol (300 ml) is refluxed for 3 h. After cooling triethylamine (0.05 mol, 7.0 g) is added to the resulting solution. The products which precipitate after cooling at room temperature are isolated by filtration and recrystallized.

2-(4-Morpholino)-4-phenyl-5-[2-(4-tolyl)-4-thiazolyl]-thiazole (14c)

This compound was obtained from 5-chloroacetyl-2-(4-morpholino)-4-phenyl-thiazole (**11c**) and 4-tolylthioamide as yellowish crystals (ethanol) in a yield of 40%, *m.p.* 157–159 °C. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 2.89$ (s, 3H, CH_3), 4.07 (m, 8H, NCH_2), 4.34 (m, 8H, OCH_2), 7.72 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.88 (m, 3H, $\text{CH}_{\text{phenyl}}$), 8.15 (d, 2H, $\text{CH}_{\text{phenyl}}$), 8.33 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2\text{S}_2$ Calcd.: C 65.83 H 5.05 N 10.01 S 15.29 (419.6) Found: C 65.59 H 4.99 N 9.94 S 15.32.

2-(4-Morpholino)-4-phenyl-5-[2-(4-methoxyphenyl)-4-thiazolyl]-thiazole (14d)

This compound was obtained from 5-chloroacetyl-2-(4-morpholino)-4-phenyl-thiazole (**11c**) and 4-methoxythiobenzamide as colorless crystals (ethanol) in a yield of 54%, *m.p.* 180–82 °C. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 3.34$ (t, 4H, NCH_2), 3.81 (t, 4H, OCH_2), 3.83 (s, 3H, OCH_3), 6.70 (s, 1H, $\text{CH}_{\text{thiazolyl}}$), 6.90 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.35 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.61 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.84 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2\text{S}_2$ Calcd.: C 63.43 H 4.86 N 9.65 S 14.72 (435.6) Found: C 63.67 H 4.88 N 9.47 S 14.98.

4-tert-Butyl-2-(4-morpholino)-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (15a)

This compound was obtained from 5-bromoacetyl-2-(4-morpholino)-4-*tert*-butyl-thiazole (**12a**) and morpholinothiurea [4] as white crystals (ethanol) in a yield of 65%, *m.p.* 99–100 °C. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.25$

(s, 9H, CH_3), 3.38 (t, 4H, NCH_2), 3.44 (t, 4H, NCH_2), 3.77 (m, 8H, OCH_2), 6.48 (s, 1H, $\text{CH}_{\text{thiazolyl}}$).
 $\text{C}_{18}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$ Calcd.: C 54.78 H 6.64 N 14.20 S 16.25 (394.6) Found: C 54.24 H 6.64 N 13.67 S 16.18.

2-(4-Morpholino)-4-phenyl-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (15c)

This compound was obtained from 5-chloroacetyl-2-(4-morpholino)-4-phenyl-thiazole (**11c**) and morpholinothiurea [4] as white crystals (acetonitrile) in a yield of 70%, *m.p.* 196–198 °C. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 3.41$ (t, 4H, NCH_2), 3.49 (t, 4H, NCH_2), 3.77 (m, 8H, OCH_2), 6.10 (s, 1H, $\text{CH}_{\text{thiazolyl}}$), 7.32 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.58 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$ Calcd.: C 57.95 H 5.35 N 13.52 S 15.47 (414.5) Found: C 57.78 H 5.32 N 13.56 S 15.47.

5-(2-Amino-4-thiazolyl)-2-morpholino-4-phenyl-thiazole (15d)

This compound was obtained from 5-chloroacetyl-2-(4-morpholino)-4-phenyl-thiazole (**11c**) and thiourea as slight yellow crystals (ethanol/acetonitrile 1:1) in a yield of 65%, *m.p.* 194–196 °C. – ^1H NMR (dimethylsulfoxide- d_6) $\delta/\text{ppm} = 3.38$ (t, 4H, NCH_2), 3.70 (t, 4H, OCH_2), 5.97 (s, 1H, $\text{CH}_{\text{thiazolyl}}$), 7.07 (s, 2H, NH_2), 7.31 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.54 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$ Calcd.: C 55.80 H 4.68 N 16.27 S 18.62 (344.4) Found: C 56.38 H 4.92 N 16.42 S 18.75.

4-Phenyl-2-piperidino-5-(2-piperidino-4-thiazolyl)-thiazole (15e)

This compound was obtained from 5-chloroacetyl-2-(1-piperidino)-4-phenyl-thiazole (**11d**) and piperidinothiurea [4] as yellow crystals (ethanol) in a yield of 68%, *m.p.* 176–177 °C. – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.63$ (m, 12H, CH_2), 3.41 (t, 4H, NCH_2), 3.48 (t, 4H, NCH_2), 5.99 (s, 1H, $\text{CH}_{\text{thiazolyl}}$), 7.30 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.60 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{22}\text{H}_{26}\text{N}_4\text{S}_2$ Calcd.: C 64.35 H 6.38 N 13.65 S 15.62 (410.6) Found: C 64.32 H 5.90 N 13.42 S 15.64.

5-(2-Amino-5-thiazolyl)-2-piperidino-4-phenyl-thiazole (15h)

This compound was obtained from 5-chloroacetyl-2-(1-piperidino)-4-phenyl-thiazole (**11d**) and thiourea as slight yellow crystals (ethanol/acetonitrile 1:1) in a yield of 63%, *m.p.* 268–270 °C. – ^1H NMR (dimethylsulfoxide- d_6) $\delta/\text{ppm} = 1.58$ (m, 6H, CH_2), 3.40 (t, 4H, NCH_2), 5.96 (s, 1H, $\text{CH}_{\text{thiazolyl}}$), 7.04 (s, 2H, NH_2), 7.33 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.52 (d, 2H, $\text{CH}_{\text{phenyl}}$).
 $\text{C}_{17}\text{H}_{18}\text{N}_4\text{S}_2$ Calcd.: C 59.61 H 5.30 N 16.35 S 18.72 (342.5) Found: C 59.68 H 5.16 N 16.05 S 18.79.

Preparation of 4-Substituted 2-Dialkylamino-5-(2-dialkylamino-5-formyl-4-thiazolyl)-thiazoles (16) (General Procedure)

To a mixture of DMF (35 ml) and phosphoroxychloride (0.06 mol, 9.2 g) a solution of a 4-substituted 2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)-thiazole **15** (0.05 mol) in DMF (50 ml) is added under stirring at room temperature. The mixture is subsequently heated at 70 °C for 1 hour and purified, after cooling, into ice water (400 ml). After addition of aqueous

sodium hydroxide solution until receiving a weakly alkaline reaction (pH 9–10) the products **16a** and **16b** formed in 70 and 78% yield, resp., crystallise and can be isolated by filtration.

4-tert-Butyl-2-(4-morpholino)-5-[5-formyl-2-(4-morpholino)-4-thiazolyl]-thiazole (16a)

This compound was obtained from 4-tert-butyl-2-(4-morpholino)-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (**15a**) as white crystals (ethanol), *m.p.* 171–172 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1643 \text{ cm}^{-1}$. – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 1.21$ (s, 9H, CH_3), 3.41 (t, 4H, NCH_2), 3.61 (t, 4H, NCH_2), 3.78 (m, 8H, OCH_2), 9.62 (s, 1H, CHO).

$\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_3\text{S}_2$ Calcd.: C 54.00 H 6.20 N 13.26 S 15.18 (422.6) Found: C 54.45 H 6.29 N 12.93 S 15.01.

5-[5-Formyl-2-(4-morpholino)-4-thiazolyl]-4-phenyl-2-(4-morpholino)-thiazole (16b)

This compound was obtained from 2-(4-morpholino)-4-phenyl-5[2-(4-morpholino)-4-thiazolyl]-thiazole (**15c**) as luminously yellow crystals (acetonitrile), *m.p.* 200 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1637 \text{ cm}^{-1}$. – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 3.74$ (m, 8H, NCH_2), 3.80 (m, 8H, OCH_2), 7.28 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.51 (d, 2H, $\text{CH}_{\text{phenyl}}$), 9.23 (s, 1H, CHO).

$\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3\text{S}_2$ Calcd.: C 57.00 H 5.01 N 12.66 S 14.49 (442.5) Found: C 57.33 H 4.79 N 12.60 S 14.75.

5-(5-Formyl-2-piperidino-4-thiazolyl)-4-phenyl-2-(4-piperidino)-thiazole (16c)

This compound was obtained from 4-phenyl-2-piperidino-5-(2-piperidino-4-thiazolyl)-thiazole (**15e**) as yellowish brown crystals (ethanol), *m.p.* 185–186 °C. – IR (potassium bromide): $\nu_{\text{CO}} = 1637 \text{ cm}^{-1}$. – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 1.66$ (m, 12H, CH_2), 3.63 (m, 8H, NCH_2), 7.26 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.53 (d, 2H, $\text{CH}_{\text{phenyl}}$), 9.20 (s, 1H, CHO).

$\text{C}_{23}\text{H}_{26}\text{N}_4\text{OS}_2$ Calcd.: C 62.98 H 5.98 N 12.78 S 14.62 (438.6) Found: C 62.79 H 5.68 N 12.66 S 14.47.

Preparation of 4-Substituted 2-Dialkylamino-5-[2-dialkylamino-5-(2-cyanovinyl-4-thiazolyl)-thiazoles (17) (General Procedure)

A mixture of a 2-dialkylamino-5-(2-dialkylamino-5-formyl-4-thiazolyl)-thiazole (**16**) (0.01 mol), malononitrile (0.012 mol, 0.8 g) or 4-nitrophenyl-acetonitrile (0.012 mol, 1.95 g), triethylamine (0.5 ml), and acetic acid anhydride (10 ml) is refluxed for 1 hour. The products which crystallise by cooling of the reaction mixture are isolated by filtration and recrystallised.

4-tert-Butyl-2-(4-morpholino)-5-[2-(4-morpholino)-5-(2,2-dicyanovinyl-4-thiazolyl)]-thiazole (17a)

This compound was obtained from 4-tert-butyl-2-(4-morpholino)-5-[5-formyl-2-(4-morpholino)-4-thiazolyl]-thiazole (**16a**) and malononitrile as orange crystals (acetonitrile) in a yield of 67%, *m.p.* 126–127 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 437$ (lg ϵ 4.42). – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 1.17$ (s, 9H, CH_3), 3.43 (t, 4H, NCH_2), 3.72 (t, 4H, NCH_2), 3.79 (m, 8H, OCH_2), 7.59 (s, 1H, CH).

$\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}_2\text{S}_2$ Calcd.: C 56.14 H 5.57 N 17.86 S 13.63 (442.6) Found: C 56.48 H 5.29 N 17.66 S 13.57.

2-(4-Morpholino)-5-[2-(4-morpholino)-5-(2,2-dicyanovinyl-4-thiazolyl)]-4-phenyl-thiazole (17b)

This compound was obtained from 5-[5-formyl-2-(4-morpholino)-4-thiazolyl]-4-phenyl-2-(4-morpholino)-thiazole (**16b**) and malononitrile as luminously red crystals (acetic acid) in a yield of 60%, *m.p.* 289–290 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 482$ (lg ϵ 4.26). – $^1\text{H NMR}$ (1,1,2,2-tetrachloro-1,2-dideuterioethane) $\delta/\text{ppm} = 3.66$ (m, 8H, NCH_2), 3.82 (m, 8H, OCH_2), 7.17 (s, 1H, CH), 7.40 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.57 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_2\text{S}_2$ Calcd.: C 58.76 H 4.51 N 17.13 S 13.07 (486.6) Found: C 58.35 H 4.28 N 17.03 S 12.85.

5-[5-(2,2-Dicyanovinyl)-2-piperidino-4-thiazolyl]-4-phenyl-2-piperidino-thiazole (17c)

This compound was obtained from 5-(5-formyl-2-piperidino-4-thiazolyl)-4-phenyl-2-(4-piperidino)-thiazole (**16c**) and malononitrile as luminously red crystals (acetic acid) in a yield of 63%, *m.p.* 250–252 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 492$ (lg ϵ 4.28). – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 1.68$ (m, 12H, CH_2), 3.56 (t, 4H, NCH_2), 3.64 (t, 4H, NCH_2), 7.20 (s, 1H, CH), 7.32 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.45 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{26}\text{H}_{26}\text{N}_6\text{S}_2$ Calcd.: C 64.17 H 5.39 N 17.27 S 13.18 (486.6) Found: C 64.35 H 5.30 N 17.25 S 13.27.

2-(4-Morpholino)-5-[2-(4-morpholino)-5-[[2-cyano-2-(4-nitrophenyl)-vinyl]-4-thiazolyl]]-4-phenyl-thiazole (17d)

This compound was obtained from 5-[5-formyl-2-(4-morpholino)-4-thiazolyl]-4-phenyl-2-(4-morpholino)-thiazole (**16b**) and 4-nitrophenylacetoneitrile as darkly red crystals (acetic acid) in a yield of 56%, *m.p.* 267–269 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 492$ (lg ϵ 4.26). – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 3.56$ (t, 4H, NCH_2), 3.68 (t, 4H, NCH_2), 3.82 (m, 8H, OCH_2), 7.00 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.19 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.26 (s, 1H, CH), 7.57 (d, 2H, $\text{CH}_{\text{phenyl}}$), 8.01 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{29}\text{H}_{26}\text{N}_6\text{O}_4\text{S}_2$ Calcd.: C 59.36 H 4.47 N 14.32 S 10.93 (586.7) Found: C 59.00 H 4.90 N 13.89 S 10.79.

5-[[2-Cyano-2-(4-nitrophenyl)-vinyl]-4-thiazolyl]-4-phenyl-2-(piperidino)-5-[2-piperidino)-thiazole (17e)

This compound was obtained from 5-(5-formyl-2-piperidino-4-thiazolyl)-4-phenyl-2-(4-piperidino)-thiazole (**16c**) and 4-nitrophenylacetoneitrile as darkly red crystals (acetic acid) in a yield of 59%, *m.p.* 269–271 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 516$ (lg ϵ 4.36). – $^1\text{H NMR}$ (deuteriochloroform) $\delta/\text{ppm} = 1.69$ (m, 12H, CH_2), 3.55 (t, 4H, NCH_2), 3.65 (t, 4H, NCH_2), 7.00 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.18 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.29 (s, 1H, CH), 7.60 (d, 2H, $\text{CH}_{\text{phenyl}}$), 8.00 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{31}\text{H}_{30}\text{N}_6\text{O}_2\text{S}_2$ Calcd.: C 63.89 H 5.19 N 14.42 S 11.01 (582.7) Found: C 64.22 H 5.05 N 14.46 S 11.46.

Preparation of 4-Substituted 2-Dialkylamino-5-[2-dialkylamino-5-(4-nitrophenylazo)-4-thiazolyl]-thiazoles (18) (General procedure)

To a suspension of a 4-substituted 2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)-thiazole **15** (0.01 mol) in methanol (50 ml) a solution of diazotated 4-nitroanilin (0.01 mol) in a mixture of acetic acid (20 ml) and concentrated sulfuric acid

(3 ml) is added under stirring and cooling. After stirring at room temperature for 0.5 h the reaction mixture is diluted with water and neutralized by addition of aqueous sodium hydroxide solution. The azo dyes formed precipitate and can be isolated by suction.

4-tert-Butyl-2-(4-morpholino)-5-[2-(4-morpholino)-5-(4-nitrophenylazo)-4-thiazolyl]-thiazole (18a)

This compound was obtained from 4-tert-butyl-2-(4-morpholino)-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (**15a**) as darkly green crystals (toluene) in a yield of 72%, *m.p.* 251–252 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 594$ (lg ϵ 4.35). – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.46$ (s, 9H, CH_3), 3.55 (m, 8H, NCH_2), 3.73 (t, 4H, NCH_2), 3.82 (m, 8H, OCH_2), 7.70 (d, 2H, $\text{CH}_{\text{phenyl}}$), 8.20 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{24}\text{H}_{29}\text{N}_7\text{O}_4\text{S}_2$ Calcd.: C 53.02 H 5.38 N 18.04 S 11.80 (543.6) Found: C 53.37 H 5.02 N 17.85 S 11.92.

2-(4-Morpholino)-5-[2-(4-morpholino)-5-(4-nitrophenylazo)-4-thiazolyl]-4-phenyl-thiazole (18b)

This compound was obtained from 2-(4-morpholino)-4-phenyl-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (**15c**) as brass coloured crystals (DMF) in a yield of 69%, *m.p.* 297–298 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 593$ (lg ϵ 4.44). – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 3.33$ (t, 4H, NCH_2), 3.66 (m, 8H, NCH_2 and OCH_2), 3.85 (t, 4H, OCH_2), 7.29 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.58 (m, 4H, $\text{CH}_{\text{phenyl}}$), 8.23 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{26}\text{H}_{25}\text{N}_7\text{O}_4\text{S}_2$ Calcd.: C 55.40 H 4.47 N 17.40 S 11.39 (647.2) Found: C 55.80 H 4.42 N 16.99 S 11.03.

4-Phenyl-2-(piperidino)-5-[2-piperidino-5-(4-nitrophenylazo)-4-thiazolyl]-thiazole (18c)

This compound was obtained from 4-phenyl-2-piperidino-5-(2-piperidino-4-thiazolyl)-thiazole (**15e**) as brass coloured crystals (DMF) in a yield of 61%, *m.p.* 260–262 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 591$ (lg ϵ 4.47). – ^1H NMR (deuteriochloroform) $\delta/\text{ppm} = 1.58$ (m, 6H, CH_2), 1.71 (m, 6H, CH_2), 3.34 (t, 4H, NCH_2), 3.65 (t, 4H, NCH_2), 7.29 (m, 3H, $\text{CH}_{\text{phenyl}}$), 7.60 (m, 4H, $\text{CH}_{\text{phenyl}}$), 8.18 (d, 2H, $\text{CH}_{\text{phenyl}}$).

$\text{C}_{28}\text{H}_{29}\text{N}_7\text{O}_2\text{S}_2$ Calcd.: C 60.08 H 5.22 N 17.52 S 11.46 (647.2) Found: C 60.23 H 5.33 N 17.33 S 11.37.

Preparation of 5-Arylmethylene-4-(2-dialkylamino-5-thiazolyl)-2,5-dihydrothiazoliden-2-dialkyliminium salts (19) (General Procedure)

A mixture of a 4-substituted 2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)-thiazole (**15**) (0.01 mol), 4-dimethylaminobenzaldehyde (0.01 mol, 1.5 g), and magnesium perchlorate (0.005 mol, 1.1 g) in acetic anhydride (15 ml) was refluxed for 1 hour. The products crystallise after cooling are isolated by filtration and recrystallised from acetic acid.

5-(4-Dimethylaminobenzylidene)-4-[2-(4-morpholino)-4-tert-butyl-5-thiazolyl]-2,5-dihydrothiazoliden-2-(4-morpholinium) perchlorate (19a)

This compound was obtained from 4-tert-butyl-2-(4-morpholino)-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (**15a**) as dary green crystals (acetic acid) in a yield of 69%, *m.p.* 163–

164 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 620$ (lg ϵ 4.72). – ^1H NMR (dimethylsulfoxide- d_6) $\delta/\text{ppm} = 1.27$ (s, 9H, CH_3), 3.29 (s, 6H, NCH_3), 3.47 (t, 4H, NCH_2), 3.71 (t, 4H, NCH_2), 3.85 (m, 8H, OCH_2), 7.04 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.83 (d, 2H, $\text{CH}_{\text{phenyl}}$), 8.14 (s, 1H, CH).

$\text{C}_{27}\text{H}_{36}\text{ClN}_5\text{O}_6\text{S}_2$ Calcd.: C 51.79 H 5.80 N 11.19 S 10.24 (626.2) Found: C 51.52 H 5.57 N 11.86 S 9.97.

5-(4-Dimethylaminobenzylidene)-4-[2-(4-morpholino)-4-phenyl-5-thiazolyl]-2,5-dihydrothiazoliden-2-(4-morpholinium) perchlorate (19b)

This compound was obtained from 2-(4-morpholino)-4-phenyl-5-[2-(4-morpholino)-4-thiazolyl]-thiazole (**15c**) as luminously darkly red needles (acetic acid) in a yield of 78%, *m.p.* 238–240 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 665$ (lg ϵ 4.84). – ^1H NMR (dimethylsulfoxide- d_6) $\delta/\text{ppm} = 3.18$ (s, 6H, NCH_3), 3.65 (t, 4H, NCH_2), 3.76 (t, 4H, NCH_2), 3.85 (m, 8H, OCH_2), 6.82 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.20–7.35 (m, 5H, $\text{CH}_{\text{phenyl}}$), 7.54 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.71 (s, 1H, CH).

$\text{C}_{29}\text{H}_{33}\text{ClN}_5\text{O}_6\text{S}_2$ Calcd.: C 53.81 H 5.14 N 10.82 S 9.91 (647.2) Found: C 53.82 H 5.02 N 11.63 S 9.71.

5-(4-Dimethylaminobenzylidene)-4-(2-piperidino-4-phenyl-5-thiazolyl)-2,5-dihydrothiazoliden-2-(1-piperidinium) perchlorate (19c)

This compound was obtained from 4-phenyl-2-piperidino-5-(2-piperidino-4-thiazolyl)-thiazole (**15e**) as brass coloured crystals (acetic acid) in a yield of 71%, *m.p.* 238–240 °C. – UV: $\lambda_{\text{max}}/\text{nm} = 659$ (lg ϵ 4.80). – ^1H NMR (dimethylsulfoxide- d_6) $\delta/\text{ppm} = 1.68$ (m, 12H, CH_2), 3.15 (s, 6H, NCH_3), 3.67–3.90 (m, 8H, NCH_2), 6.80 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.22–7.34 (m, 5H, $\text{CH}_{\text{phenyl}}$), 7.56 (d, 2H, $\text{CH}_{\text{phenyl}}$), 7.68 (s, 1H, CH).

$\text{C}_{31}\text{H}_{36}\text{ClN}_5\text{O}_4\text{S}_2$ Calcd.: C 57.97 H 5.65 N 10.91 S 9.99 (642.2) Found: C 57.62 H 5.29 N 10.93 S 9.91.

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