On the Formation and Reactivity of *N*(2),*N*(2')-Tetrasubstituted 2,4-Diamino-5-(2-amino-4-thiazolyl)thiazoles

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By the reaction of weak bases with *N*(2)-disubstituted 2-amino-4-thiazoliniminium chlorides **3**, easily available by the reaction of thioureas **1** with α-chloroacetonitrile **2**, *N*(2),*N*(2')-persubstituted 2,4-diamino-5-(2-amino-4-thiazolyl)thiazoles **8** are formed. These new bis-thiazoles react, as exemplified with the dimorpholino derivative **8a**, with different electrophilic reagent, such as phenyl isothiocyanate **9**, 4-nitrophenyldiazonium salt **11**, or 4-dialkylaminobenzaldehydes **13** at their 5*H*-substituted thiazole moieties to give the corresponding thioanilides **10**, azo compounds **12**, and methine dyes **14**, respectively. With sodium nitrite and the Vilsmeier reagent the thiazole **8a** is transformed, *via* unstable intermediates, into the tricyclic 2,7-dimorpholinothiazolo[4,5-*c*]thiazolo[4,5-*e*]pyridazine **16** and 2,7-dimorpholinothiazolo[4,5-*b*]thiazolo[4,5-*d*]pyridine **19**, respectively.

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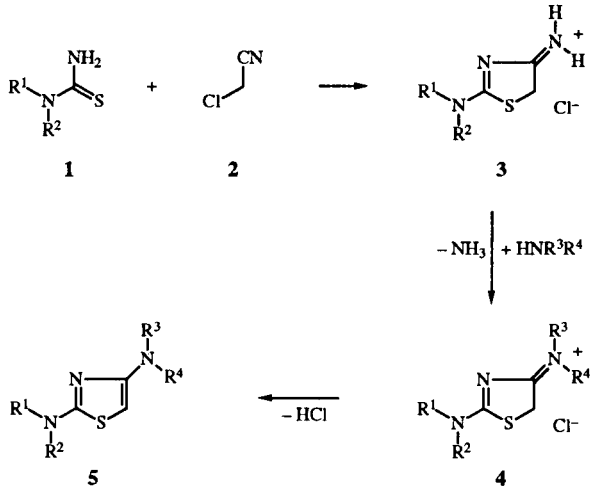
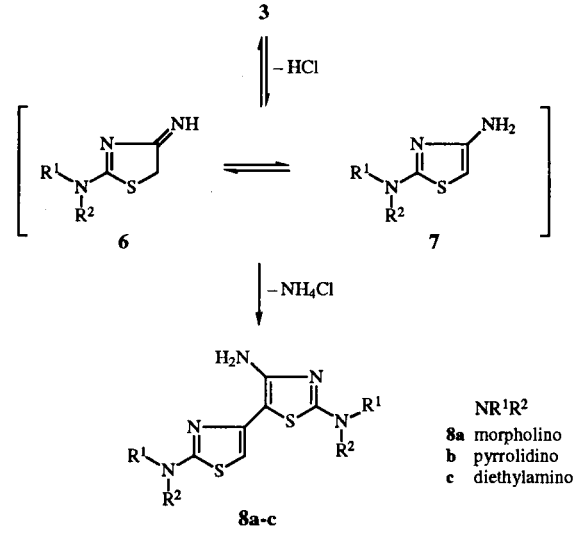
Although the reaction of thiourea **1** with chloroacetonitrile **2** is known for a long time [1] the chemical properties of the resulting 2-amino-4-thiazoliniminium chloride **3** (R^1, R^2 = H) have not been intensively studied. Therefore a series of additional derivatives of this class of compounds have been prepared and their properties studied more in detail [2]. Thereby it was found that the 2-amino-4-thiazoliniminium chlorides **3** are able to react very easily with different types of nucleophiles. With secondary alkylamines, *e.g.*, they are transformed, depending on the amount of amine used, into *N*(4)-disubstituted 2-dialkylamino-4-thiazoliniminium salts **4** or 2,4-bis-dialkylaminothiazoles **5**, a nearly unknown class of bis-amino-substituted thiazoles [3].



The successful transformation of the 2-amino-4-thiazoliniminium chlorides **3** into 2,4-dialkylaminothiazoles **5** made them versatile educts for preparing organic dyes [3b] and also allows the transfer of the *N*(4)-unsubstituted 2-dialkylamino-4-thiazoliniminium chlorides **3** into the corresponding *N*(4)-unsubstituted 2,4-diaminothiazoles **7**.

By performing this transformation similarly to that reported [4] it was found that neither the expected *N*(4)-unsubstituted 2,4-diaminothiazoles **7** nor their tautomeric 2-amino-4-thiazolinimines **6** could be obtained in detectable amounts. Instead of the expected products, triamino-substituted bis-thiazoles of structure **8** have been obtained in moderate yields. Their formation can be explained as result of the reaction of one equivalent of the intermediately formed 2,4-diaminothiazole **7** with one equivalent of the starting 2-amino-4-thiazoliniminium chloride **3** followed by elimination of ammonium chloride.

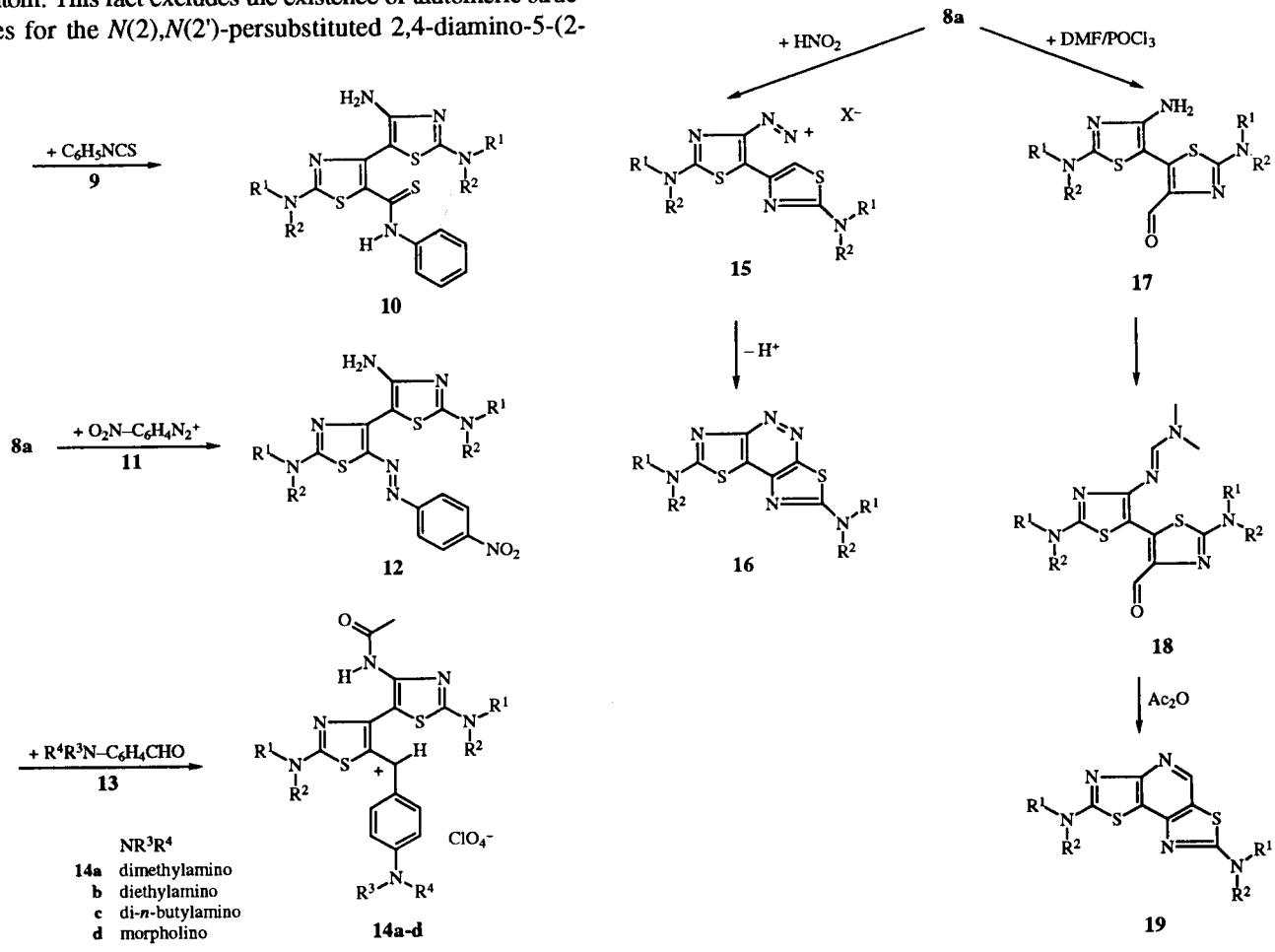


The formation of the triamino substituted bis-thiazoles **8** from the 2-amino-4-thiazoliniminium chlorides **3** has some analogies in the transformation of 2-aryl-4-thiazolinones into 2-aryl-4-hydroxy-5-(2-aryl-4-thiazolyl)thiazoles [5].

The transformation has been accomplished with three differently *N*(2)-disubstituted 2-amino-4-thiazoliniminium chlorides **3**, namely with the 2-morpholino-, 2-pyrrolidino-, and 2-diethylamino-4-thiazoliniminium chlorides **3a-c**. The reactions have been performed by refluxing each of these compounds in methanolic solution with triethylamine for few minutes. The 4-amino-2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)-thiazoles **8a-c** thus obtained in moderate yields are weakly coloured compounds which are stable in pure form under argon, however, rather unstable in air.

These thiazoles **8a-c** exhibit in their ^1H and ^{13}C nmr spectra characteristic signals which could be assigned unambiguously to all their H and C atoms. Whereas the C(5) bonded H-atoms in the 2-amino-4-thiazole fragment and the *N*(4) bonded H-atoms in the 2,4-diaminothiazole fragment of the compounds **8** are detectable, *e.g.*, in the ^1H nmr spectra by singlets at about 6.00 ppm and at about 5.20 ppm, respectively, the C(2) atoms in both their thiazole moieties are detectable in their ^{13}C nmr spectra by signals at about 165 and 170 ppm. From *J*-modulated spin-echo experiments it follows that the C(5) atom in each of the 5-bonded 2-amino-4-thiazolyl moieties of compounds **8** is linked with only one H-atom. This fact excludes the existence of tautomeric structures for the *N*(2),*N*(2')-persubstituted 2,4-diamino-5-(2-amino-4-thiazolyl)thiazoles **8** in contradiction to the tautomeric structures found for the *N*(4)-unsubstituted 2,4-diaminothiazoles **7** which exist, preferably, in a *N*(2)-disubstituted 2-amino-4-thiazolinimine structure **6**.

In their chemical reactivity the new 4-amino-2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)thiazoles **8** exhibit some analogies to the reactivity of simple 2-dialkylaminothiazoles or 2,4-bis-dialkylaminothiazoles **5** which are able to react with electrophilic reagents rather easily [3b]. Thus, the 4-amino-2-dialkylamino-5-(2-dialkylamino-4-thiazolyl)thiazoles **8** can react, as exemplified with the morpholino compound **8a**, with phenyl isothiocyanate **9** to give the thioanilide **10** and with aromatic diazonium salts, like 4-nitrophenyl diazonium salt **11**, to give the 2-morpholino-4-(2-morpholino-4-thiazolyl)-5-(4-nitrophenylazo)thiazole **12**. With aromatic aldehydes, such as 4-dialkylaminobenzaldehydes **13**, the same bisthiazole **8a** gives rise to the [2-morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl]-(4-dialkylaminophenyl)methinium perchlorates **14a-d**, respectively, which are deeply coloured compounds. Their chemical constitution follows unambiguously from their analytical and spectroscopic data.



A rather unexpected reaction occurs, however, if the 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole **8a** is allowed to react with nitrous acid. Instead of the formation of the corresponding 2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole 4-diazonium salt **15** the formation of a neutral compound has been observed. This compound is, according to its analytical and spectroscopic data, the tricyclic 2,7-bismorpholinothiazolo[4,5-*c*]thiazolo[4,5-*e*]pyridazine **16**. It has been formed, evidently, by an intramolecular coupling of the corresponding intermediate diazonium salt **15** formed in the course of the nitrosation reaction with one of its thiazole moieties.

The ^{1}H nmr spectra of tricyclic compound **16** is characterised by the absence of any proton signals between 7.00 and 9.00 ppm indicating the absence of typical heteroaromatic protons therein.

A similar intramolecular cyclisation has been found in the course of the reaction of the 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole **8a** with the Vilsmeier reagent prepared from dimethylformamide and phosphoryl chloride. Instead of the formation of the corresponding 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole-5-aldehyde **17** the formation of the 2,7-dimorpholinothiazolo[4,5-*b*]thiazolo[4,5-*d*]pyridine **19** occurs. Its formation can be explained by the intermediate formation of 4-(3-dimethylformamidino)-2-morpholino-5-(5-formyl-2-morpholino-4-thiazolyl)thiazole **18** which can be isolated as an unstable compound after the addition of water and aqueous bases to the reaction mixture. This compound can be transformed into tricyclic compound **19** by short heating in acetic anhydride.

Because in the ^{1}H nmr spectrum of the amidine derivative **18** the characteristic signals of the cyclisation product **19** can be detected to some extent. The instability of **18** and the tendency to cyclize easily into product **19** is documented.

The constitution of 2,7-dimorpholinothiazolo[4,5-*b*]thiazolo[4,5-*d*]pyridine **19** is supported by its elemental analytical and nmr spectroscopic data. Thus, the tricyclic pyridine compound **19** exhibit in its ^{1}H nmr spectra proton signals at about 3.70, 3.80, and at 8.54 ppm. Due to their chemical shifts, their intensity, and their splittings these signals can be attributed to the H-atoms at both the morpholino moieties as well as to the H-atom at the pyridine moiety of compound **19**.

EXPERIMENTAL

Melting points were determined by using a Boetius heating-block microscope. The nmr spectra were recorded on a Gemini 300 MHz spectrometer (Varian, Zurich, Switzerland) with hexamethyldisilazane as the internal standard and the mass spectra were measured with a sector-field spectrometer AMD 402 (Intectra GmbH, Harpstedt, Germany). The elemental analytical data were obtained by using a CHNS analyser 932 (LECO, U.S.A) and the uv/vis spectra by using a Lambda 2 spectrometer (Perkin Elmer, Ueberlingen, Germany).

Preparation of *N*(2),*N*(2')-Tetrasubstituted 2,4-Diamino-5-(2-amino-4-thiazolyl)thiazoles **8**. General Procedure.

A mixture of 0.1 mole of the requisite 2-dialkylamino-4-thiazoliniminium chloride **3** and 10.1 g (0.1 mole) of triethylamine in 100 ml of methanol is refluxed until the evolution of ammonia is completed. After cooling the resulting solution, the precipitate is filtered and washed with methanol. Compound **8c** (52%) is recrystallised from 1-butanol. Compounds **8a** and **8b** were obtained in 65% and 60% yields respectively, upon recrystallization from morpholine by the addition of methanol to the cooled mixture.

4-Amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**).

This compound had mp 198-199°; ^{1}H nmr (dideuteriotetrachloroethane): δ 3.39-3.42 (m, 8H, CH_2), 3.72-3.78 (m, 8H, CH_2), 5.21 (s, 2H, NH_2), 5.89 (s, 1H, CH); ^{13}C nmr (dideuteriotetrachloroethane): δ 48.1, 48.7, 66.2, 66.3, 90.7, 94.2, 146.1, 151.4, 167.3, 171.5; ms: (130°) m/z (%) 353 (100, M^+), 241 (8), 214 (12), 176 (4).

Anal. Calcd. for $C_{14}H_{19}N_5S_2O_2$ (353): C, 47.59; H, 5.38; N, 19.83; S, 18.13. Found: C, 47.48; H, 5.40; N, 19.54; S, 18.09.

4-Amino-2-pyrrolidino-5-(2-pyrrolidino-4-thiazolyl)thiazole (**8b**).

This compound had mp 251°; ^{1}H nmr (deuteriochloroform): δ 1.93-2.06 (m, 8H, CH_2), 3.35-3.51 (m, 8H, CH_2), 5.37 (s, 2H, NH_2), 5.71 (s, 1H, CH); ms: (240°) m/z (%) 321 (100, M^+), 225 (15), 198 (12), 161 (4).

Anal. Calcd. for $C_{14}H_{19}N_5S_2$ (321): C, 52.33; H, 5.92; N, 21.81; S, 19.94. Found: C, 52.58; H, 6.23; N, 21.92; S, 20.12.

4-Amino-2-diethylamino-5-(2-diethylamino-4-thiazolyl)thiazole (**8c**).

This compound had mp 126-127°; ^{1}H nmr (deuteriochloroform): δ 1.19-1.26 (m, 12H, CH_3), 3.40-3.51 (m, 8H, CH_2), 5.27 (s, 2H, NH_2), 5.71 (s, 1H, CH); ms: (180°) m/z (%) 325 (100, M^+), 310 (8), 296 (10), 281 (8), 227 (25).

Anal. Calcd. for $C_{14}H_{23}N_5S_2$ (325): C, 51.69; H, 7.07; N, 21.53; S, 19.69. Found: C, 51.92; H, 7.58; N, 21.46; S, 19.51.

4-Amino-2-morpholino-5-[2-morpholino-5-(*N*-phenylthiocarbamido)thiazol-4-yl]thiazole (**10**).

A mixture of 1.8 g (0.05 mole) of 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**) and 0.7 g (0.05 mole) of phenyl isothiocyanate in 50 ml of toluene are refluxed for 10 minutes. After cooling, the orange coloured precipitate formed is filtered, washed with ether, and dried, yield 0.9 g (36%), mp 214-215°; ^{1}H nmr (DMSO-d6): δ 3.25 (t, 4H, CH_2), 3.44 (t, 4H, CH_2), 3.58 (t, 4H, CH_2), 3.70 (t, 4H, CH_2), 6.74 (s, 2H, NH_2), 7.12 (t, 1H, H_{arom}), 7.32 (t, 2H, H_{arom}), 7.63 (d, 2H, H_{arom}), 10.91 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{24}N_6S_3O_2$ (488.0): C, 51.64; H, 4.92; N, 17.21; S, 19.67. Found: C, 51.98; H, 4.94; N, 17.34; S, 19.58.

4-Amino-2-morpholino-5-[5-(4-nitrophenylazo)-2-morpholinothiazol-4-yl]thiazole (**12**).

To a solution of 3.5 g (0.01 mole) of 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**) in 50 ml of acetic acid, a

solution of 0.01 mole 4-nitrophenyldiazonium hydrosulfate, prepared by the reaction of 1.4 g (0.01 mole) of 4-nitroaniline with 0.8 g (0.011 mole) of sodium nitrite in 20 ml of acetic acid and 2 ml of concentrated sulfuric acid at 0°, was added. After stirring for 10 minutes at room temperature the mixture is diluted with 50 ml of a concentrated aqueous solution of sodium acetate and then the precipitate is isolated by filtration, yield 3.1 g (56%), mp 304-306° (acetic acid); ^{1}H nmr (DMSO-d_6): δ 3.65-3.84 (m, 16H, CH_2), 7.31 (d, 2H, H_{arom}), 8.10 (d, 2H, H_{arom}), 8.34 (s, 2H, NH_2); uv/vis (dichloromethane): λ_{max} 668 nm; ms: (350°), m/z (%) 502 (19, M^+), 207 (12), 352 (30), 149 (100).

Anal. Calcd. for $C_{20}H_{22}N_8S_2O_4$ (502.0): C, 47.81; H, 4.38; N, 22.31; S, 12.75. Found: C, 48.05; H, 4.34; N, 22.01; S, 12.45.

Preparation of [2-Morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl]-(4-dialkylaminophenyl)methinium Perchlorates **14.** General Procedure.

A mixture of 0.5 g (1.4 mmoles) of 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**) and 1.4 mmoles of the corresponding 4-dialkylaminobenzaldehyde in 20 ml of acetic anhydride is heated 5 minutes at 100° and then mixed with a solution of 0.16 g of magnesium perchlorate in 2 ml of acetic anhydride. After cooling the reaction mixture the precipitates formed in 60-70% yield are isolated by filtration, washed with ether and recrystallised from acetic acid.

[2-Morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl]-(4-dimethylaminophenyl)methinium Perchlorate (**14a**).

This compound had mp 277-279°; uv/vis (dichloromethane): λ_{max} 648 nm (log ε 4.93); ms: (350°) m/z (%) 526 (34, M^+-$HClO_4$), 483 (100), 409 (10), 364 (38), 305 (15).

Anal. Calcd. for $C_{25}H_{31}ClN_6O_7S_2$ (626.5): C, 47.88; H, 4.95; N, 13.40; S, 10.21. Found: C, 48.25; H, 5.36; N, 13.21; S, 10.49.

[2-Morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl](4-diethylaminophenyl)methinium Perchlorate (**14b**).

This compound had mp 205-208°; ^{1}H nmr (deuterionitromethane): δ 1.27 (t, 6H, CH_3), 2.53 (s, 3H, CH_3), 3.61 (q, 4H, CH_2), 3.66-3.73 (m, 2H, CH_2), 3.78-3.85 (m, 6H, CH_2), 3.85-3.94 (m, 6H, CH_2), 3.96-4.04 (m, 2H, CH_2), 6.93 (d, 2H, H_{arom}), 7.67 (d, 2H, H_{arom}), 7.75 (s, 1H, CH), 11.93 (s, 1H, NH); uv/vis (dichloromethane): λ_{max} 658 nm (log ε 4.97).

Anal. Calcd. for $C_{27}H_{35}ClN_6O_7S_2$ (654.5): C, 49.50; H, 5.34; N, 12.83; S, 9.77. Found: C, 49.51; H, 5.68; N, 12.65; S, 9.90.

[2-Morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl](4-*n*-dibutylaminophenyl)methinium Perchlorate (**14c**).

This compound had mp 162-165°; uv/vis (dichloromethane): λ_{max}: 662 nm (log ε 4.96).

Anal. Calcd. for $C_{31}H_{43}ClN_6O_7S_2$ (710.5): C, 52.36; H, 6.05; N, 11.82; 9.00. Found: C, 52.32; H, 6.40; N, 11.64; S, 9.08.

[2-Morpholino-4-(4-acetamido-2-morpholino-5-thiazolyl)-5-thiazolyl][4-(4-morpholino)phenyl]methinium Perchlorate (**14d**).

This compound had mp >360°; uv/vis (dichloromethane): λ_{max} 628 nm (log ε 4.76); ms: (300°), m/z (%) 568 (26, M^+-$HClO_4$), 525 (100), 395 (25), 364 (30), 353 (15).

Anal. Calcd. for $C_{27}H_{33}ClN_6O_8S_2$ (668.5): C, 48.46; H, 4.94; N, 12.56; S, 9.57. Found: C, 48.46; H, 5.15; N, 12.46; S, 9.76.

2,7-Dimorpholinothiazolo[4,5-*c*]thiazolo[4,5-*e*]pyridazine (**16**).

To a mixture of 1.8 g (5 mmoles) of 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**) in 30 ml of acetic acid and 3 ml concentrated sulphuric acid, 0.4 g (6 mmoles) of sodium nitrite, dissolved in 1 ml of water, are added with stirring. After allowing the solution to stand at room temperature for 1 hour, it is neutralised with 2 *N* aqueous sodium hydroxide and the precipitate is isolated by filtration, washed with boiling acetonitrile, and dried, yield 1.2 g (67%), mp 265°; ^{1}H nmr (perdeuterioacetic acid): δ 3.52-3.74 (m, 4H, CH_2), 3.74-3.91 (m, 8H, CH_2), 3.91-4.12 (m, 4H, CH_2); ms (290°), m/z (%): 364 (96, M^+), 333 (19), 307 (100), 301 (18), 147 (31), 105 (29).

Anal. Calcd. for $C_{14}H_{16}N_6O_2S_2$ (364.0): C, 46.15; H, 4.39; N, 23.07; S, 17.58. Found: C, 46.24; H, 4.70; N, 22.89; S, 17.17.

4-(3-Dimethylformamidino)-2-morpholino-5-(5-formyl-2-morpholino-4-thiazolyl)thiazole (**18**).

To a mixture of 3.8 g (25 mmoles) of phosphoryl chloide in 10 ml of dimethylformamide 4.4 g, (12.5 mmoles) of 4-amino-2-morpholino-5-(2-morpholino-4-thiazolyl)thiazole (**8a**), dissolved in 20 ml of dimethylformamide, are added with stirring at room temperature. After stirring the mixture for 4 hours it was poured into ice and buffered at *p*H 9-10 by the addition of 2 *N* aqueous sodium hydroxide. The product formed was isolated by filtration, washed with water, and dried, yield 3.6 g (71%), mp 254-257° (acetonitrile); ^{1}H nmr (dideuteriotetrachloroethane): δ 3.01 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.48-3.53 (m, 4H, CH_2), 3.54-3.59 (m, 4H, CH_2), 3.73-3.80 (m, 4H, CH_2), 3.80-3.86 (m, 4H, CH_2), 8.55 (s, 1H, CH), 10.24 (s, 1H, CHO); ms: (280°) m/z (%) 435 (68, M^+), 407 (28), 390 (32), 363 (100), 306 (68), 235 (20).

Anal. Calcd. for $C_{18}H_{24}N_6O_3S_2$ (436.0): C, 49.54; H, 5.50; N, 19.26; S, 14.68. Found: C, 49.64; H, 5.69; N, 19.15; S, 14.61.

2,7-Dimorpholinothiazolo[4,5-*b*]thiazolo[4,5-*d*]pyridine (**19**).

A mixture of 2.0 g (5.2 mmoles) of 4-(3-dimethylformamidino)-2-morpholino-5-(5-formyl-2-morpholinothiazol-4-yl)thiazole (**18**) in 50 ml of acetic anhydride are refluxed for 2 minutes. The product which crystallizes at cooling is isolated by filtration, washed with ether, and dried, yield 1.5 g (73%); mp 298-300° (acetonitrile); ^{1}H nmr (dideuteriotetrachloroethane): δ 3.65-3.70 (m, 8H, CH_2), 3.79-3.82 (m, 8H, CH_2), 8.54 (s, 1H, CH); ^{13}C nmr (dideuteriotetrachloroethane): δ 48.5, 48.8, 66.2, 66.3, 112.6, 121.1, 138.6, 153.1, 163.2, 169.8, 173.2; ms: (280°) m/z (%) 363 (87, M^+), 306 (83), 238 (51), 171 (36), 155 (52), 149 (23), 139 (100), 91 (75).

Anal. Calcd. for $C_{15}H_{17}N_5O_2S_2$ (363.0): C, 49.58; H, 4.68; N, 19.28; S, 17.63. Found: C, 50.07; H, 4.87; N, 19.39; S, 17.66.

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