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Reaction of 5-halo-1,2,3-thiadiazoles with aliphatic diamines. Synthesis and intramolecular cyclization of bis(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfides

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Bis[1,2,3]triazolo[1,5-*f*:5',1'-*b*][1,3,6]thiadiazepine and [1,5-*g*:5',1'-*b*][1,3,7]thiadiazocine ring systems have been synthesized from 5-halo-1,2,3-thiadiazoles and aliphatic diamines. We have found that the last step of the process is the cyclization of initially formed bis(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfides. The structures of the intermediates and products were supported by different NMR spectroscopic methods (¹H coupled ¹³C NMR, 2D HETCOR, HMBC and 1D INADEQUATE experiments) and mass spectrometry. Differences in the reaction pathway for aliphatic and less nucleophilic aromatic diamines were determined.

Introduction

In a previous paper¹ we reported the synthesis of 3,1,5benzothiadiazepines from 5-halo-1,2,3-thiadiazoles and vicinal aromatic diamines which proceeded *via* sulfide as the intermediate (Scheme 1). In continuation of this work we were interested in studying the behavior of aliphatic diamines towards the same 1,2,3-thiadiazoles. In this paper we would like to report our results in this field.



Scheme 1



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A. Reaction of 5-halo-1,2,3-thiadiazoles with aliphatic diamines

Our preliminary investigations² have shown that the reaction of ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate **1a** with ethylene-

diamine **2a** gives a 1,3,6-thiadiazepine derivative. Moreover, intermediates different to those found for *ortho*-phenylenediamines¹ were isolated. In order to study the mechanism, and to know the scope and limitations of this process, various aliphatic di- and polyamines **2a**–**f** were allowed to react with 1,2,3-thiadiazoles **1a,b**. Monoamines react with bromide **1a** in a sequence of reactions, including (1) halogen substitution, (2) Dimroth rearrangement and (3) heteroarylation of the resulting thiolate **4** with a second equivalent of **1a**. The same sequence is followed for the aliphatic di- and polyamines **2a**–**f** (Scheme 2, Table 1). In general, polar solvents and base promote all three processes.³ Although the second amino group of *ortho*-phenyl-enediamine is not nucleophilic enough to substitute a halogen under these conditions, all amino groups of aliphatic amines **2a**–**f** are sufficiently reactive. As a result, the reaction readily



Scheme 2

Ami	ne 2	3		5		
	R		R ₁		R ₁	R ₂
а	NH, VNH,	a	OEt	а	OEt	OEt
	-	g	NHMe	g	NHMe	NHMe
				h i	OEt NHMe	NHMe OEt
b	NH ₂	Ь	OEt	b	OEt	OEt
с	H_2N N H_2	с	OEt	с	OEt	OEt
d	H N NH2	d	OEt	d	OEt	OEt
e	H ₂ N NH ₂ N NH ₂	e	OEt	e	OEt	OEt
f	H ₂ N NH ₂ N NH ₂	f	OEt	f	OEt	OEt

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affords multiply substituted products 3, and further transformation yields symmetrical compounds 5 with a (1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfide moiety on each amino group. Thus, upon treatment of 5-halo-1,2,3-thiadiazoles 1a,b with ethylenediamines 2b-d in refluxing ethanol in the presence of triethylamine, bis-sulfides **5b-d**,g were obtained in good yields. The multistep process itself, is working simultaneously and independently on several reaction centers, providing a plethora of intermediates. Indeed, however many of them can be detected in the reaction of polyamine with 5-halo-1,2,3-thiadiazole, they all finally yield poly(1,2,3-triazolyl-1,2,3-thiadiazolyl)sulfide 5 under the conditions mentioned above. On the other hand, changing the reaction conditions and the ratio of starting materials allows intermediate products to be obtained. Oligo(1,2,3-thiadiazolyl)amines 3a-f can be obtained when a non polar solvent such as chloroform, is used. However, the rearrangement cannot be completely excluded because of the strong basic character of the oligoamine. This observation, and the necessity of obtaining a product that is substituted at all amine functions with a thiadiazole, prevents the use of excess amine. The latter is usual in the synthesis of 5-(N-alkyl)amino-1,2,3-thiadiazoles, in order to trap the hydrogen bromide generated.^{3a} The use of triethylamine as acid scavenger promotes the Dimroth rearrangement. Therefore, the best yields were about 40-60%. As compounds of type 3 may undergo further transformation even in chloroform, the reaction mixture contains some thiolates of type 4 that are the products of the Dimroth rearrangement of one or both 1,2,3-thiadiazole rings. The thiolates were visible on TLC but were not isolated, as well as any other intermediates on the way to sulfide 5. The reaction of 1a with 1,2-diaminopropane 2b in chloroform was the only case where we have isolated an intermediate product. When the reaction mixture was diluted with ethanol the [3+1] adduct 6 (in Scheme 3) was obtained in 12% yield. The formation of 6 does show that the 1,2,3-thiadiazole ring at C-1 of the 1,2-propane rearranges faster and this suggests that sterical hindrance reduces the rate of Dimroth rearrangement of 5-alkylamino-1,2,3-thiadiazoles.

Thus, the structure of the main product in the reaction of 5-halo-1,2,3-thiadiazole with oligoamines depends upon a variety of factors including reaction conditions (solvent,

temperature, presence of base) and the ratio of the starting materials. The nature of the starting materials, which influences the comparative rates of substitution of bromothiadiazole 1a, Dimroth rearrangement and substitution of bromothiadiazole **1a** with the resulting thiol also plays a significant role. Indeed, treatment of 1a with ethylenediamine 2a in refluxing ethanol without an additional base already afforded a significant amount of bis(sulfide) 5a. On the other hand, 1,4-diaminobutane derivative 3d requires stronger conditions for rearrangement. Compound 3d does not rearrange in ethanol with 1 equivalent of triethylamine at room temperature. Only after heating, does further reaction to 5d take place. In the case of tris(aminoethyl)amine 2e and DAB-(NH₂)₄ 2f, even after prolonged heating in ethanol-triethylamine, TLC control reveals remaining tris-substituted compounds 3e,f. In order to convert all intermediates into final polysulfides 5e,f, heating at 80-100 °C in DMF was necessary.

B. Unsymmetrically substituted sulfides

We were interested in preparing compounds 3a,g in order to find a route to differently substituted (containing ester and amide groups at the same time) bis(sulfides) 5h,i. Compound 3a was easily obtained and upon heating at reflux in ethanol with methylamide 1b afforded 5h. However, when the methylamide 1b was treated with ethylenediamine in chloroform we could not obtain the disubstituted product 3g. Various reaction conditions (change of solvent, temperature, the sequence of reagents) resulted in almost the same mixture of products and in all experiments most of amide 1b remained unconverted. Therefore, 1b is reactive enough to be substituted by thiolates, but fails to react with amines. Traces of compound 3g were detected in the ¹H NMR spectrum, displaying the characteristic signal for the ethylene protons at 3.5 ppm whereas the other material appeared to be bis(sulfide) 5g and the products of single or double Dimroth rearrangement of 3g. These experiments did not allow isolation of 3g but bis(sulfide) 5i could be obtained. Indeed, when the reaction mixture was separated from starting methylamide 1b and refluxed in ethanol with ester 1a, a mixture with an approximate 1 : 2 ratio of 5g and 5i was obtained. The latter was isolated by column chromatography. It





$$\begin{split} \mathbf{j} \ \ & \mathbf{R}_1 \!=\! \mathbf{H}, \, \mathbf{R}_2 \!=\! \mathbf{OEt}, \, \mathbf{k} \, \mathbf{R}_1 \!=\! \mathbf{CH}_3, \, \mathbf{R}_2 \!=\! \mathbf{CH}_3, \\ & \mathbf{m} \, \mathbf{R}_1 \!=\! \mathbf{H}, \, \mathbf{R}_2 \!=\! \mathbf{CH}_3, \, \mathbf{n} \, \mathbf{R}_1 \!=\! \mathbf{H}, \, \mathbf{R}_2 \!=\! \mathbf{H} \end{split}$$

Scheme 3

1 a

Table 2 Compounds 3,5,8: yields (%)/melting points (°C)

is obvious that in this case the rates of the Dimroth rearrangement and the second substitution of halogen by thiol are much higher than that of the initial substitution of halogen.

C. Cyclization reactions

With the compounds 3, 5 and 6 in hand, the possibility of their cyclization into seven-membered and larger rings was investigated. The results of this study are shown in Scheme 3 and Table 2. Firstly, we observed that 3a was converted into bis[1,2,3]triazolo[1,5-f:5',1'-b][1,3,6]thiadiazepine 7a in a yield of about 20% on heating at reflux in ethanol in the presence of triethylamine. Later, it was found that sulfides 5a-c and 6 afforded 1,3,6-thiadiazepines (1,3,7-thiadiazocines) 7a-c under the same conditions. Compound 6 gave only 30% of cyclic product 7b whereas bis(sulfides) 5a-c surprisingly provided the best yields of thiadiazepines 7a,b or 1,3,7-thiadiazocine 7c. All attempts to obtain nine-membered rings by cyclization of bis-(sulfide) 5d were unsuccessful. It is evident that cyclization of 3 goes through a double Dimroth rearrangement followed by an intramolecular substitution of bis(thiolate) 4. However, this process is not common in the literature. Examples of bis(thiol) cyclization to cyclic sulfides via acid-catalyzed dehydration⁴ or desulfurization of initially formed disulfides with P(NMe₂)₃⁵ were reported. Intramolecular cyclization of bis(sulfides) seems to be even more remarkable and also more promising for the preparation of 1,3,6-thiadiazepines. Ring formation of this type was described for compounds containing two methylsulfanyl groups either under demethylation conditions (sodium methanethiolate in DMF or lithium in liquid ammonia)⁶ or by using pyridinium chloride.⁷ In the case of our bis(sulfides) 5, bis(1,2,3-thiadiazole-5-yl)disulfide 9 (Scheme 4) was detected after work-up indicating the easily oxidized 5-mercapto-1,2,3thiadiazole to be one of the by-products. The other 1,2,3-thiadiazole ring probably decomposed after being removed from 5 with a nucleophile (hydroxide, triethylamine). It is also necessary to outline the role of the ester groups on both the



^{*a*} Was isolated when thiadiazepine 7m was formed from 1a and 2m. ^{*b*} These compounds were characterized earlier.¹

1,2,3-triazole and 1,2,3-thiadiazole rings in the formation of thiadiazepine 7. Bis(sulfide) 5g, when heated in DMF-Et₃N for several days was unchanged and compounds **5h**,i with combined ester/amide functions produce only sulfide bond cleavage

Compound BaC3C4C0CH3NCH3XC5C4C0CH3C5C4C0CH3C13 3a 131.95141.91159.0462.2513.9751.8454.76147.26160.5462.9314.31171.12132.39163.6061.6214.39 4b 132.02141.81158.90662.2513.9751.8454.76159.68147.26160.5462.9314.31 4c 131.06141.94159.1362.18140147.60160.24862.9314.31 4c 131.06141.94159.1362.2113.9561.86147.12160.5362.8614.25 4b 132.15141.72159.1562.2214.0652.56147.12160.5362.88147.26160.5362.8614.25 4c 131.06141.94159.1562.2214.0146.0539.56CH3159.87147.14160.6162.9314.35 4c 133.06143.25140.1652.50147.12160.5362.98147.26160.5362.98147.26 55 132.16143.37159.1814.0146.0552.60147.12160.6362.93147.12160.5362.98147.12160.53147.12160.53147.12160.53147.14160.6162.93147.14160.61147.35163.53163.53163.56147.35 6a 130.26 <t< th=""><th></th><th>Triazole</th><th></th><th></th><th></th><th></th><th></th><th></th><th>Thiadiazc</th><th>ole-S</th><th></th><th></th><th></th><th>Thiadiazc</th><th>ole-NH</th><th></th><th></th><th></th></t<>		Triazole							Thiadiazc	ole-S				Thiadiazc	ole-NH			
3a50.1350.13171.12132.39163.6061.6214.394a131.95141.91159.0462.2914.0447.6959.68147.26160.5362.8614.314b132.02141.81158.9662.2513.9751.8454.76 CH159.99147.18160.5362.8614.254c131.40°141.60158.8813.951.994CH3159.68147.10160.5362.2814.264c131.40°141.60158.8813.9052.1819.94CH3159.68147.12160.5362.8614.254c131.06141.94159.1362.1814.0146.0529.35CH2159.68147.14160.6162.9314.334c131.06141.72159.1562.3214.0146.0529.35CH2159.87147.14160.6162.9314.334c130.20138.04159.8961.9914.21159.87147.14160.6162.9314.33163.5061.746a130.20138.616.93153.6462.93147.14160.6162.93143.33169.63132.43163.5061.746a130.20138.7199.8662.0114.355.2CH159.87147.14160.6162.93143.33169.63163.5061.7414.336b130.20131.3138.5160.262.1114.355.2CH55.23147.1416	Compound	CS	C4	CO	CH_2	CH_3	NCH ₂	×	C5	C4	CO	CH_2	CH3	C5	C4	CO	CH_2	CH3
4a[31:95][41:91][59:04] 62.29 [4,04] 47.69 [59:68] 147.26 [60:54] 62.93 [4.3]4b[32:02][41:81][58:96] 62.25 [3.97]51:84 54.76 CH[59:68] 147.18 [60:53] 62.86 [4.25]4c[31:06][14:194][59:13] 62.18 [14:01] 46.05 29.35 CH ₃ [59:98] 147.19 [60:48] 62.93 [42:36]4c[31:06][14:194][59:13] 62.18 [14:01] 46.05 29.35 CH ₃ [50:63] 62.86 14.26 4c[31:106][14:12][59:15] 62.23 [14:01] 46.05 29.35 CH ₃ 169.63 124.33 169.63 163.63 61.36 4c[31:206][33:04][59:18] 62.12 14.01 46.05 52.60 58.65 CH ₃ 169.23 62.93 14.33 169.63 169.63 163.63 61.36 6a[30:20][38:04][59:8] 61.93 147.14 160.61 62.93 14.33 169.63 163.63 61.74 14.33 6a[30:20] $18:7$ CH ₃ 56.2 CH 159.87 147.14 160.61 62.93 14.33 169.63 163.63 61.36 6a[30:20] $18:7$ CH ₃ 56.2 CH 17.74 169.61 62.93 14.33 169.63 153.243 163.50 61.74 6a[31:30.6] 137.4 19.33 56.2 CH 17.77 147.1	3a						50.13							171.12	132.39	163.60	61.62	14.39
4b 132.02 141.81 158.96 62.25 13.97 51.84 54.76 CH 159.99 147.18 160.53 62.86 14.25 4c 131.40^a 141.60 158.88 13.95 19.94 CH, 159.68 147.09 160.48 142.6 4c 131.06 141.94 159.13 62.18 14.01 46.05 29.35 CH, 159.68 147.10 160.48 5 132.15 141.72 159.15 62.22 14.01 46.05 29.35 CH, 159.63 147.12 160.53 62.88 14.26 6a 132.15 141.72 159.15 62.22 14.21 160.29 147.14 160.61 62.93 14.33 163.63 61.74 14.33 6a 130.20 138.04 159.89 61.29 147.14 160.61 62.93 14.33 163.63 163.50 61.74 14.33 6a 130.66 138.04 159.89 61.93 132.43 163.50 61.74 14.33 6b 129.4^a 137.4 199.83 62.01 14.3 56.2 CH 199.63 132.43 163.50 61.74 14.33 6c 130.6 138.74 199.83 62.01 147.14 160.61 62.93 14.33 169.63 132.43 163.50 61.74 14.33 6a 130.6 138.74 199.83 62.01 14.33 56.2 CH 129.74 147.14 160.61 62.93 <t< td=""><td>4a</td><td>131.95</td><td>141.91</td><td>159.04</td><td>62.29</td><td>14.04</td><td>47.69</td><td></td><td>159.68</td><td>147.26</td><td>160.54</td><td>62.93</td><td>14.31</td><td></td><td></td><td></td><td></td><td></td></t<>	4a	131.95	141.91	159.04	62.29	14.04	47.69		159.68	147.26	160.54	62.93	14.31					
4c 131.40^a 141.60 158.88 13.95 $19.94CH_3$ 159.68 147.09 160.48 5 131.06 141.94 159.13 62.18 14.01 46.05 $29.35CH_2$ 160.29 147.12 160.53 62.88 14.26 6a 132.15 141.72 159.15 62.32 14.06 52.60 $58.65CH_3$ 160.29 147.14 160.61 62.93 14.33 163.60 61.74 14.33 6a 130.20 138.04 159.89 61.99 147.14 160.61 62.93 14.33 169.63 163.50 61.74 14.33 6a 130.20 138.04 159.89 61.99 147.14 150.87 147.14 160.61 62.93 14.33 163.50 61.74 14.33 6a 130.20 138.04 159.89 61.99 14.21 49.33 $56.2CH$ 52.61 52.93 54.33 160.51 62.93 14.33 169.63 123.43 163.50 61.74 14.33 6b 129.4^a 137.4 159.86 61.9 $17.8CH_3$ $56.2CH$ $17.8CH_3$ $56.2CH$ $17.8CH_3$ 160.2 62.11 14.3 $27.7CH_2$ 6c 131.3 138.5 160.2 62.11 14.9 $27.7CH_2$ $27.7CH_2$ 147.14 150.86 14.33 169.63 132.43 163.50 61.74 14.33 11 124.60 134.72 14.9 $27.7CH_2$ $27.7CH_2$ <td>4b</td> <td>132.02</td> <td>141.81</td> <td>158.96</td> <td>62.25</td> <td>13.97</td> <td>51.84</td> <td>54.76 CH</td> <td>159.99</td> <td>147.18</td> <td>160.53</td> <td>62.86</td> <td>14.25</td> <td></td> <td></td> <td></td> <td></td> <td></td>	4b	132.02	141.81	158.96	62.25	13.97	51.84	54.76 CH	159.99	147.18	160.53	62.86	14.25					
4c131.06141.94159.136.2.1814.0146.0529.35CH2160.29147.12160.536.2.8814.265132.15141.72159.156.2.3214.0652.6058.65 CH3159.87147.14160.6162.9314.33163.5061.7414.336a130.20138.04159.8961.9914.2149.3318.57 CH3159.87147.14160.6162.9314.33163.5061.7414.336a130.20138.04159.8961.9914.2149.3356.2 CH356.2 CH3<		131.40^{a}	141.60	158.88		13.95		19.94CH ₃	159.68	147.09	160.48							
5 132.15 141.72 159.15 62.32 14.06 52.60 58.65 CH 159.87 147.14 160.61 62.93 14.33 163.50 61.74 14.33 6a 130.20 138.04 159.89 61.99 14.21 49.33 18.57 CH ₃ 18.57 CH ₃ 18.57 CH ₃ 18.57 CH ₃ 14.33 163.50 61.74 14.33 6b 130.6 138.5 160.2 6.2.1 14.3 53.0 56.2 CH 17.8 CH ₃ 66.2 17.8 CH ₃ 17.7 CH ₂ 17	4c	131.06	141.94	159.13	62.18	14.01	46.05	29.35CH2	160.29	147.12	160.53	62.88	14.26					
6a 130.20 138.04 159.89 61.99 14.21 49.33 18.57CH3 6b 130.6 138.5 160.2 6.2.1 14.3 53.0 56.2 CH 6b 130.6 138.5 160.2 6.2.1 14.3 53.0 56.2 CH 6c 131.3 138.5 160.2 6.2.1 14.3 27.7 CH2 6c 131.3 138.5 160.2 62.1 14.9 27.7 CH2 11 124.60 134.72 47.9 27.7 CH2 47.78	S	132.15	141.72	159.15	62.32	14.06	52.60	58.65 CH	159.87	147.14	160.61	62.93	14.33	169.63	132.43	163.50	61.74	14.33
6a 130.20 138.04 159.89 61.99 14.21 49.33 0 6b 130.6 138.5 160.2 6.2.1 14.3 53.0 56.2 CH 6b 129.4° 137.4 159.8 62.0 17.8 CH ₃ 6c 131.3 138.5 160.2 62.1 14.3 27.7 CH ₂ 11 124.60 134.72 47.9 27.7 CH ₂ 17.8								18.57CH ₃										
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129.4 ^a 137.4 159.8 62.0 17.8 CH ₃ 6c 131.3 138.5 160.2 62.1 14.3 27.7 CH ₂ 11 124.60 134.72 47.78 77.7 27.7 CH ₂	6b	130.6	138.5	160.2	62.1	14.3	53.0	56.2 CH										
6c 131.3 138.5 160.2 62.1 14.3 44.9 27.7 CH ² 11 124.60 134.72 47.78		129.4^{a}	137.4	159.8	62.0			17.8 CH ₃										
11 124.60 134.72 47.78 ⁻	6c	131.3	138.5	160.2	62.1	14.3	44.9	27.7 CH ₂										
	11	124.60	134.72				47.78	I										



products, with virtually no cyclization. Thus, ester functions are necessary at the heterocyclic ring for the intra- and intermolecular nucleophilic aromatic substitutions to occur.

D. Structural investigations

The structures of dithiadiazolyldiamines 3, bis(sulfides) 5, adduct 6 and 1,3,6-thiadiazepines 7 were completely supported by NMR spectroscopy. ¹³C NMR chemical shifts are summarized in Table 3. We can clearly distinguish the signals due to the 1,2,3-triazole or the 1,2,3-thiadiazole rings, that are either connected through S or NH, and their substituents. The ¹H NMR spectra of these compounds are rather simple, especially for symmetrical structures and contain characteristic signals for the methylene protons at 3.64 ppm for compounds 3, and at 4.6-5.2 ppm for methylene groups attached to the triazole nitrogen (5,6,7). Signals of ester groups on a thiadiazole ring occupy a downfield position (4.58 and 1.52 ppm for CH₂ and CH₃, respectively) as compared with the corresponding resonances for triazole ethoxycarbonyl groups at 4.37 and 1.33 ppm. The signals in the ¹H and ¹³C NMR spectra were assigned based on the analysis of HETCOR and HMBC data. 2D experiments were made to reveal the ${}^{1}J_{CH}$ connectivities, but in the case of bis(sulfides) 5, due to the lack of protons these data were not sufficient to make a complete assignment. Therefore, a 1D INADEQUATE experiment was performed for compounds 5b and 5c because of their high solubility, and the carboncarbon coupling constants were determined. With the help of this information we were able to assign these groups of signals to either the 1,2,3-triazole or 1,2,3-thiadiazole ring. However it was still impossible to establish the difference between similar heterocyclic carbons in unsymmetrical bis(sulfide) 5b. Spinspin coupling constants between ¹³C nuclei for triazole and thiadiazole rings which are of interest and are not readily available in the literature⁸ are presented in Table 4.

Mass spectra of bis(sulfides) 5 were taken using the electrospray technique. It is worth knowing that the EI-MS technique, though not allowing us to obtain molecular ions of bis(sulfides) 5a-c, showed the formation of corresponding heterocycles 7 during gas phase fragmentation. The most intensive peaks of the electron impact MS of 5 corresponded to the molecular ion following fragmentation of thiadiazepine(azocine). Interestingly, the fragmentation pattern of 5d does not contain peaks corresponding to the appropriate thiadiazonine.

	Triazole		Thiadiazole	
Compound	${}^{1}J_{\rm C5-C4}$	${}^{1}J_{\text{C4-CO}}$	${}^{1}J_{\rm C5-C4}$	${}^{1}J_{\text{C4-CO}}$
4b	73.6 73.9 73.4	95.2 94.7	90.2 90.7	66.3 66.9

The parent heterocyclic system 9,10-dihydrobis[1,2,3]triazolo[1,5-f:5',1'-b][1,3,6]thiadiazepine 11 was obtained from ester 7a by saponification followed by decarboxylation of diacid 10 (Scheme 5). Compound 11 was subjected to crystallographic analysis. The compound shows no molecular symmetry. The thiadiazepine ring occurs in a boat conformation with atoms S1 and C4 at the opposite side of the fused triazole rings with respect to the best plane through the seven-membered ring. This best plane makes an angle of 26.1(1)° and 13.0(1)° with the best planes through the five-membered rings. Both triazole rings make an angle of 49.0(1)° to each other. (Fig. 1).



Fig. 1 Molecular structure of parent heterocycle 11.

E. Reactions with aromatic diamines

For aromatic diamines, the main route to 3,1,5-benzothiadiazepine 7 proceeds via sulfide 8, but for the reaction of 5-bromo-1,2,3-thiadiazole 1a with phenylenediamines containing electron rich functions 2j-m, the same pathway as for the aliphatic oligoamines was observed. In this case, bis(sulfides) of type 5 were detected among the intermediates. It was found that in ethanol solution in the presence of triethylamine at room temperature, with a 1:4 ratio of starting compounds 2j-m: 1a, both amino groups were substituted and products of type 5j-m were formed. The same conditions for 2n produce only sulfide 8n. Analogously to compounds 5a-c, the EI-MS spectra of bis(sulfides) 5j-m revealed the transformation into thiadiazepines 7j-m in the gas phase. At the same time, treatment of initially isolated 5-amino-1,2,3-thiadiazole 12j-m with 1 eq. bromoester 1a in basic media at room temperature afforded sulfides 8j-m in good yields. When thiadiazepines 7 were formed in refluxing ethanol-triethylamine, both compounds 5 and 8 were detected as intermediates in the reaction mixture by means of TLC analysis, although both of them disappeared to the extent that the thiadiazepine ring was formed. We may argue that the reaction may simultaneously proceed via two different intermediates 5 and 8. As proof of this supposition, isolated 5m was transformed into 7m on refluxing in ethanol with Et₃N in 79% yield. Unexpectedly, 4-methylphenylenediamine 2m undergoes nucleophilic substitution of both amino groups more readily then diamines 2k and 2j. So far, we are not able to explain this fact. While diamines 2j,k produce only 18-35% of bis(sulfides) 5j,k, and the other products were found to be monosulfides 8 and even 5-arylamino-1,2,3-thiadiazoles 12, the yield of 5m is remarkably high. The formation of bis-(sulfide) 5m occurred even when starting materials 1a : 2m were combined in a 2 : 1 ratio. In this case, when the reaction is over, one can see by TLC control the unconverted diamine 2m along with 5m. Moreover, when thiadiazepine 7m was formed from 1a and 2m, bis(1,2,3-thiadiazolyl) substituted phenylenediamine 3m was unexpectedly obtained along with disulfide 9 as a byproduct. Compound 3m could be generated in this reaction either by direct heteroarylation of phenylenediamine or by transformation of sulfide 8m for which the transposition of thiadiazole ring from sulfur to amino group (Smiles-type rearrangement), followed by Dimroth rearrangement could be supposed. We tried to obtain bis(substituted) 3m by heteroarylation of phenylenediamine 2m but the only product was the monosubstituted compound 12m. On the contrary, treatment of sulfide 8m with NaH in dimethyl formamide easily afforded 3m in more than 70% yield. The analogous product 3n was obtained from sulfide 8n. Compounds 3m,n also afford cyclization products 7m,n in a yield of 25-30%.

Conclusion

In conclusion, various vicinal diamines react with 5-halo-1,2,3thiadiazoles to form the bis[1,2,3]triazolo[1,5-b:5',1'-f][1,3,6]thiadiazepine system 7. The mechanism of the transformation depends upon the reactivity of the diamine. This was proved by isolation of the intermediates shown in Table 2. Thus, for aromatic diamines sulfide 8 is initially formed, and electronrich phenylenediamines also produce bis(sulfides) 5. Highly reactive aliphatic diamines in polar basic media gave compounds 5 exclusively, while the use of nonpolar solvents afforded bis(substituted) products 3. The intermediates 3,5,8underwent transformation into seven (or eight)-membered rings.

Experimental

Materials and methods

¹H and ¹³C NMR spectra were recorded respectively on a Bruker WM-250, Bruker WM-300 and Bruker DRX-400 in either (CD₃)₂SO or CDCl₃ solutions. 2D NMR experiments were carried out using standard pulse sequences from the Bruker NMR Suite 2.6 software. ESI-MS spectra were scanned on a Micromass Quatro II (infusion of 50 il MeOH–CH₂Cl₂ – NH₄OAc(0.1 M in MeOH) with Harvard pump, model 11), electron impact mass spectra were obtained on a Varian MAT 311 machine. Products were analyzed by TLC on DC-Plastikfolien Kieselgel 60 F 254 plates. Melting points were taken in open capillaries and are uncorrected. Commercial samples of amines **2a–f,k–n** were used. 4-Ethoxyphenylenediamine **2j** was obtained by reduction of 2-nitro-4-ethoxyaniline with hydrazine over palladium.

Diethyl 5,5'-[ethane-1,2-diyldi(imino)]bis(1,2,3-thiadiazole-4carboxylate) 3a. A solution of bromoester 1a (0.5 g, 2.1 mmol) and 0.75 equivalents of ethylenediamine 2a (0.1 g) in chloroform (5 mL) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in ethanol acidified with hydrochloric acid, and the precipitated product was filtered off and crystallized from ethanol yielding 0.47 g (60%) of white crystals, mp 148 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.44 (6H, t, J = 7.2 Hz, 2CH₃), 3.64 (4H, m, CH₂CH₂), 4.45 (4H, q, J = 7.2 Hz, 2OCH₂), 8.06 (2H, t, 2NH). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 14.39 (qt, J = 127.4, 2.7 Hz, 2CH₃), 50.13 (tdt, J = 139.9, 3.2, 3.2 Hz, CH₂CH₂), 61.62 (tq, J = 148.3, 4.4 Hz, 2OCH₂), 132.39 (d, J = 1.5 Hz, C4-thiadiazole), 163.60 (t, J = 3.4 Hz, CO), 171.12 (td, J = 4.6, 2.6 Hz, C5-thiadiazole). EIMS m/z (rel. int.): 372 (M⁺,9), 190 (31). Anal. Calcd for C₁₂H₁₆N₆O₄S₂: C, 38.70; H, 4.33; N, 22.57; S, 17.22. Found C, 38.73; H, 4.30; N, 22.53; S, 17.29%.

Diethyl 5,5'-[propane-1,2-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3b. A solution of bromoester **1a** (0.5 g, 2.1 mmol) and 0.75 equivalents of 1,2-propylenediamine **2b** (0.12 g) in chloroform (5 mL) was refluxed for 3 hours. The solvent was evaporated and the crude product was purified by column chromatography using chloroform as the eluent. Yield 42%, mp 107 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.42–1.48 (9H, m, 3CH₃), 3.50 (3H, m, CH + CH₂), 4.45 (4H, m, 2OCH₂), 7.86 (1H, d, J = 7.2 Hz, NHCH), 8.07 (1H, t, J = 5.2 Hz, NHCH₂). EIMS *m/z* (rel. int.): 387 (MH⁺,100). Anal. Calcd for C₁₃H₁₈N₆O₄S₂: C, 40.40; H, 4.69; N, 21.75. Found C, 40.37; H, 4.70; N, 21.80%.

Diethyl 5,5'-[propane-1,3-diyldi(imino)]bis(1,2,3-thiadiazole-4-carboxylate) 3c. Prepared from **1a** and **2c** as described for **3b**. Yield 47%, mp 91 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 250 MHz): 1.45 (6H, t, J = 7.1 Hz, 2CH₃), 2.15 (2H, m, J = 6.7 Hz, CH₂ centr.), 3.43 (4H, m, J = 6.1 Hz, 2CH₂), 4.46 (4H, q, J = 7.1 Hz, 2CH₂ ester), 7.93 (2H, m, 2NH). EIMS *m*/*z* (rel. int.): 386 (M⁺, 4), 169 (100). Anal. Calcd for C₁₃H₁₈N₆O₄S₂: C, 40.40; H, 4.69; N, 21.75. Found C, 40.33; H, 4.68; N, 21.72%.

Diethyl 5,5'-[butane-1,4-diyldi(imino)]bis(1,2,3-thiadiazole-4carboxylate) 3d. Prepared from **1a** and **2d** as described for **3a**. Yield 53%, mp 106 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 250 MHz): 1.84 (4H, m, 2CH₂), 3.34 (4H, m, 2NHCH₂), 4.45 (4H, q, *J* = 7.0 Hz, 2OCH₂), 7.88 (2H, m, 2NH).11.45 (6H, t, *J* = 7.0 Hz, 2CH₃), EIMS *m*/*z* (rel. int.): 400 (M⁺, 0.8), 203 (9), 126 (20). Anal. Calcd for C₁₄H₂₀N₆O₄S₂: C, 41.99; H, 5.03; N, 20.98. Found C, 42.05; H, 5.09; N, 20.89%.

N'-4-Ethoxycarbonyl-1,2,3-thiadiazol-5-yl-N,N-bis[2-(4-ethoxycarbonyl-1,2,3-thiadiazol-5-ylamino)ethyl]ethane-1,2-

diamine 3e. To a solution of **1a** (1 g, 4.22 mmol) in ethanol (50 mL), tris(2-aminoethyl)amine **2e** (0.21 g, 1.40 mmol) was added and the reaction mixture was refluxed overnight. After cooling, the precipitate was filtered off and crystallized from ethanol. Yield 44%, mp 144 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.35 (9H, t, J = 7.3, 3CH₃), 2.93 (6H, m, 3NCH₂), 3.32 (6H, m, 3NHCH₂), 4.28 (6H, q, J = 7.3 Hz, 3OCH₂), 8.16 (3H, m, 3NH). ESI-MS 615 (MH⁺). Anal. Calcd for C₂₁H₃₀N₁₀S₃O₆: C, 41.03; H, 4.92; N, 22.79; S, 15.65. Found C, 40.97; H, 4.90; N, 22.83; S, 15.56%.

Tetra-[4-ethoxycarbonyl-([1,2,3]-thiadiazol-5-yl)]-DAB-Am-4 3f. To a solution of 1a (1 g, 4.22 mmol) in 50 mL of ethanol DAB-(NH₂)₄, 2f (0.44 g, 1.05 mmol, 75% reagent) was added and the reaction mixture was refluxed for 2 days. The solvent was removed, chloroform added and precipitate was filtered off and dried in a vacuum over P₂O₅. Yield 25%, mp 188 °C. ¹H NMR δ_H (DMSO-D₆, 400 MHz): 1.33 (12H, t, *J* = 7.1 Hz, 4CH₃), 1.65 (4H, m, NCH₂CH₂CH₂CH₂N), 2.00 (8H, m, NHCH₂CH₂CH₂N), 3.11 (12H, m, 6NCH₂), 3.35 (8H, m, 4NHCH₂), 4.35 (8H, q, *J* = 7.1 Hz, 4OCH₂), 8.44 (4H, t, *J* = 5.4 Hz, 4NH). ¹³C NMR δ_C (DMSO-D₆, 100 MHz): 14.28 (CH₃), 21.90, 48.98, 49.51, 51.20, 60.44 (OCH₂), 130.96 (C4-thiadiazole), 162.21 (CO), 170.53 (C5-thiadiazole). Anal. Calcd for C₃₆H₅₆N₁₄S₄O₈: C, 45.94; H, 6.00; N, 20.83. Found C, 45.81; H, 6.07; N, 20.69%.

5,5'-[(4-methyl-1,2-phenylene)di(imino)]bis(1,2,3-Diethyl thiadiazole-4-carboxylate) 3m. Sulfide 8m (0.15g, 0.34 mmol) was dissolved in dry DMF under stirring and cooling on the ice bath. Sodium hydride (0.1 g, 60% dispersion in mineral oil) was added and reaction was stirred for 1 hour at room temperature and quenched with water. Upon acidification, the product precipitated and was filtered off and washed with ethanol. Yield 74%, mp 138 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆+CCl₄, 250 MHz): 1.40 (3H, t, J = 7.0 Hz, CH₃), 1.41 (3H, t, J = 7.0 Hz, CH₃), 2.41 (3H, s, CH₃), 4.42 (2H, q, J = 7.0 Hz, CH₂), 4.43 (2H, q, J = 7.0 Hz, CH₂), 7.21 (1H, d, J = 7.6 Hz, C3H), 7.34 (1H, s, C1H), 7.43 (1H, d, J = 8.2 Hz, C4H), 9.93 (1H, s, NH), 10.04 (1H, s, NH). EIMS m/z (rel. int.): 434 (M⁺,20). Anal. Calcd for C17H18N6S2O4: C, 46.99; H, 4.18; N, 19.34. Found C, 46.91; H, 4.22; N, 19.30%.

Diethyl 5,5'-[(1,2-phenylene)di(imino)]bis(1,2,3-thiadiazole-4carboxylate) 3n. Prepared from **8n** as described for **3m**. Yield 79%, mp 132 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆+CCl₄, 250 MHz): 1.41 (6H, t, *J* = 7.0 Hz, 2CH₃), 4.43 (4H, q, *J* = 7.0 Hz, 2CH₂), 7.41–7.47 (2H, m, CH-arom.), 7.53–7.59 (2H, m, CH-arom), 10.07 (2H, s, 2NH). EIMS *m*/*z* (rel. int.): 420(M⁺,31). Anal. Calcd for C₁₆H₁₆N₆S₂O₄: C, 45.71; H, 3.84; N, 19.99. Found C, 45.76; H, 3.81; N, 20.03%.

5,5'-{Ethane-1,2-diylbis[(4-ethoxycarbonyl-1H-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4- ethoxycarbonyl-1,2,3-thiadiazole) 5a. To a solution of bromoester 1a (0.5 g, 2.1 mmol) and ethylenediamine 2a (0.03 g, 0.52 mmol) in ethanol (30 mL), triethylamine (0.3 mL, 2.1 mmol) was added and the mixture was refluxed for 5 hours. The product began to precipitate from the boiling solution and after cooling was filtered off and crystallized from ethanol yielding 0.30 g (84%) of white crystals, mp 209 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.33 (6H, t, J = 7.1 Hz, 2CH₃-triaz.), 1.51 (6H, t, J = 7.1 Hz, 2CH₃-thiadiaz.), 4.38 (4H, q, J = 7.1 Hz, 2OCH₂-triaz.), 4.57 (4H, q, J = 7.1 Hz, 2OCH₂-thiadiaz.), 5.18 (4H, s, CH₂CH₂). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 14.04 (qt, J = 127.6, 2.7 Hz, 2CH₃-triaz.), 14.31 (qt, J = 127.6, 2.7 Hz, 2CH₃-thiadiaz.), 47.69 (tt, J = 146.8, 3.6 Hz, CH_2CH_2), 62.29 (tq, J = 148.8, 4.4 Hz, 2 OCH_2 -triaz.), 62.93 (tq, J = 149.0, 4.4 Hz, 20CH₂-thiadiaz.), 131.95 (t, J = 1.1 Hz, C5-triaz.), 141.91 (s, C4-triaz.), 147.26 (s, C4-thiadiaz.), 159.04 (t, J = 3.2 Hz, CO-triaz.), 159.68 (s, C5-thiadiaz.), 160.54 (t, J)J 3.2 Hz, CO-thiadiaz.). ESI-MS 685 (MH⁺). EIMS m/z (rel. int.): 529(1), 370(28), 339(38), 240(50), 199(32), 157(60), 114(55), 85(100). Anal. Calcd for C₂₂H₂₄N₁₀O₈S₄: C, 38.59; H, 3.53; N, 20.46; S, 18.73. Found C, 38.62; H, 3.56; N, 20.74; S, 18.51%.

5,5'-{Propane-1,2-diylbis[(4-ethoxycarbonyl-1H-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5b. Prepared from 1a and 2b as described for 5a. Yield 73%, mp 123 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.315 (3H, t, J = 7.1 Hz, CH₃-triaz.), 1.317 (3H, t, J = 7.1 Hz, CH₃-triaz.), 1.519 (3H, t, J = 7.1 Hz, CH₃-thiadiaz.), 1.521 (3H, t, J = 7.1 Hz, CH₃-thiadiaz.), 1.77 (3H, d, J = 6.8 Hz, CH₃), 4.366 (2H, q, J = 7.1 Hz, OCH₂-triaz.), 4.371 (2H, q, J = 7.1 Hz, OCH₂triaz.), 4.581 (2H, q, J = 7.1 Hz, OCH₂-thiadiaz.), 4.585 (2H, q, J = 7.1 Hz, OCH₂-thiadiaz.), 4.88, 5.43 (2H, AB-syst., J = 14.3, 9.9, 4.0 Hz, CH₂), 5.77 (1H, dqd, J = 9.9, 6.8, 4.0 Hz, CH). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 13.95 (qt, J = 127.6, 3.6 Hz, CH₃triaz.), 13.97 (qt, J = 127.5, 2.6 CH₃-triaz.), 14.25 (qt J = 127.6, 2.7 Hz, 2CH₃-thiadiaz.), 19.94 (qdt, J = 130.5, 3.9, 2.0 Hz, CH_3), 51.84 (tt, J = 145.7, 5.9Hz, CH_2CH), 54.76 (dm, J = 145.5 Hz, CH), 62.20 (tq, J = 148.6, 4.9 Hz, OCH₂-triaz.), 62.25 (tq, J = 149.0, 4.6 Hz, OCH₂-triaz.), 62.86 (tq J = 149.1, 4.5 Hz, 2OCH₂-thiadiaz.), 131.40 (d, J = 1.8 Hz, C5-triaz.CH), 132.02 (t, J = 2.1 Hz, C5-triaz.CH₂), 141.60 (s, C4-triaz.), 141.81 (s, C4-triaz.), 147.09 (s, C4-thiadiaz.), 147.18 (s, C4-thiadiaz.), 158.88 (t, J = 3.2 Hz, CO-triaz.), 158.96 (t,

J = 3.2 Hz, CO-triaz.), 159.68 (s, C5-thiadiaz.), 159.99 (s, C5-thiadiaz.), 160.48 (t, J = 3.4 Hz, CO-thiadiaz.), 160.53 (t, J = 3.2 Hz, CO-thiadiaz.). ESI-MS 699 (MH⁺). EIMS *m*/z (rel. int.): 514(1), 384(18), 352(12), 318(14), 235(43), 157(58), 129(37), 116(45), 85(100). Anal. Calcd for C₂₃H₂₆N₁₀O₈S₄: C, 39.53; H, 3.75; N, 20.04. Found C, 39.59; H, 3.78; N, 20.01%.

5,5'-{Propane-1,3-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-tri-

azole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5c. Prepared from 1a and 2c as described for 5a. Yield 59%, mp $125 \,^{\circ}\text{C}$. ¹H NMR δ_{H} (CDCl₃, 400 MHz): 1.33 (6H, t, J = 7.1 Hz, 2CH₃-triaz.), 1.52 (6H, t, J = 7.1 Hz, 2CH₃-thiadiaz.), 2.66 (2H, quintet, J = 6.7 Hz, $CH_2CH_2CH_2$), 4.39 (4H, q, J = 7.1 Hz, 2OCH₂-triaz.), 4.58 (4H, q, J = 7.1 Hz, 2OCH₂-thiadiaz.), 4.64 (4H, t, J = 6.7 Hz, $CH_2CH_2CH_2$). ¹³C NMR δ_C (CDCl₃, 100 MHz): 14.01 (qt, J = 127.5, 2.6 Hz, 2CH₃-triaz.), 14.26 (qt, J = 127.6, 2.7 Hz, 2CH₃-thiadiaz.), 29.35 (tq, J = 132.3, 3.0 Hz, $CH_2CH_2CH_2$), 46.05 (tt, J = 143.9, 4.5 Hz, $CH_2CH_2CH_2$), 62.18 $(tq, J = 148.7, 4.4 Hz, OCH_2-triaz.), 62.88 (tq, J = 149.1, 4.4$ Hz, OCH₂-thiadiaz.), 131.06 (t, J = 2.4 Hz, C5-triaz.), 141.94 (s, C4-triaz.), 147.12 (s, C4-thiadiaz.), 159.13 (t, J = 3.4 Hz, CO-triaz.), 160.29 (s, C5-thiadiaz.), 160.53 (t, J = 3.2 Hz, CO-thiadiaz.). ESI-MS 699 (MH⁺). EIMS m/z (rel. int.): 384(18), 352(10), 318(18), 245(40), 218(33), 169(44), 130(30), 116(36), 85(100). Anal. Calcd for C23H26N10O8S4: C, 39.53; H, 3.75; N, 20.04. Found C, 39.54; H, 3.71; N, 20.29%.

5,5'-{Butane-1,4-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-**1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5d.** Prepared from **1a** and **2d** as described for **5a**. Yield 91%, mp 178 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.34 (6H, t, *J* = 7.1 Hz, 2CH₃), 1.51 (6H, t, *J* = 7.1 Hz, 2CH₃), 1.97 (4H, m, 2CH₂), 4.40 (4H, q, *J* = 7.1 Hz, 2COCH₂), 4.54 (4H, m, 2NCH₂), 4.58 (4H, q, *J* = 7.1 Hz, 2COCH₂). ESI-MS 713 (MH⁺). EIMS *m/z* (rel. int.): 456(2), 428(3), 395(9), 256(100), 182(19), 70(17), 55(67). Anal. Calcd for C₂₄H₂₈N₁₀O₈S₄: C, 40.44; H, 3.96; N, 19.65; S, 17.99. Found C, 40.38; H, 4.00; N, 17.93; S, 17.38%.

N,N',N"-Tris{4-ethoxycarbonyl-5-[(4-ethoxycarbonyl-1,2,3thiadiazol-5-yl)sulfanyl]-1H-1,2,3-triazol-1-yl}aminoethylamine 5e. To a solution of bromoester 1a (1.0 g, 4.2 mmol) and tris-(2-aminoethyl)amine 2e (0.11 g, 0.70 mmol) in DMF (15 mL), triethylamine (0.6 mL, 4.2 mmol) was added and the mixture was heated at 90 °C for 2 days. Then, the mixture was diluted with water, the product filtered off and purified by column chromatography with CH₂Cl₂-ethanol 10 : 1 yielding 0.58 g (76%) of sulfide **5e**, mp 114 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.30 (9H, m, 3CH₃-triaz.), 1.48 (9H, m, 3CH₃-thiadiaz.), 3.14 (6H, m, 3NCH₂), 4.37 (6H, m, 3OCH₂-triaz.), 4.52 (12H, m, 30CH₂-thiadiaz. + 3N-triaz.-CH₂). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 13.98 (CH3-triaz.), 14.24 (CH3-thiadiaz.), 46.52 (NCH₂CH₂), 53.22 (NCH₂CH₂), 62.05 (OCH₂-triaz.), 62.83 (OCH2-thiadiaz.), 131.31 (C5-triaz.), 141.44 (C4-triaz.), 147.05 (C4-thiadiaz.), 159.33 (CO-triaz.), 160.57 (CO-thiadiaz. + C5thiadiaz.). ESI-MS 1083 (M⁺). Anal. Calcd for $C_{36}H_{42}N_{16}O_{12}S_6$: C, 39.92; H, 3.91; N, 20.69. Found C, 39.89; H, 3.90; N, 20.71%.

DAB-dendr-([4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl]-NH)₄

5f. Prepared from **1a** and **2f** as described for **5e**. Yield 61%, mp 102 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.30 (12H, m, 4CH₃-triaz.), 1.39 (4H, m, NCH₂*CH*₂*CH*₂CH₂N), 1.49 (12H, t, J = 7.1 Hz, 4CH₃-thiadiaz.), 2.02 (8H, m, NHCH₂*CH*₂CH₂N), 2.44 (12H, m, 6NCH₂), 4.36 (8H, m, 4OCH₂-triaz.), 4.53 (8H, q, J = 7.1 Hz, 4OCH₂-thiadiaz.), 4.62 (8H, m, 4N-triaz.-CH₂). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 14.07 (CH₃-triaz.), 14.32 (CH₃-thiadiaz.), 24.40, 27.88, 47.55, 50.48, 53.44, 62.07 (OCH₂-triaz.), 62.82 (OCH₂-thiadiaz.), 130.83 (C5-triaz.), 141.59 (C4-triaz.), 146.88 (C4-thiadiaz.), 159.38 (CO-triaz.), 160.68 (CO-thiadiaz. + C5-thiadiaz.). ESI-MS 1566 (MH⁺). Anal.

Calcd for $C_{56}H_{72}N_{22}O_{16}S_8$: C, 42.96; H, 4.63; N, 19.68. Found C, 42.76; H, 4.39; N, 19.73%.

5,5'-{Ethane-1,2-diylbis[(4-(*N*-methylcarbamoyl)-1*H*-1,2,3triazole-1,5-diyl)sulfanyl]}bis(4-(*N*-methylcarbamoyl)-1,2,3-thiadiazole) **5g**. Prepared from **1b** and **2a** as described for **5a**. Yield 45%, mp 236 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 250 MHz): 2.76 (6H, d, *J* = 4.0 Hz, 2CH₃), 2.91 (6H, d, *J* = 4.0 Hz, 2CH₃), 5.04 (4H, s, 2CH₂), 8.54 (2H, q, *J* = 4.3 Hz, 2NH), 8.94 (2H, q, *J* = 4.0 Hz, 2NH). ESI-MS 625 (M⁺). EIMS *m*/*z* (rel. int.): 300(1), 288(2), 231(2), 203(22), 174(6), 146(9), 114(6), 98(7), 86(24), 74(14), 58(100). Anal. Calcd for C₁₈H₂₀N₁₄O₄S₄: C, 34.61; H, 3.23; N, 31.39. Found C, 36.65; H, 3.20; N, 31.42%.

5,5'-{Ethane-1,2-diylbis[(4-ethoxycarbonyl-1*H*-1,2,3-triazole-**1,5-diyl)sulfanyl]}bis**(4-(*N*-methylcarbamoyl)-1,2,3-thiadiazole) **5h.** To a solution of **3a** (0.25 g, 0.67 mmol) and 5-chloro-1,2,3thiadiazole **1b** (0.24 g, 1.30 mmol) in ethanol (30 mL), triethylamine (0.1 mL, 0.70 mmol) was added and the mixture was heated at reflux for 5 hours. After cooling, the product was filtered off and crystallized from ethanol yielding 0.22 g (50%) of **5h.** mp 216 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.32 (6H, t, *J* = 7.2 Hz, 2CH₃), 3.10 (6H, d, *J* = 5.1 Hz, 2NHCH₃), 4.38 (4H, q, *J* = 7.2 Hz, 2OCH₂), 5.10 (4H, s, 2CH₂), 7.41 (2H, q, *J* = 5.1 Hz, 2NH). ESI-MS 655 (M⁺). EIMS *m*/*z* (rel. int.): 402 (1), 370 (22), 338 (27), 240 (22), 199 (20), 147 (42). Anal. Calcd for C₂₀H₂₂N₁₂O₆S₄: C, 36.69; H, 3.39; N, 25.67. Found C, 36.74; H, 3.35; N, 25.65%.

5,5'-{Ethane-1,2-diylbis[(4-(N-methylcarbamoyl)-1H-1,2,3triazole-1,5-diyl)sulfanyl]}bis(4-ethoxycarbonyl-1,2,3-thiadiazole) 5i. A solution of chloroamide 1b (1.0 g, 5.6 mmol) and ethylenediamine 2a (0.25 g, 4.2 mmol) in chloroform (5 mL) was heated at reflux for 3 hours. The reaction mixture was diluted with ethanol, acidified with hydrochloric acid, and the precipitate was filtered off, suspended in ethanol and refluxed for 5 hours with bromoester 1a (1.33 g 5.6 mmol) and triethylamine (0.8 mL, 5.6 mmol). After cooling, the precipitate was filtered off and appeared to be a mixture of 5i and 5g (64 : 36) according to ¹H NMR data. The mixture was separated by means of column chromatography using CH₂Cl₂-EtOH 10:1 as the eluent: d 0.4 gave 0.59 g (32%) of 5i, mp 220 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.50 (6H, t, J = 7.2 Hz, 2CH₃), 2.99 (6H, d, J = 5.2 Hz, 2NHCH₃), 4.57 (4H, q, J = 7.2 Hz, 2OCH₂), 5.10 (4H, s, 2CH₂), 7.12 (2H, q, J = 5.2 Hz, 2NH). Anal. Calcd for C₂₀H₂₂N₁₂O₆S₄: C, 36.69; H, 3.39; N, 25.67. Found C, 36.64; H, 3.43; N, 25.60%.

5,5'-{4-Ethoxy-1,2-phenylenebis[(4-methyl-1H-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5j. Bromoester 1a (1.0 g, 4.2 mmol) and 4-ethoxy-1,2-phenylenediamine 2j (0.16 g, 1.0 mmol) were suspended in ethanol (30 mL) triethylamine (0.6 mL, 4.2 mmol) was added and the mixture was stirred at room temperature for 2 days. The precipitate was filtered off and crystallized from ethanol yielding 0.15 g (18%) of **5**j, mp 173 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 400 MHz): 1.22 (6H, t, J = 7.1 Hz, 2CH₃), 1.43 (9H, t, J = 7.0 Hz, 3CH₃), 4.18 (2H, q, J = 7.0 Hz, CH₂), 4.29 (2H, q, J = 7.1 Hz, OCH₂), 4.30 (2H, q, J = 7.1 Hz, OCH₂), 4.46 (2H, q, J = 7.1 Hz, OCH₂), 4.47 (2H, q, J = 7.1 Hz, OCH₂), 7.39 (1H, dd, J = 8.9, 2.8 Hz, C5H), 7.77 (1H, d, J = 2.8 Hz, C3H), 7.97 (1H, d, J = 8.9 Hz, C6H). ESI-MS 777 (MH⁺). EIMS m/z (rel. int.): 530 (2), 502 (9), 430 (11), 330 (36), 302 (60), 258 (86), 229 (89), 202 (100). Anal. Calcd for C₂₈H₂₈N₁₀O₉S₄: C, 43.29; H, 3.63; N, 18.03. Found C, 43.34; H, 3.70; N, 18.10%.

5,5'-{4,5-Dimethyl-1,2-phenylenebis[(4-methyl-1*H*-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5k. Prepared from 1a and 2k as described for 5j. Yield 35%, mp 210 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 250 MHz): 1.21 (6H, t, J = 7.0 Hz, 2CH₃), 1.43 (6H, t, J = 7.0 Hz, 2CH₃), 2.43 (6H, s, 2CH₃), 4.29 (4H, q, J = 7.0 Hz, 2CH₂), 4.47 (4H, q, J = 7.3 Hz, 2CH₂), 7.84 (2H, s, 2CH). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 75 MHz): 14.0, (2CH₃-triaz.), 14.3, (2CH₃-thiadiaz.), 20.1, (2 CH₃), 62.4, (2OCH₂-triaz.), 62.7, (2OCH₂-thiadiaz.), 128.2, (2CH-arom.), 129.1, (2NC-arom.), 134.4, (C5-triaz.), 141.3, (C4-triaz.), 142.3, (2CH₃C-arom.), 147.1, (C4-thiadiaz.), 158.9, (CO-triaz.), 160.2, (C5-thiadiaz.), 160.7 (CO-thiadiaz.). ESI-MS 761 (MH⁺). EIMS *m*/*z* (rel. int.): 514(1), 486(6), 414(15), 314(15), 286(54), 242(59), 214(100), 157(23). Anal. Calcd for C₂₈H₂₈N₁₀O₈S₄: C, 44.20; H, 3.71; N, 18.41; S, 16.86. Found C, 44.16; H, 3.73; N, 18.35; S, 16.97%.

5,5'-{4-Methyl-1,2-phenylenebis[(4-methyl-1H-1,2,3-triazole-1,5-diyl)sulfanyl]}bis(4-methyl-1,2,3-thiadiazole) 5m. Prepared from 1a and 2m as described for 5j. Yield 76%, mp 190 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.32 (6H, t, J = 7.2 Hz, 2CH₃triaz.), 1.470 (3H, t, J = 7.1 Hz, CH₃-thiadiaz.), 1.474 (3H, t, J = 7.1 Hz, CH₃-thiadiaz.), 2.55 (3H, dd, J = 0.9, 0.8 Hz, CH₃), 4.386 (2H, q, J = 7.2 Hz, OCH₂-triaz.), 4.388 (2H, q, J = 7.2 Hz, OCH₂-triaz.), 4.52 (2H, q, J = 7.2 Hz, OCH₂-thiadiaz.), 4.53 $(2H, q, J = 7.2 \text{ Hz}, \text{ OCH}_2\text{-thiadiaz.}), 7.34 (1H, dq, J = 1.8)$ 0.9 Hz, C3H), 7.42 (1H, d, J = 8.2 Hz, C6H), 7.60 (1H, ddq, J = 8.2, 1.8, 0.8 Hz, C5H). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 13.95 (qt, J = 127.5, 2.6 Hz, 2CH₃-triaz.), 14.20 (qt, J = 127.5, 2.6 Hz, 2CH₃-thiadiaz.), 21.48 (qt, J = 128.4, 4.1 Hz, CH₃), 62.32 (tq, J = 148.9, 4.4 Hz, 2OCH₂-triaz.), 62.66 (tq, J = 148.7, 4.3 Hz, OCH₂-thiadiaz.), 62.67 (tq, J = 148.9, 4.4 Hz, OCH₂thiadiaz.), 128.19 (d, J = 167.6 Hz, C6-arom.), 128.24 (d, J = 8.0 Hz, C2-arom.), 129.10 (dddd, J = 164.3, 6.7, 5.5, 1.1 Hz, C3-arom.), 130.51 (dt, J = 8.7, 1.8 Hz, C1-arom.), 132.95 (dddq, J = 163.9, 9.0, 3.4, 1.8 Hz, C5-arom.), 134.26 (s, C5-triaz.), 134.39 (s, C5-triaz.), 141.30 (s, C4-triaz.), 141.43 (s, C4-triaz.), 143.75 (dq, J = 8.2, 5.9 Hz, C4-arom.), 147.05 (s, C4-thiadiaz.), 147.17 (s, C4-thiadiaz.), 158.81 (t, J = 3.2 Hz, CO-triaz.), 159.86 (s, C5-thiadiaz.), 160.01 (s, C5-thiadiaz.), 160.62 (t, J = 3.4 Hz, CO-thiadiaz.), 160.64 (t, J = 3.4 Hz, CO-thiadiaz.). ESI-MS 747 (MH⁺). EIMS m/z (rel. int.): 472(15), 400(9), 300(13), 272(46), 228(67), 200(100), 116(36), 89(57). Anal. Calcd for C₂₇H₂₆N₁₀O₈S₄: C, 43.42; H, 3.51; N, 18.75; S, 17.17. Found C, 43.38; H, 3.59; N, 18.55; S, 17.00%.

Ethyl 5-[(1-methyl-2-{4-ethoxycarbonyl-5-[(4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl)sulfanyl]-1*H*-1,2,3-triazol-1-yl}ethyl)-

amino]-1,2,3-thiadiazole-4-carboxylate 6. A solution of bromoester 1a (0.5 g, 2.1 mmol) and 0.75 equivalents of 1,2propylenediamine 2b (0.12 g) in chloroform (5 mL) was refluxed for 3 hours. After removal of the solvent, the residue was dissolved in ethanol and kept for two days, The product slowly precipitated and was filtered off yielding 0.046 g (12%) of 6, mp 178 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.33 (3H, t, J = 7.2 Hz, CH₃-triaz.), 1.44 (3H, t, J = 7.2 Hz, CH₃-thiadiaz.NH), 1.48 $(3H, d, J = 6.5 Hz, CH_3)$, 1.52 $(3H, t, J = 7.2 Hz, CH_3$ thiadiaz.), 3.87 (1H, dqt, J = 8.9, 6.5, 6.2 Hz, CH), 4.38 (2H, q, J = 7.1 Hz, OCH₂-triaz.), 4.42 (2H, qd, J = 7.1, 1.8 Hz, OCH₂thiadiaz.NH), 4.58 (2H, q, J = 7.2 Hz, OCH₂-thiadiaz.), 4.70 (1H, d, J = 6.2 Hz, CH2), 7.85 (1H, d, J = 8.9 Hz, NH).¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 14.06 (qt, J = 127.5, 2.6 Hz, CH₃triaz.), 14.33 (qt, J = 127.3, 2.6 Hz, CH_3 -thiadiaz.NH + CH₃thiadiaz.), 18.57 (qd, J = 128.8, 2.9 Hz, CH₃), 52.60 (t, J = 143.2 Hz, CH₂), 58.65 (d, J = 139.7 Hz, CH), 61.74 (tq, J = 148.2, 4.5 Hz, OCH₂-thiadiaz.NH), 62.32 (tq, J = 148.7, 4.3 Hz, OCH₂triaz.), 62.93 (tq, J = 149.1, 4.5 Hz, OCH₂-thiadiaz.), 132.15 (t, J = 2.5 Hz, C5-triaz.), 132.43 (d, J = 1.5 Hz, C4-thiadiaz.NH), 141.72 (s, C4-triaz.), 147.14 (s, C4-thiadiaz.), 159.15 (t, J = 3.2 Hz, CO-triaz.), 159.87 (s, C5-thiadiaz.), 160.61 (t, J = 3.4 Hz, CO-thiadiaz.), 163.50 (t, J = 3.2 Hz, CO-thiadiaz.NH), 169.63 (dd, J = 3.8, 2.3 Hz, C5-thiadiaz.NH). ESI-MS 543 (MH⁺). EIMS m/z (rel. int.): 514(3), 384(3), 352(68), 307(12), 235(100),

221(38), 139(55), 116(54), 85(86), 68(67). Anal. Calcd for $\rm C_{18}H_{22}N_8O_6S_3$: C, 39.84; H, 4.09; N, 20.65. Found C, 39.92; H, 4.01; N, 20.49%.

Diethyl 9,10-dihydrobis[1,2,3]triazolo[1,5-f:5',1'-b][1,3,6]thiadiazepine-3,5-dicarboxylate 7a. A suspension of 5a (1.0 g, 1.46 mmol) in ethanol (20 mL) with triethylamine (0.6 mL, 4.3 mmol) was refluxed and enough DMF was added to dissolve all the starting material. After 2 days of refluxing the reaction mixture was diluted with water (60 mL) and extracted with dichloromethane $(3 \times 20 \text{ mL})$. Evaporation of the solvent gave a crude product which was crystallized from ethanol to give 0.45 g (91%) of thiadiazepine 7a, mp 192 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.45 (6H, t, J = 7.1 Hz, 2CH₃), 4.47 (4H, q, J = 7.1 Hz, 2OCH₂), 5.12 (4H, s, CH₂CH₂). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 14.21 (qt, J = 127.5, 2.6 Hz, $2CH_3$), 49.33 (tt, J = 146.6, 3.7 Hz, CH_2CH_2), 61.99 (tq, J = 148.7, 4.5 Hz, 2OCH₂), 130.20 (tt, J = 1.5, 1.5 Hz, C5-triaz.), 138.04 (s, C4-triaz.), 159.89 (t, J = 3.4 Hz, CO). EIMS m/z (rel. int.): 338 (M⁺, 100). Anal. Calcd for C12H14N6O4S: C, 42.60; H, 4.17; N, 24.84; S, 9.48. Found C, 42.53; H, 4.20; N, 24.91; S, 5.60%. When the ethanol filtrate combined with the water layer from extraction was acidified with HCl, the precipitated product (0.20 g) was characterized as bis(4-ethoxycarbonyl-1,2,3-thiadiazol-5-yl)disulfide 9. The spectroscopic and analytical data of this product were identical to those reported earlier.1

Diethyl 9-methyl-9,10-dihydrobis[1,2,3]triazolo[1,5-*f*:5',1'-*b*]-[1,3,6]thiadiazepine-3,5-dicarboxylate 7b. Prepared from 5b as described for 7a. Yield 73%, mp 168 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆, 400 MHz): 1.33–1.37 (9H, m, 3CH₃), 4.38 (2H, q, *J* = 7.1 Hz, CH₂), 4.39 (2H, q, *J* = 7.1 Hz, CH₂), 5.16, 5.27 (2H, AB-syst., *J* = 15.1, 5.5, 1.1 Hz, CH₂), 5.59 (1H, m, CH). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 75 MHz): 14.3 (CH₂*CH*₃), 14.3 (CH₂*CH*₃), 17.8 (CH₃), 53.0 (CH), 56.2 (CH₂), 62.0 (OCH₂), 62.1 (OCH₂), 129.4, 130.6, 137.4, 138.5, 159.8 (CO), 160.2 (CO). EIMS *mlz* (rel. int.): 352 (M⁺, 100). Anal. Calcd for C₁₃H₁₆N₆O₄S: C, 44.31; H, 4.58; N, 23.85; S, 9.10. Found C, 44.38; H, 4.54; N, 23.97; S, 9.31%.

Diethyl 6,7-dihydro-5*H*-bis[1,2,3]triazolo[1,5-g:5',1'-*b*]-[1,3,7]thiadiazocine-1,11-dicarboxylate 7c. Prepared from 5c as described for 7a. Yield 79%, mp 203 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 250 MHz): 1.41 (6H, t, *J* = 7.0 Hz, 2CH₃), 2.19 (2H, m, CH₂*CH*₂CH₂), 4.28–4.48 (8H, m, 2OCH₂ + *CH*₂CH₂*CH*₂). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 75 MHz): 14.3 (2CH₃), 27.7 (CH₂*CH*₂CH₂), 44.9 (2NCH₂), 62.1 (2OCH₂), 131.3, 138.5, 160.2 (2CO). EIMS *m*/*z* (rel. int.): 352 (M⁺, 100). Anal. Calcd for C₁₃H₁₆N₆O₄S: C, 44.31; H, 4.58; N, 23.85. Found C, 44.29; H, 4.61; N, 23.80%.

2-Ethoxy-8,10-bis(ethoxycarbonyl)di[1,2,3]triazolo[1,5-a;5', 1'-d][3,1,5]benzothiadiazepine 7j. To a solution of 1a (1.0 g, 4.22 mmol) and 4-ethoxy-1,2-phenylenediamine 2j (0.33 g 2.1 mmol) in ethanol (80 mL), triethylamine (0.6 mL, 4.2 mmol) was added and the reaction mixture was refluxed overnight. Then a second portion of triethylamine (1.2 mL) was added and soon the product precipitated from the boiling solution. After refluxing for an additional hour, the reaction mixture was cooled, and the product was filtered off and crystallized from ethanol yielding 0.38 g (42%) of thiadiazepine 7j, mp 168 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 250 MHz): 1.42 (3H, t, J = 7.0 Hz, CH₂), 1.43 (3H, t, J = 7.0 Hz, CH₃), 1.47 (3H, t, J = 7.0 Hz, CH₃ethoxy), 4.26 (2H, q, J = 7.0 Hz, OCH₂ethoxy), 4.40 (2H, q, J = 7.0 Hz, OCH₂), 4.41 (2H, q, J = 7.0 Hz, OCH₂), 7.41 (1H, dd, J = 9.2, 2.7 Hz, C3H), 7.52 (1H, d, J = 2.7 Hz, C1H), 7.99 (1H, d, J = 9.2 Hz, C4H). EIMS m/z (rel. int.): 430 (M⁺, 18). Anal. Calcd for $C_{18}H_{18}N_6O_5S$: C, 50.23; H, 4.22; N, 19.52; S, 7.45. Found C, 50.31; H, 4.20; N, 19.70; S, 7.20%.

Ethyl 5-[1-(2-amino-4-ethoxyphenyl)-4-ethoxycarbonyl-1,2,3triazol-5-ylsulfanyl]-1,2,3-thiadiazole-4-carboxylate 8j. A solution of 12j (0.9 g, 2.9 mmol) and triethylamine (0.8 mL, 5.7 mmol) in ethanol (50 mL) was refluxed for 3 hours, then cooled to room temperature and bromoester 1a (0.7 g, 2.9 mmol) was added. The reaction mixture was stirred for 1 h and a half of the solvent was removed. The product that precipitated from the solution upon cooling was filtered off and crystallized from ethanol (1.16 g) 86%, mp 130 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl_4 , 250 MHz): 1.23 (3H, t, J = 7.0 Hz, CH_3 ethoxy), 1.35 (3H, t, J = 7.0 Hz, CH₃), 1.41 (3H, t, J = 7.0 Hz, CH₃), 3.97 (2H, q, J = 7.0 Hz, OCH₂ethoxy), 4.30 (2H, q, J = 7.0 Hz, OCH₂), 4.43 $(2H, q, J = 7.0 \text{ Hz}, \text{OCH}_2), 5.22 (2H, \text{ br s}, \text{NH}_2), 6.14 (1H, \text{ dd},$ J = 8.5, 2.5 Hz, C5H), 6.35 (1H, d, J = 2.5 Hz, C3H), 6.94 (1H, d, J = 8.5 Hz, C6H). EIMS m/z (rel. int.): 464 (M⁺, 6), 205 (100). Anal. Calcd for C₁₈H₂₀N₆O₅S₂: C, 46.54; H, 4.34; N, 18.09; S, 13.81. Found C, 46.60; H, 4.37; N, 17.98; S, 13.40%.

Ethyl 5-[N-(2-amino-4-ethoxyphenyl)amino]-1,2,3-thiadiazole-4-carboxylate 12j. A solution of ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate 1a (1.71 g, 7.2 mmol) and diamine 2j (2.2 g, 14.5 mmol) in DMF (20 mL) was stirred at room temperature, and the reaction was monitored with TLC. After the starting compound had disappeared, the reaction mixture was diluted with water. The precipitate was filtered off and crystallized from ethanol (0.94 g) 56%, mp 145 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆ + CCl₄, 250 MHz): 1.35 (3H, t, J = 7.0 Hz, CH₃), 1.42 (3H, t, J = 7.0 Hz, CH₃), 3.96 (2H, q, J = 7.0 Hz, OCH_2), 4.41 (2H, q, J = 7.0 Hz, OCH_2), 5.01 (2H, br s, NH_2), 6.12 (1H, dd, J = 8.5, 2.4 Hz, C5H), 6.33 (1H, d, J = 2.4 Hz, C3H), 6.96 (1H, d, J = 8.5 Hz, C6H), 8.98 (1H, s, NH). EIMS m/z (rel. int.): 308 (M⁺, 81). Anal. Calcd for C₁₃H₁₆N₄O₃S: C, 50.64; H, 5.23; N, 18.17; S, 10.40. Found C, 50.61; H, 5.28; N, 18.10; S, 10.37%.

9,10-Dihydrobis[1,2,3]triazolo[1,5-f:5',1'-b][1,3,6]thiadi-

azepine-3,5-dicarboxylic acid 10. To an aqueous solution of NaOH (0.36 g, 9.0 mmol in 100 mL), thiadiazepine 7a (1.52 g, 4.5 mmol) was added and the suspension was refluxed until a clear solution formed, then this was acidified with conc. HCl and the precipitated acid filtered off as colourless crystals (1.05 g, 83%), mp 213 °C. ¹H NMR $\delta_{\rm H}$ (DMSO-D₆, 400 MHz): 5.08 (4H, s, 2CH₂). EIMS *m*/*z* (rel. int.): 282 (M⁺, 2), 238(46), 194(51). Anal. Calcd for C₈H₆N₆O₄S: C, 34.05; H, 2.14; N, 29.78; S, 11.36. Found C, 34.11; H, 2.17; N, 29.49; S, 11.53%.

9,10-Dihydrobis[1,2,3]triazolo[1,5-f:5',1'-b][1,3,6]thiadi-

azepine 11. Acid **10** (1.70 g, 6.0 mmol) was heated at 175 °C in DMSO (20 mL) for 8 hours. The DMSO was removed *in vacuo*

and the residue was washed with ethanol to give **11** (1.13 g, 97%), mp 156 °C. ¹H NMR $\delta_{\rm H}$ (CDCl₃, 400 MHz): 5.09 (4H, s, CH₂CH₂), 7.76 (2H, s, 2CH-triaz.). ¹³C NMR $\delta_{\rm C}$ (CDCl₃, 100 MHz): 47.78 (tt, J 145.8, 3.7 Hz, CH₂CH₂), 124.60 (dt, J 14.7, 1.3 Hz, C5-triaz.), 134.72 (d, J 199.3 Hz, C4-triaz.). EIMS *m*/*z* (rel. int.): 194 (M⁺, 100). Anal. Calcd for C₆H₆N₆S: C, 37.11; H, 3.11; N, 43.27; S, 16.51. Found C, 37.06; H, 3.13; N, 43.35; S, 16.75%.

Single crystals of compound **11** suitable for X-ray diffraction were obtained by crystallization from ethanol.

Crystal structure determination of compound 11: †

Crystal data: $C_6H_6N_6S$, M = 194.24, monoclinic, a = 13.4019(2), b = 8.1355(1), c = 7.8447(1) Å, $\beta = 101.744(1)$, U = 837.41(2) Å³, T = 299(1) K, space group $P2_1/c$ (no. 14), Z = 4, μ (Cu–K_a) = 3.129 mm⁻¹, 5685 measured reflections, 1513 unique ($R_{int} = 0.046$) which were used in all calculations. The final R1 = 0.0437 (for 1421 data with $I > 2\sigma(I)$) and wR2 = 0.1405 (all data).

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[†] CCDC reference number 214711. See http://www.rsc.org/suppdata/ ob/b3/b307693h/ for crystallographic data in .cif or other electronic format.

References

- N. N. Volkova, E. V. Tarasov, L. Van Meervelt, S. Toppet, W. Dehaen and V. A. Bakulev, J. Chem. Soc., Perkin Trans. 1, 2002, 13, 1574.
- 2 N. N. Volkova, E. V. Tarasov, W. Dehaen and V. A. Bakulev, *Chem. Commun.*, 1999, 2273–2274.
- 3 (a) Yu. Yu. Morzherin, E. V. Tarasov and V. A. Bakulev, *Khim. Geterotsikl. Soedin.*, 1994, **4**, 554–559; (b) G. L'abbé and E. Vanderstede, *J. Heterocycl. Chem.*, 1989, **26**, 1811–1814.
- 4 D. Kotkar, S. W. Mahajan, A. K. Mandal and P. K. Ghosh, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1749–1752.
- 5 (a) R. Okazaki, T. Hasegawa and Y. Shishido, J. Am. Chem. Soc., 1984, **106**, 5271–5273; (b) S. Ito, A. Ota, H. Suhara, K. Tabashi and Y. Kawashima, Chem. Pharm. Bull., 1993, **41**, 1066–1073.
- 6 R. B. Katz, M. B. Mitchell and P. G. Sammes, *Tetrahedron*, 1989, 45, 1801–1814.
- 7 F. Trecourt and G. Queguiner, J. Chem. Res., 1982, (S) 76–77; (M) 912–942.
- 8 M. Witanowski and Z. Biedrzycka, *Magn. Reson. Chem.*, 1994, **32**, 62–66.