On Triazoles XXX [1]. Synthesis of [1,2,4]Triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5-thiones

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Different 2-Q-6,7,8,9-(bi-, tri- or tetra)substituted[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thione derivatives representing a novel ring system were synthesised. In the case of 8-aryl-substituted derivatives ring-chain tautomerism was observed in DMSO-d_6 or deuteriochloroform solutions. In some cases both ring and chain tautomers could be isolated in crystalline form. The structure of products obtained was proved by nmr using also model compounds prepared for this purpose.

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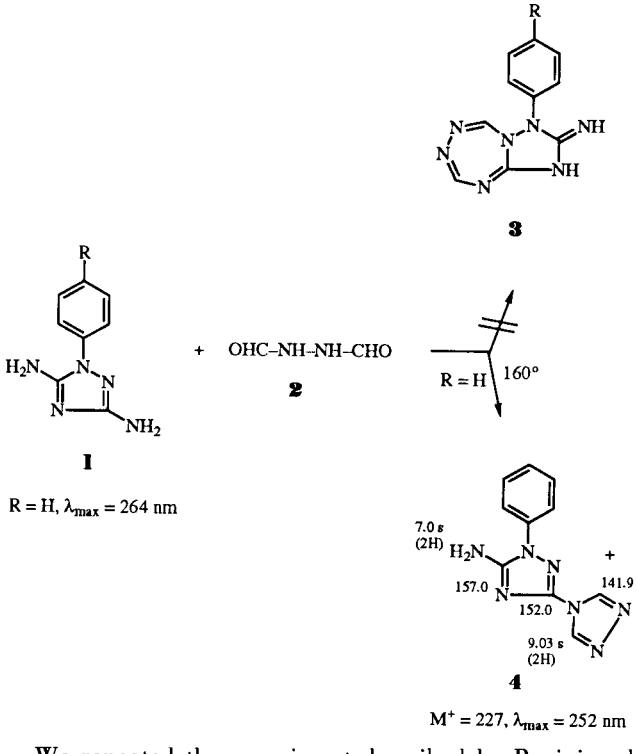
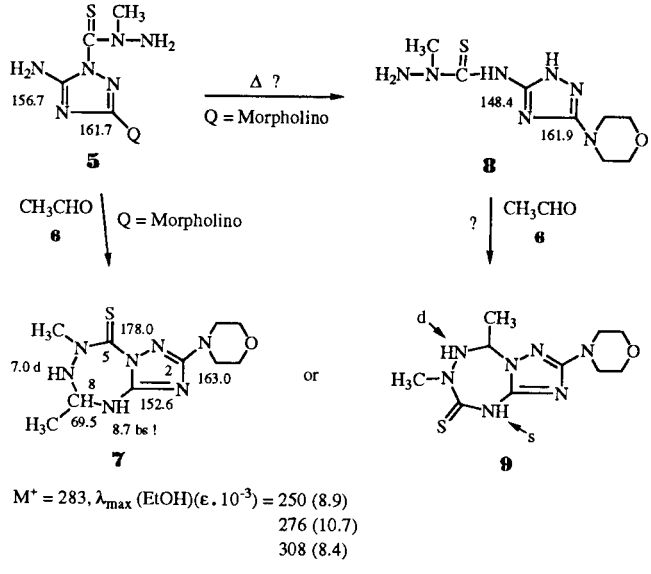
Starting from biological considerations it was decided to synthesize [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thione derivatives **7** (Scheme 2). The literary search provided only one example describing this ring system [2]. The authors melted 1-phenylguanazole (**1**, R = H) and 1-*p*-tolylguanazole (**1**, R = CH_3) with 1,2-diformylhydrazine (**2**) at 160°. Structure **3** was proposed for the products characterised by their melting points and analytical data obtained in the above reaction that was later on corrected by Russian authors [3] on the basis of ir data and some speculation to **4** (Scheme 1).

Scheme 1



We repeated the experiment described by Papini and Checci [2] using **1** (R = H) and 1,2-diformylhydrazine (**2**) and obtained a product with the melting point described previously and posessing the expected molecular weight in the mass spectra (M^+ = 227) (Scheme 1). As proved by its pmr and cmr spectra its structure was **4** in which the newly built in CH groups of the 1,2,4-triazol-4-yl moiety were equivalent. The unequivocal decision between the two possible positional isomers [5-amino-3-(1,2,4-triazol-4-yl)-1-phenyl-4*H*-1,2,4-triazole and 3-amino-5-(1,2,4-triazol-4-yl)-1-phenyl-4*H*-1,2,4-triazole] was made on the basis of the chemical shifts of the amino group and the triazole carbon atom 5. It was known [4,5] that in the case of 1-substituted 5-amino-1*H*-1,2,4-triazole derivatives the chemical shift of the 5-amino group was 6-7 ppm and that of the corresponding carbon atom 5 was 156-157 ppm, respectively, in DMSO-d_6 solutions, while in the case of 2-substituted-5-amino-2*H*-1,2,4-triazole derivatives the above shifts were at 4-5.5 ppm and 162-165 ppm, respectively. Thus the chemical shifts 7.0 and 157.0, respectively, measured for the product in the above reaction have to correspond to a 1-substituted derivative, *i.e.* structure **4**. Structure **4** is also in agreement with the uv spectrum showing the same uv maxima as the starting material **1** (λ max = 252 nm and

Scheme 2



M^+ = 283, λ_{max} (EtOH)(ε . 10^{-3}) = 250 (8.9)
276 (10.7)
308 (8.4)

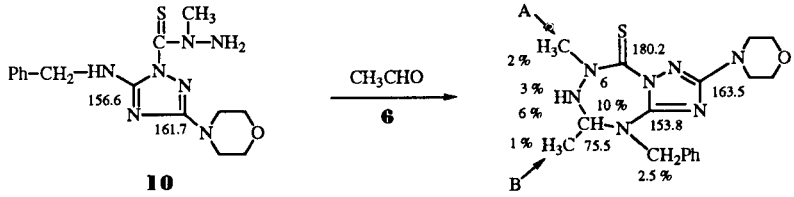
264 nm, respectively), while in the case of **3** as a consequence of the long chain of conjugated double bonds present a strong bathochromic shift of the uv maxima had to be expected. Consequently, the [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine ring system has to be considered as a new ring system, not described yet.

The synthesis of the [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine ring system was attempted starting from the thiohydrazide derivative **5** (Q = morpholino) (Scheme 2) described recently [6] having a methyl group on the nitrogen atom attached to the thiocarbonyl group of the thiohydrazide moiety that was expected to exclude the ring closure to the six membered [1,2,4]triazolo[1,5-*a*][1,3,5]triazine type products. This was reacted with acetaldehyde (**6**) to yield a high melting (mp 226-228°) product showing the expected molecular weight (M^+ = 283) in the mass spectrum and the expected chemical shift of the newly built in carbon atom 8 of the tetrazepine ring (δ = 69.5 ppm) in the cmr spectra.

However, it was known [6] that the **5** type thiohydrazides easily rearranges on heating by moving the thiohydrazide moiety from the nitrogen atom 1 of the triazole ring to nitrogens 2 or 4, or to the exocyclic amino group. The possibility of the rearrangement of the thiohydrazide moiety to nitrogens 2 or 4 could be excluded on the basis of the practically unchanged chemical shifts of the triazole carbon atoms of **7** in the cmr spectra as compared with those of the starting material **5**. On the other hand on the basis of cmr it was not possible to exclude the rearrangement to the exocyclic nitrogen atom to yield **8** and through it the formation of **9** instead of **7** as the chemical surrounding of the triazole carbon atoms of the above two products was analogous. Moreover the NH signals in pmr spectra appeared as a doublet and broad singlet suggesting rather structure **9** then structure **7** for which two doublets had to be expected (Scheme 2).

The unequivocal decision between structures **7** and **9** was possible with the help of DNOE experiments made with the benzyl derivative **11** synthesised from the known [6] thiohydrazide **10** having the benzyl group fixed to the nitrogen atom 9 of the tetrazepine ring (Scheme 3). The irradiation of the *N*-methyl hydrogens 6 (Experiment A) caused a 3% DNOE on the NH-7 and — as a consequence of the nonplanarity of the tetrazepine ring — a 1% DNOE on the *C*-methyl hydrogens 8. On the other hand, irradiation of the *C*-methyl hydrogens 8 (Experiment B) caused a 10% DNOE on the CH hydrogen 8 attached, a 6% DNOE on the NH-7 hydrogen, a 2.5% DNOE on the benzyl CH_2 hydrogens and — again as a consequence of the non planarity of the tetrazepine ring — a 2% DNOE on the *N*-

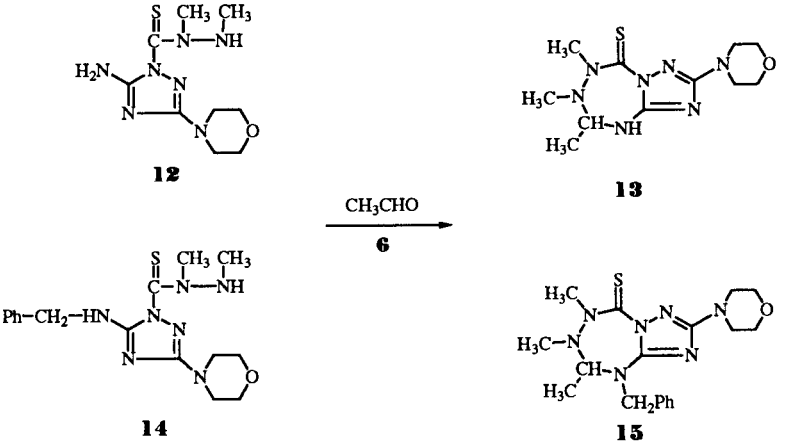
Scheme 3



10 **11**

λ_{max} (EtOH) ($\varepsilon \cdot 10^{-3}$) = 254 (9.8)
274 (14.4)
310 (7.4)

Scheme 4



12 **13**

14 **15**

Table I

Compound No	Q	Ar	Conditions of Preparation: Reaction time (hours)	Yield (%)	Mp (°C) (Crystallized from)	Molecular Formula (MW)	Analysis Calcd./Found: C	H	N	S	Cl
19/1	Morpholino	Phenyl	4	68	194-196 (2-PrOH)	$C_{15}H_{19}N_7OS$ (345.43)	52.16 52.09	5.54 5.65	28.38 28.44	9.28 9.21	
20/1	Morpholino	Phenyl	16	50	212-214 (DMF + H_2O)	$C_{15}H_{19}N_7OS$ (348.43)	52.16 52.23	5.54 5.72	28.38 28.26	9.28 9.32	
19/2	Morpholino	3-Hydroxyphenyl	3	69	187-189 (CH_3CN)	$C_{15}H_{19}N_7O_2S$ (361.43)	49.85 49.76	5.30 5.43	27.13 27.09	8.87 8.98	
20/2	Morpholino	3-Hydroxyphenyl	16	65	201-203 (DMF + H_2O)	$C_{15}H_{19}N_7O_2S$ (361.40)	49.85 50.01	5.30 5.54	27.13 27.11	8.87 8.78	
19/3	Morpholino	2,6-Dichlorophenyl	1	83	152-154 (2-PrOH)	$C_{15}H_{17}Cl_2N_7OS$ (414.32)	43.49 43.50	4.14 4.23	23.66 23.58	7.74 7.68	
20/3	Morpholino	2,6-Dichlorophenyl	16	40	208-210 (DMF + H_2O)	$C_{15}H_{17}Cl_2N_7OS$ (414.32)	43.49 48.38	4.14 4.20	23.66 23.72	7.74 7.71	
19/4	Morpholino	4-Chlorophenyl	3	75	192-194 (CH_3CN)	$C_{15}H_{18}ClN_7OS$ (379.88)	47.43 47.55	4.78 4.93	25.81 25.76	8.44 8.40	
19/5	Morpholino	3-Nitrophenyl	3	84	198-200 (CH_3CN)	$C_{15}H_{18}N_8O_3S$ (390.43)	46.15 46.02	4.65 4.56	28.70 28.82	8.21 8.30	
19/6	Morpholino	4-Nitrophenyl	2	78	218-220 (CH_3CN)	$C_{15}H_{18}N_8O_3S$ (390.43)	46.15 46.22	4.65 4.78	28.70 28.65	8.21 8.23	
19/7	Morpholino	4-Cyanophenyl	2	72	240-242 (CH_3CN)	$C_{16}H_{18}N_8OS$ (370.44)	51.88 52.02	4.90 5.13	30.25 30.16	8.66 8.63	
19/8	Morpholino	4-Dimethylamino-phenyl	5	72	185-187 (CH_3CN)	$C_{17}H_{24}N_8OS$ (388.50)	52.56 52.55	6.23 6.34	28.84 28.75	8.25 8.22	
19/9	Morpholino	4-Hydroxy-3-methoxyphenyl	5	76	198-200 (CH_3OH-H_2O)	$C_{16}H_{21}N_7O_3S$ (391.46)	49.09 48.98	5.41 5.44	25.05 25.13	8.91 8.14	
19/10	Morpholino	3,4,5-Trimethoxy-phenyl	4	79	180-182 (CH_3CN)	$C_{18}H_{25}N_7O_4S$ (435.51)	49.64 49.60	5.79 5.88	22.51 22.48	7.36 7.32	
19/11	Morpholino	3,4-Methylene-dioxyphenyl	5	71	160-162 (2-PrOH)	$C_{16}H_{19}N_7O_3S$ (389.44)	49.35 49.45	4.92 5.11	25.18 25.09	8.23 8.16	
19/12	Morpholino	4-Carbamoylmethyl-eneoxyphenyl	5	87	236-238 (DMF-H_2O)	$C_{17}H_{22}N_8O_3S$ (418.49)	48.79 48.66	5.30 5.11	26.78 26.94	7.66 7.61	
19/13	Methylthio	Phenyl	4	72	185-187 (CH_3OH)	$C_{12}H_{14}N_6S_2$ (306.42)	47.04 47.16	4.61 4.85	27.43 27.44	20.93 20.89	
19/14	Methylthio	3-Hydroxyphenyl	3	83	192-194 (CH_3CN)	$C_{12}H_{14}N_6OS_2$ (322.42)	44.71 44.56	4.38 4.28	26.07 26.14	19.89 19.92	
19/15	Methylthio	2,6-Dichlorophenyl	[1]	54	178-180 (CH_3CN)	$C_{12}H_{12}Cl_2N_6S_2$ (375.71)	38.41 38.44	3.22 3.41	22.39 22.36	17.09 16.98	18.89 18.93
19/16	Methylthio	4-Chlorophenyl	3	79	190-192 (Dioxane)	$C_{12}H_{13}ClN_6S_2$ (340.86)	42.29 42.35	3.84 4.01	24.66 24.60	18.81 18.78	10.40 10.41
19/17	Methylthio	3-Nitrophenyl	2	82	214-216 (Dioxane)	$C_{12}H_{13}N_7O_2S_2$ (351.42)	41.02 40.97	3.73 3.86	27.90 27.91	18.25 18.20	
19/18	Methylthio	4-Nitrophenyl	2	73	231-233 (Dioxane)	$C_{12}H_{13}N_7O_2S_2$ (351.42)	41.02 41.13	3.73 3.91	27.90 27.85	18.25 18.31	
19/19	Methylthio	4-Cyanophenyl	3	91	224-226 (CH_3CN)	$C_{13}H_{13}N_7S_2$ (331.43)	47.11 47.13	3.95 4.02	29.58 29.61	19.35 19.33	
19/20	Methylthio	4-Dimethylamino-phenyl	5	86	168-170 (Dioxane)	$C_{14}H_{19}N_7S_2$ (349.49)	48.12 48.22	5.48 5.64	28.05 28.02	18.35 18.30	
19/21	Methylthio	4-Hydroxy-3-methyoxyphenyl	5	71	214-216 (CH_3OH)	$C_{13}H_{16}N_6O_2S_2$ (352.44)	44.30 44.23	4.58 4.75	23.84 23.76	18.20 18.23	
19/22	Methylthio	3,4,5-Trimethoxy-phenyl	4	91	229.321 (Diozane)	$C_{15}H_{20}N_6O_3S_2$ (396.50)	45.44 45.46	5.08 5.21	21.20 21.18	16.17 16.24	

Table I (continued)

Compound No	Q	Ar	Conditions of Preparation: Reaction time (hours)	Yield (%)	Mp (°C) (Crystallized from)	Molecular Formula (MW)	Analysis Calcd./Found: C	H	N	S	Cl
19/23	Methylthio	3,4-Methylene-dioxyphenyl	5	92	213-215 (Dioxane)	$C_{13}H_{14}N_6O_2S_2$ (350.43)	44.56 44.61	4.03 4.14	23.98 24.07	18.30 18.28	
19/24	Methylthio	4-Carbamoylmethyl-eneoxyphenyl	5	86	188-190 (2-PrOH)	$C_{14}H_{17}N_7O_2S_2$ (379.47)	44.31 44.44	4.52 4.65	25.84 25.92	16.90 16.87	
19/25	Methylthio	4-Fluorophenyl	3	93	209-211 (CH_3CN)	$C_{12}H_{13}FN_6S_2$ (324.41)	44.43 44.28	4.04 4.13	25.91 26.01	19.77 19.68	5.86 5.81

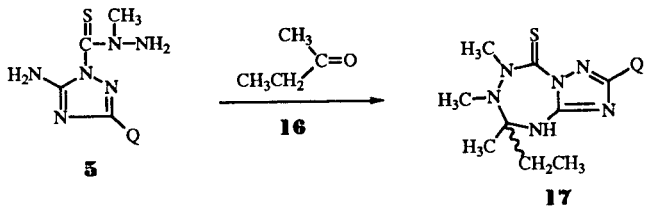
[1] Reaction provided at laboratory temperature for 2 days.

methyl hydrogens 6. This experiment proved unequivocally the steric closeness of the *C*-methyl (8) and benzyl CH_2 (9) groups excluding the possibility of the isomeric **9** type structure and giving an unequivocal proof for the structure **11**. The complete analogy of the uv, pmr and cmr spectra of derivatives **7** and **11** (Schemes 2 and 3) gave also proof for structure **7** of the "nonbenzylated" derivative.

The [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione structure of derivatives **7** and **11** was further corroborated by repeating the ring closure reactions with the corresponding *N,N'*-dimethyl derivatives **12** and **14** to yield derivatives **13** and **15** (Scheme 4). Their analogous spectral data with those of **7** and **11**, respectively, (see Experimental) were again in full agreement with the structure proposed. Interestingly, **13** appeared in DMSO-d_6 solution at 38° as a 1:1 mixture of the two conformers arising from the flexibility of the [1,2,4,6]tetrazepine ring as proved by its pmr and cmr spectra taken at 38° and 100° (see Experimental). In case of the "overcrowded" benzyl derivative **15** most probably owing to the relatively bulky group trying to keep the quasiequatorial position only one conformer appeared to be stable in nmr solutions.

Repeating the reaction of **5** (Q = morpholino and methylthio) with an aliphatic ketone, namely 2-butanone (**16**) lead again to a **7** type [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thione derivative **17** (Scheme 5) as proved by the complete analogy of its uv, pmr and cmr spectra with those of **7** (see Experimental).

Scheme 5



However, from the reaction mixtures of derivatives **5** (Q = morpholino and methylthio) and aromatic aldehydes **18**, depending on the solvents used, either the Shiff bases **19** or their [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thione tautomers **20** crystallised (Scheme 6). Dissolving either derivatives **19** or their ring-tautomers **20** in nmr solvents (deuteriochloroform or DMSO-d_6) the pure tautomeric forms initially present could be detected, but after

Scheme 6

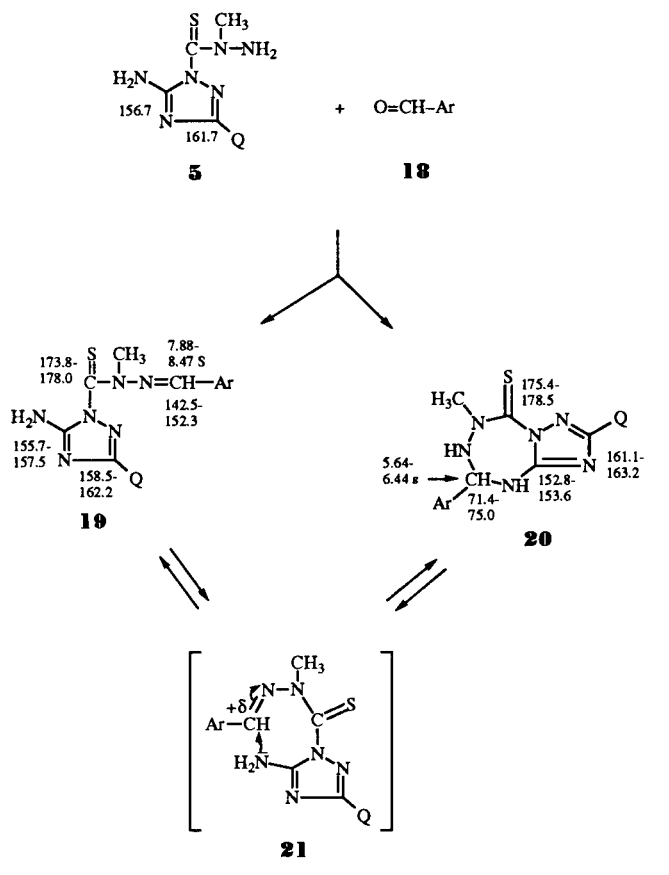


Table II

Compound No	IR [cm^{-1}] νNH_2/ ν C-S	PMR δ CH	δ NH_2	δ CH_3	δ Q	δ Ar	CMR δ CH	δ C-3/ δ C-5	δ Q	δ CH_3/ δ C = S	δ Ar
19/1	3400 3290 1275	8.26 s (1H)	6.85 s (2H)	3.84 s (3H)	3.28 m (4H) 3.65 m (4H)	7.42 s (5H)	147.2	162.2 155.8	45.9 65.7	37.3 176.6	127.8 128.6 130.6 134.0
20/1	3188 2964 1275	5.76 s (1H)	7.4 s (7) (1H) 8.5 s (9) (1H)	3.35 s	3.28 t (J = 4 Hz) 3.66 t (J = 4 Hz)	7.42 s (5H)	75.0	163.2 153.1	45.8 65.7	44.3 178.1	127.1 128.6 128.9 138.8
19/2	3380 3320 1273	8.17 s (1H)	6.85 s (2H)	3.83 s (3H)	3.22 m (4H) 3.64 m (4H)	7.1-7.3 m (4H) 9.67 s (1H)	148.0	162.1 156.0	45.9 65.6	37.4 176.4	113.8 118.0 119.4 129.6 135.2 157.6
20/2	3220 2968 1275	5.64 bs (1H)	7.4 s (7) (1H) 8.45 s (9)	3.37 s (3H)	3.27 t (J = 4.5 Hz) 3.65 t	7.1-7.3 m (4H) 9.6 s (1H)	74.9	163.2 153.4	46.0 65.6	44.0 178.5	113.6 115.6 117.9 129.4 140.1 155.4
19/3	3380 3280 1270	8.31 s (1H)	7.0 s (2H)	3.81 s (3H)	3.21 m (4H) 3.61 m (4H)	7.4-7.6 m (3H)	142.5	162.2 156.3	46.0 65.6	37.5 178.0	129.3 129.9 131.5 134.3
20/3	3250 [2] 2970 1275	6.44 d (J = 7 Hz)	6.0 d (7) 7.4 s (1H)	3.61 s (3H)	3.36 t (4H) (J = 5 Hz) 3.70 t (4H) (J = 5 Hz)	7.3-7.4 m (3H)	71.4	163.2 152.8	45.9 65.6	44.0 178.1	129.7 131.1 131.5 134.7
19/4	3390 3290 1275	8.26 s (1H)	6.9s (2H)	3.83 s (3H)	3.21 m (4H) 3.64 m (4H)	7.53 d 2H (J = 8.5 Hz) 7.70 d 2H (J = 8.5 Hz)	145.6	162.1 156.2	45.9 65.6	37.2 176.7	128.7 129.2 132.9 135.2
19/5	3380 [1] 3285 1275	7.96 s	6.7 s	3.84 s	3.38 t (J = 4.5 Hz) (4H) 3.73 t (J = 4.5 Hz) (4H)	7.60 t (1H) (J = 8 Hz) 8.04 d (2H) (J = 8 Hz) 8.25 d (1H) (J = 8 Hz) 8.52 s	143.3	161.7 156.7	45.8 65.6	37.1 177.2	121.8 124.3 129.7 133.7 136.0 148.0
20/5 [3]							74.2	163.2 152.8	45.8 65.6	44.4 178.4	122.0 123.3 130.3 133.3 136.0 141.0
19/6	3395 3290 1269	8.37 s (1H)	7.0 s (2H)	3.85 s (3H)	3.22 t (J = 4.5 Hz) (4H) 3.64 t (J = 4.5 Hz) (4H)	7.92 d (J = 8.8 Hz) (2H) 8.32 d (J = 8.8 Hz) (2H)	143.5	162.1 156.5	45.8 65.5	37.2 177.4	123.9 128.4 140.3 148.2
20/6 [3]							74.9	163.1 153.3	45.8 65.5	44.8 178.7	123.4 128.7 140.3 144.9

Table II (continued)

Compound No	IR [cm^{-1}] ν NH_2/ ν C=S	PMR δ CH	δ NH_2	δ CH_3	δ Q	δ Ar	CMR δ CH	δ C-3/ δ C-5	δ Q	δ CH_3/ δ C = S	δ Ar
19/7	3385 3290 1274	8.30 *s* (1H)	7.0 *s* (2H)	3.84 *s* (3H)	3.24 m (4H) 3.64 m (4H)	7.8 d (J = 8.3 Hz) (2H) 7.94 d (J = 8.3 Hz) (2H)	144.1	162.2 156.3	45.8 65.6	37.1 177.3	112.3 118.5 128.1 132.6 138.5
19/8	3380 3290 1269	8.15 *s* (1H)	6.7 *s* (2H)	3.82 *s* (3H)	3.19 *s* (4H) 3.63 m (4H)	2.97 *s* (6H) 6.72 d (2H) (J = 8.8 Hz) 7.51 d (2H) (J = 8.8 Hz)	150.5	162.0 155.7	47.1 65.6	38.0 174.6	39.6 111.6 120.8 129.4 152.2
19/9	3405 3310 1273	8.14 *s* (1H)	6.8 *s* (2H)	3.83 *s* (3H)	3.18 m (4H) 3.62 m (4H)	3.77 *s* (3H) 6.83 d (1H) (J = 8.2 Hz) 7.14 d (1H) (J = 8.2 Hz) 7.27 *s* (1H) 9.67 (1H)	148.1	162.1 155.9	46.1 65.6	37.4 175.6	55.6 110.7 115.6 123.0 125.4 148.6 149.8
19/10	3430 3310	7.88 *s* (1H)	6.3 *s* (2H)	3.83 *s* (3H)	3.32 t (J = 4.6 Hz) (4H) 3.70 t (J = 4.6 Hz) (4H)	3.89 *s* (6H) 3.90 *s* (3H) 6.96 *s* (2H)	147.1	161.0 157.5	46.0 66.1	38.0 176.2	56.1 60.7 105.3 128.8 148.8 153.4
19/11	3400 3310 1279	8.18 *s* (1H)	6.8 *s* (2H)	3.82 *s* (3H)	3.21 m (4H) 3.64 m (4H)	7.00 d (1H) (J = 1 Hz) 7.15 d (1H) (J = 8.1 Hz) 7.23 d (1H) (J = 8.1 Hz)	147.9	162.1 156.0	46.0 65.6	37.3 176.0	101.6 105.6 108.4 124.6 128.4 147.3 149.7
19/12	3445 3315 1271 1684 [1]	8.22 *s* (1H)	6.8 *s* (2H)	3.83 *s* (3H)	3.21 m (4H) 3.65 m (4H)	4.49 *s* (2H) 7.02 d (2H) (J = 8.6 Hz) 7.42 *s* (1H) 7.64 d (2H) (J = 8.6 Hz)	147.9	162.1 155.9	46.0 65.6	37.5 175.9	66.9 115.1 127.1 129.4 160.0 169.5
19/13	3400 3275 1273	8.31 *s* (1H)	6.8 *s* (2H)	3.92 *s* (3H)	2.42 *s* (3H)	7.45 m (3H) 7.66 m (2H)	148.0	159.0 155.8	13.3	36.9 175.7	127.9 128.7 130.9 133.6
20/13 [3]							75.0	161.1 153.6	13.3	44.4 177.5	127.2 127.8 128.3 138.5
19/14	3435 3305 1271	8.22 *s* (1H)	6.8 *s* (2H)	3.90 *s* (3H)	2.43 *s* (3H)	6.8-7.3 m (4H) 9.7 *s* (1H)	148.8	159.0 155.7	13.2	37.1 175.6	114.1 118.3 119.4 129.7 134.8 157.6
19/15	3340 3220	8.36 *s* (1H)	6.8 *s* (2H)	3.90 *s* (3H)	2.39 *s* (3H)	7.45 dd (1H) 7.55 dd (2H) (J = 7 Hz and 2 Hz)	143.6	159.4 155.8	13.3	36.8 177.5	129.4 129.7 129.7 132.0 134.6

Table II (continued)

Compound No	IR [cm^{-1}]	PMR					CMR				
	ν NH_2/ ν C=S	δ CH	δ NH_2	δ CH_3	δ Q	δ Ar	δ CH	δ C-3/ δ C-5	δ Q	δ CH_3/ δ C = S	δ Ar
19/16	3360 [1] 3270 1272	7.93 *s* (1H)	6.4 *s* (2H)	3.89 *s* (3H)	2.44 *s* (3H)	7.4 d (2H) (J = 8.2 Hz) 7.6 d (2H) (J = 8.2 Hz)	146.4	159.0 155.9	13.2	36.8 175.8	128.9 129.3 132.6 135.5
19/17	3410 3280 1273	8.47 *s* (1H)	6.9 *s* (2H)	3.92 *s* (3H)	2.44 *s* (3H)	7.76 t (1H) (J = 8 Hz) 8.04 d (1H) (J = 8 Hz) 8.28 d (1H) (J = 8 Hz)	145.1	159.2 156.0	13.2	36.8 176.4	122.2 124.8 130.4 133.3 135.7 148.8
19/18	3390 3295 1269	8.43 *s* (1H)	6.9 *s* (2H)	3.93 *s* (3H)	2.44 2 (3H)	8.51 *s* (1H) 7.88 d (2H) (J = 8.7 Hz) 8.31 d (2H) (J = 8.7 Hz)	144.8	159.3 156.0	13.2	36.7 176.6	123.9 128.6 139.9 148.4
19/19	3370 3280 1270	8.36 *s* (1H)	6.9 *s* (2H)	3.92 *s* (3H)	2.43 *s* (3H)	7.80 d (2H) (J = 8.3 Hz) 7.94 d (2H) (J = 8.3 Hz)	145.2	159.3 156.0	13.3	36.8 176.5	112.7 118.3 128.2 132.7 138.1
20/19 [3]							74.5	162.7 153.4	13.3	44.7 178.1	111.7 118.2 128.2 132.3 138.0
19/20	3345 3270 1268	8.17 *s* (1H)	6.7 *s* (2H)	3.88 *s* (3H)	2.41 *s* (3H)	2.97 *s* (6H) 6.75 d (2H) (J = 9 Hz) 7.48 d (2H) (J = 9 Hz)	150.3	158.6 155.8	13.4	37.3 173.8	39.7 113.4 122.2 131.4 152.5
19/21	3365 3270 1267	8.16 *s* (1H)	6.8 *s* (2H)	3.88 *s* (3H)	2.41 *s* (3H)	6.82 d (1H) (J = 8.2 Hz) 7.11 dd (1H) (J = 1.6 Hz) 7.20 d (1H) (J = 1.6 Hz)	149.9	158.5 155.9	13.3	36.8 174.8	55.5 110.3 115.6 123.3 127.1 148.1 148.4
19/22	3395 3290 1277	8.43 *s* (1H)	6.9 *s* (2H)	3.89 *s* (3H)	2.41 *s* (3H)	3.70 *s* (3H) 3.78 *s* (6H) 7.0 *s* (2H)	146.5	159.0 156.1	13.3	36.3 176.0	55.9 60.3 105.3 129.5 140.1 153.4
19/23	3360 3285 1259	8.22 *s* (1H)	6.8 *s* (2H)	3.89 *s* (3H)	2.43 *s* (3H)	6.09 *s* (2H) 7.0-7.25 m (3H)	149.9	158.7 155.8	13.3	36.9 175.1	101.6 106.0 108.4 125.0 128.0 147.8 149.9
19/24	3390 3285 1265	8.26 *s* (1H)	6.8 *s* (2H)	3.90 *s* (3H)	2.42 *s* (3H)	7.02 d (2H) (J = 8.8 Hz) 7.6 d (2H) (J = 8.8 Hz)	148.0	159.1 155.8	13.6	37.2 175.2	67.0 115.4 126.9 129.8 160.2 169.9

Table II (continued)

Compound No	IR [cm^{-1}]	PMR					CMR				
	ν NH_2/ ν C=S	δ CH	δ NH_2	δ CH_3	δ Q	δ Ar	δ CH	δ C-3/ δ C-5	δ Q	δ CH_3/ δ C=S	δ Ar
19/25	3385 3270 1279	8.32 *s* (1H)	6.8 *s* (2H)	3.91 *s* (3H)	2.43 *s* (3H)	7.32 t (2H) (J = 8.8 Hz) 7.72 dd (2H) (J = 5.7 Hz and 8.8 Hz)	146.9	159.0 155.8	13.2	36.9 175.7	116.0 130.1 130.3 148.6 165.6
20/26 [3]							74.4	161.2 153.5	13.2	44.5 178.0	115.0 129.3 129.5 163.5

[1] ν C=O. [2] Taken in deuteriochloroform. [3] Not isolated. Spectral data read from the tautomeric mixture.

standing the solutions tautomeric equilibria occurred depending on the quality of solvents and temperature. The formation of ring tautomers **20** from the chain tautomers **19** could be explained through intermediate **21** (Scheme 6). In some cases both, ring and chain tautomers could be isolated in crystalline form (see *e.g.* **19/1-20/1**, **19/2-20/2** and **19/3-20/3**, Table I) serving examples for 1-(5-amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methyl-*N'*-(substituted arylidene)carbothiohydrazide **19** and 6-methyl-8-(substituted phenyl)-3-Q-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]-tetrazepine-5(7*H*)-thione **20** desmotropes.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained by a Pye Unicam SP 8-150 instrument. The ^{1}H-nmr and the ^{13}C-nmr measurements were performed using Brucker WM-250 and Brucker WP-80 SY instruments. The ms spectra were recorded on a Kratos MS25RFA instrument using direct inlet probe.

5-Amino-1-phenyl-3-(1,2,4-triazol-4-yl)-1,2,4-triazole (**4**).

Compound **4** was prepared according to [2], yield 31%, mp 257-258° (ethanol), lit [2] mp 256-258°, lit [3] mp 242°; ir: ν NH = 3360 and 3290 cm^{-1}; ν C=N = 1630, 1570 and 1545 cm^{-1}; pmr (DMSO-d_6): δ, ppm 7.0 (s, 2H, NH_2), 7.6 (m, 5H, PhH), 9.0 (s, 2H, triazole 2′ and 5′); cmr (DMSO-d_6): δ, ppm 125.1 (*o*-PhC), 129.6 (*p*-PhC), 131.3 (*m*-PhC), 138.1 (*s*-PhC), 141.9 (C-2′ and C-5′), 152.0 (C-3), 157.0 (C-5); uv (ethanol): λ max (ε 10^{-3}): 252 nm (9.6); ms: M^+ = 227.

Anal. Calcd. for $C_{10}H_9N_7$ (MW 227.23): C, 52.86; H, 3.99; N, 43.15. Found: C, 53.02; H, 4.11; N, 43.01.

±6,8-Dimethyl-2-morpholino-5,6,7,8-tetrahydro[1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**7**).

A solution of 2.55 g (0.01 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**5**, Q = morpholino) [6] and 0.84 ml (0.015 mole) of acetaldehyde in 250 ml of methanol was stirred for 24 hours. After evaporation of the solvent *in vacuo* the residue was triturated with 2-propanol to yield 2.35 g (85%) of ±6,8-dimethyl-2-morpholino-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**7**) that after recrystallisation from methanol melted at 226-228°; ir: ν C=S = 1275 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.24 [d (J = 6 Hz), 3H, CCH_3], 3.24 [t (J = 4.5 Hz), 4H, NCH_2], 3.50 (s, 3H, NCH_3), 3.64 [t (J = 4.5 Hz), 4H, OCH_2], 4.71 (m, 1H, CH-8), 7.0 [d (J = 5.5 Hz), 1H, NH-7], 8.7 (bs, 1H, NH-9); cmr (DMSO-d_6): δ, ppm 20.6 (C*C*H_3), 44.7 (NCH_3), 45.8 (NCH_2), 65.6 (OCH_2), 69.5 (C-8), 152.6 (C-9a), 163.0 (C-2), 178.0 (C-5); uv (95% ethanol + 5% water): λ max nm (ε 10^{-3}) 250 (8.9), 276 (10.7), 308 (8.4); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε 10^{-3}) 276 (11.5); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε 10^{-3}) 272 (9.3), 308 (5.5); ms: M^+ = 283.

Anal. Calcd. for $C_{10}H_{17}N_7OS$ (MW 283.36): C, 42.39; H, 6.05; N, 34.60; S, 11.32. Found: C, 42.26; H, 6.13; N, 34.45; S, 11.35.

±9-Benzyl-6,8-dimethyl-2-morpholino-5,6,7,8-tetrahydro[1,2,4]-triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**11**).

The mixture of 1.04 g (0.003 mole) of 1-(5-benzylamino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**10**) [6], 0.475 ml (0.009 mole) of acetaldehyde and 10 ml of ethanol was refluxed with stirring for 10 hours. After cooling the precipitated crystals were filtered off to yield 0.7 g (62%) of ±9-benzyl-6,8-dimethyl-2-morpholino-5,6,7,8-tetrahydro[1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**11**) that after recrystallisation from ethanol melted at 191-193°; ir: ν C=S = 1275 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.30 [d (J = 6 Hz), 3H, CCH_3], 3.26 [t (J = 5 Hz), 4H, NCH_2], 3.50 (s, 3H, NCH_3), 3.65 [t (J = 5 Hz), 4H, OCH_2], 4.65 (s, 2H, $PhCH_2$), 4.72 (m, 1H, CH), 7.2 (m, 6H, NH + PhH); irradiated at 3.50 ppm, DNOE on 7.2 ppm (NH, 3%), 1.30 ppm (CCH_3, 1%); irradiated at 1.30 ppm, DNOE on 4.72 ppm (CH, 10%), 7.2 ppm (NH, 6%), 4.65 ppm ($PhCH_2$, 2.5%) and 3.50 (NCH_3, 2%); cmr (deuteriochloroform): δ, ppm 17.8 (C*C*H_3), 46.1 (NCH_3 + NCH_2), 52.9 ($PhCH_2$), 66.6 (OCH_2), 75.5 (C-8), 128.0, 128.1, 128.9, 136.5 (PhC), 153.8 (C-9a), 163.5 (C-2), 180.2 (C-5); uv (95% ethanol + 5% water): λ max nm (ε 10^{-3}) 254 (9.8), 274 (14.4), 310 (7.4); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε 10^{-3}) 270 (13.8); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε 10^{-3}) 310 (4.1).

Anal. Calcd. for $C_{17}H_{23}N_7OS$ (MW 373.49): C, 54.67; H, 6.21; N, 26.25; S, 8.58. Found: C, 54.66; H, 6.28; N, 26.18; S, 8.55.

±2-Morpholino-6,7,8-trimethyl-5,6,7,8-tetrahydro[1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**13**).

The mixture of 0.81 g (0.003 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*,*N'*-dimethylcarbothiohydrazide (**12**) [6], 0.475 ml (0.009 mole) of acetaldehyde and 5 ml of ethanol was refluxed with stirring for 10 hours. The solution obtained was evaporated *in vacuo* to dryness and the residue recrystallised from 2-propanol to yield 0.39 g (44%) of ±2-morpholino-6,7,8-trimethyl-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**13**), mp 216-218°; ir: ν NH = 3270 and 3220 cm^{-1}, ν C=N = 1632 and 1576 cm^{-1}, ν C-O-C = 1120 cm^{-1}; pmr (DMSO-d_6 at 38°): δ, ppm 1.25 [d (J = 6 Hz), 3H, CCH_3], 2.47 (s, 1.5H, N'CH_3), 2.63 (s, 1.5H, N'CH_3), 3.24 [t (J = 4.5 Hz), 4H, NCH_2], 3.54 (s, 1.5H, NCH_3), 3.55 (s, 1.5H, NCH_3), 3.64 [t (J = 4.5 Hz), 4H, OCH_2], 4.60 [qi (J = 3 and 4 Hz), 0.5H, CH], 4.80 [qa (J = 4 Hz), 0.5H, CH], 8.58 [d (J = 3 Hz), 0.5H, NH], 8.62 (s, 0.5H, NH); pmr (DMSO-d_6 at 100°): δ, ppm 1.27 [d (J = 6 Hz), 3H, CCH_3], 2.58 (bs, 3H, N'CH_3), 3.27 [t (J = 5 Hz), 4H, NCH_2], 3.55 (s, 3H, NCH_3), 3.63 [t (J = 5 Hz), 4H, OCH_2], 4.66 (bs, 1H, CH), 8.18 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 19.4 and 21.1 (CCH_3), 31.7 and 37.9 (N'CH_3), 44.9 and 45.9 (NCH_3), 45.6 (NCH_2), 65.6 (OCH_2), 69.3 and 70.9 (C-8), 151.7 and 151.8 (C-9a), 162.6 and 162.7 (C-2), 177.3 and 178.5 (C-5).

Anal. Calcd. for $C_{11}H_{19}N_7OS$ (MW 297.39): C, 44.43; H, 6.44; N, 32.97; S, 10.78. Found: C, 44.54; H, 6.57; N, 32.88; S, 10.80.

±9-Benzyl-2-morpholino-6,7,8-trimethyl-5,6,7,8-tetrahydro[1,2,4]-triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**15**).

The mixture of 1.0 g (0.00274 mole) of 1-(5-benzylamino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*,*N'*-dimethylcarbothiohydrazide (**14**) [6], 0.475 ml (0.009 mole) of acetaldehyde and 5 ml of ethanol was refluxed with stirring for 10 hours. The solution obtained was evaporated *in vacuo* to dryness and the residue recrystallised from 2-propanol to yield 0.44 g (41%) of ±9-benzyl-2-morpholino-6,7,8-trimethyl-5,6,7,8-tetrahydro[1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**15**), mp 208-210°; ir: ν NH = 3450 cm^{-1}, ν C=N = 1615 and 1565 cm^{-1}, ν C-O-C = 1108 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.31 [d (J = 6 Hz), 3H, CCH_3], 2.46 (s, 3H, N'CH_3), 3.50 [t (J = 4.5 Hz), 4H, NCH_2], 3.62 (s, 3H, NCH_3), 3.77 [t (J = 4.5 Hz), 4H, OCH_2], 4.35 (qa (J = 6 Hz), 1H, CH), 4.42 [d (J = 15 Hz), 1H, $PhCH_2$], 5.07 [d (J = 15 Hz), 1H, $PhCH_2$], 7.35-7.39 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 18.3 (CCH_3), 38.2 (N'CH_3), 45.9 (NCH_2), 47.2 (NCH_3), 53.2 (CH_2Ph), 66.5 (OCH_2), 74.7 (C-8), 128.3, 128.5, 128.8, 136.5 (PhC), 152.4 (C-9a), 162.7 (C-2), 179.1 (C-5).

Anal. Calcd. for $C_{18}H_{25}N_7OS$ (MW 387.52): C, 55.79; H, 6.50; N, 25.30; S, 8.27. Found: C, 55.70; H, 6.60; N, 25.34; S, 8.21.

±6,8-Dimethyl-8-ethyl-2-morpholino-5,6,7,8-tetrahydro[1,2,4]-triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**17a**).

The solution of 1.0 g (0.0041 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**5**, Q = morpholino) [6] in 20 ml of 2-butanone (**16**) was refluxed for 16 hours. After cooling the precipitated crystals were filtered off to yield 0.71 g (55%) of ±6,8-dimethyl-8-ethyl-2-morpholino-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**17a**) that after recrystallisation from 2-propanol melted at 197-199°; ir: ν C=S = 1276 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.03 [t (J = 7.5 Hz), 3H, CH_2CH_3], 1.42 (s, 3H, CCH_3), 1.77 (m, 2H, CH_3CH_2), 3.43 [t (J = 5 Hz), 4H, NCH_2], 3.59 (s, 3H, NCH_3), 3.75 [t (J = 5 Hz), 4H, OCH_2], 5.6 (s, 1H, 9-NH), 6.3 (bs, 1H, 7-NH); cmr (deuteriochloroform): δ, ppm 8.2 (CH_2CH_3), 25.0 (CCH_3), 35.5 (CH_2CH_3), 46.0 (NCH_3), 46.8 (NCH_2), 66.3 (OCH_2), 75.4 (C-8), 152.2 (C-9a), 163.6 (C-2), 179.9 (C-5); uv (95% ethanol + 5% water): λ max nm (ε 10^{-3}) 250 (9.1), 277 (10.8), 310 (8.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε 10^{-3}) 268 (15.0); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε 10^{-3}) 274 (6.4), 308 (4.3).

Anal. Calcd. for $C_{12}H_{21}N_7OS$ (MW 311.42): C, 46.28; H, 6.80; N, 31.48; S, 10.30. Found: C, 46.44; H, 6.96; N, 31.40; S, 10.34.

±6,8-Dimethyl-8-ethyl-2-methylthio-5,6,7,8-tetrahydro[1,2,4]tri-azolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**17b**).

The solution of 2.19 g (0.01 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**5**, Q = methylthio) [6] in 10 ml of 2-butanone (**16**) was refluxed for 10 hours. After cooling the precipitated crystals were filtered off to yield 1.33 g (52%) of ±6,8-dimethyl-8-ethyl-2-methylthio-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(9*H*)-thione (**17b**) that after recrystallisation from methanol melted at 206-208°; ir: ν C=S = 1279 cm^{-1}; pmr (DMSO-d_6): δ, ppm 0.90 [t (J = 5 Hz), 3H, CH_2CH_3], 1.27 (s, 3H, CCH_3), 1.65 [q (J = 5 Hz), 2H, CH_3CH_2), 2.47 (s, 3H, SCH_3), 3.53 (s, 3H, NCH_3), 7.1 (bs, 1H, 7-NH), 8.2 (s, 1H, 9-NH); cmr (DMSO-d_6): δ, ppm 8.0 (CH_2CH_3), 13.1 (SCH_3), 24.4 (CCH_3), 32.6 (CH_2CH_3), 46.6 (NCH_3), 79.1 (C-8), 153.0 (C-9a), 161.0 (C-2), 178.3 (C-5); uv (95% ethanol + 5% water): λ max nm (ε 10^{-3}) 249 (10.7), 288 (11.3), 310 (8.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε 10^{-3}) 271 (16.4); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε 10^{-3}) 281 (6.1), 309 (4.1).

Anal. Calcd. for $C_9H_{16}N_6S_2$ (MW 272.40): C, 39.69; H, 5.92; N, 30.85; S, 23.54. Found: C, 39.81; H, 6.04; N, 31.02; S, 23.51.

General Procedure for the Preparation of 1-(5-Amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methyl-*N'*-(substituted arylidene)carbothiohydrazides **19** and their Ring Tautomers 6-Methyl-8-(substituted phenyl)-3-Q-5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thiones **20**.

The mixture of 0.01 mole of the appropriate methyl (5-amino-3-Q-1*H*-1,2,4-triazole)-*N*-methylcarbothiohydrazide (**5**) [6], 0.012 mole of the appropriate benzaldehyde **18** and 25 ml of ethanol was refluxed for the time given in Table I. After cooling the precipitated crystals were filtered off and recrystallised from a solvent given in Table I. For spectral data see Table II.

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REFERENCES AND NOTES

[1] For Part **XXIX** see: J. Barkóczy and J. Reiter, *J. Heterocyclic Chem.*, **30**, 333 (1993).

[2] P. Papini and S. Checci, *Gazz. Chim. Ital.*, **82**, 735 (1952).

[3] N. K. Beresneva, V. A. Lopyrev and K. L. Krupkin, *Khim. Geterotsikl. Soedin.*, 1118; *Engl. Ed.*, 848 (1969).

[4] P. Dvortsák, J. Reiter, T. Somorai and P. Sohár, *Magn. Reson. Chem.*, **23**, 194 (1985).

[5] J. Reiter, L. Pongó, T. Somorai and P. Dvortsák, *J. Heterocyclic Chem.*, **23**, 401 (1986).

[6] J. Barkóczy and J. Reiter, *J. Heterocyclic Chem.*, **29**, 1677 (1992).