On Triazoles. XXVIII [1].
Synthesis of Isomeric 1,2,4-Triazolylcarbothiohydrazides

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Different **3a**, **3b**, **9**, **10** and **12** type 5-amino-1,2,4-triazolylcarbothiohydrazide isomers representing all possible isomeric types derived from 5-amino-1,2,4-triazoles were synthesised from the corresponding 5-amino-1,2,4-triazolyldithiocarbonates and hydrazines. HPLC measurements proved that in case of monosubstituted hydrazines the steric press in the intermediate **6** caused besides formation of the expected derivative **3a** the formation of compounds **4** and **5**, too, while the intermediate **7** yielded only **3b**. Thermal rearrangement of derivatives **3a** in acetic acid led to isomers **9** and **10**, respectively.

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Recently we have described the synthesis and structural elucidation of different alkyl 5-amino-3-Q-1,2,4-triazolyldithiocarbonates **1** [2]. Biological considerations prompted us to react them with hydrazine **2** (R^2 = R^3 = H) and different mono- and 1,2-disubstituted hydrazine derivatives **2** ($R^2 \neq$ H, R^3 = H and R^2, $R^3 \neq$ H, respectively) to yield the corresponding carbothiohydrazides **3** (Scheme 1). In this reaction in case of unsymmetrically substituted hydrazine derivatives **3** such as methylhydrazine **2** (R^2 = methyl, R^3 = H) or ethylhydrazine **2** (R^2 = ethyl, R^3 = H) two carbothiohydrazide isomers **3a** and **3b** respectively (Scheme 1) could be formed.

The reaction of dithiocarbonates **1** with hydrazine **2** (R^2 = R^3 = H) provided readily either at room temperature or in boiling methanol, ethanol or acetonitrile [3] the expected carbothiohydrazides **3** (R^2 = R^3 = H). Even the reaction of the disubstituted 1,2-dimethylhydrazine (**2**, R^2 = R^3 = CH_3) was a bit sluggish it also provided in boiling methanol the expected derivatives **3/14** and **3/17** (R^2 = R^3 = CH_3), respectively.

Unexpectedly, when providing the above reactions with monosubstituted hydrazines **2**, (R^2 = H, R^3 = H) in boiling ethanol, or acetonitrile only traces of the desired products **3** could be detected the corresponding triazoles **5** being the main products of the reactions formed by decomposition of the starting materials **1** (Scheme 1). Surprisingly, when providing these reactions in heterogenous mixtures of room temperature, depending on the length of the reaction time either derivatives **3a** or derivatives **3b** were isolated besides dithioesters **4** and the corresponding derivatives **5** (Scheme 1). This fact was understood when providing the reaction of methyl(5-amino-3-diallylamino-1,2,4-triazol-1-yl)dithiocarbonate **1** (Q = diallylamino, R = methyl, R^1 = H) which was a bit more soluble in methanol used as solvent than the other derivatives of **1** studied previously with methylhydrazine (**2**, R^1 = methyl, R^2 = H). In this case the heterogenous reaction mixture obtained after mixing the reactants at room temperature became within 5 minutes a clear solution that crystallised soon to yield the corresponding derivative **3a/10** (Q = diallylamino, R^1 = H, R^2 = methyl, R^3 = H). However, when the precipitated product was not filtered off and the reaction mixture was stirred further at room temperature derivative **3a/10** (Q = diallylamino, R^1 = H, R^2 = methyl, R^3 = H) once crystallised dissolved again and after 8 hours the isomeric **3b/10** (Q = diallylamino, R^1 = H, R^2 = H, R^3 = methyl) was obtained as the main product of the reaction.

Careful, time dependent examination of the reaction mixtures by hplc showed that - as expected - the initial step of these reactions is the nucleophilic attack of the primary or secondary amino group of methylhydrazine (**2**, R^2 = methyl, R^3 = H) against the central carbon atom of the

Scheme 1

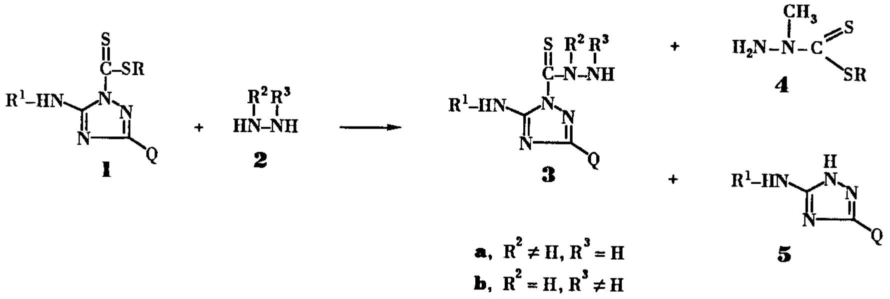


Table I

Compound No.	Q	R^1	R^2	R^3	Method	Reaction time (hours)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula	Analysis Calcd./Found			
										C	H	N	S
3/1	Methylthio	H	H	H	A	4	85	185-186	$C_4H_8N_6S_2$	23.53	3.95	41.14	31.39
								(DMF)	(204.21)	23.66	4.04	41.08	31.51
3/2	Morpholino	H	H	H	A	4	86	183-185	$C_7H_{13}N_7OS$	34.56	5.39	40.30	13.18
								(DMF+ MeCN)	(243.30)	34.50	5.51	40.27	13.32
3/3	Diallylamino	H	H	H	B	1	82	130-132	$C_9H_{15}N_7S$	42.67	5.97	38.70	12.66
								(Bz)	(253.33)	42.60	6.11	38.62	12.80
3/4	Dimethylamino	H	H	H	A	5	95	180-181	$C_5H_{11}N_7S$	29.84	5.51	48.72	15.93
								[1]	(201.25)	30.02	5.43	48.61	16.08
3/5	Piperidino	H	H	H	A	5	96	183-184	$C_8H_{15}N_7S$	39.82	6.27	40.63	13.29
								[1]	(241.32)	40.01	6.35	40.60	13.35
3/6	4-Methyl-piperazin-1-yl	H	H	H	A	4	94	194-196	$C_8H_{16}N_8S$	37.49	6.29	43.72	12.51
								(DMF)	(256.33)	37.41	6.33	43.80	12.62
3a/7	Amino	H	Methyl	H	A	1	73	184-186	$C_4H_9N_7S$	25.66	4.85	52.37	17.12
								(2-PrOH)	(187.22)	25.47	4.93	52.30	17.23
3a/8	Methylthio	H	Methyl	H	A	1	35	164-165	$C_5H_{10}N_6S_2$	27.51	4.62	38.50	29.37
								(Bz)	(218.30)	27.55	4.68	38.46	29.41
3b/8	Methylthio	H	H	Methyl	A	20	9 [2]	162-164	$C_5H_{10}N_6S_2$	27.51	4.62	38.50	29.37
								(EtOH)	(218.30)	27.48	4.65	38.56	29.36
3a/9	Morpholino	H	Methyl	H	A	4	59	144-146	$C_8H_{15}N_7OS$	37.34	5.88	38.10	12.46
								(Bz)	(257.32)	37.28	5.93	38.01	12.55
3b/9	Morpholino	H	H	Methyl	[3]		15	125-126	$C_8H_{15}N_7OS$	37.34	5.88	38.10	12.46
								(2-PrOH)	(257.32)	37.30	5.99	38.24	12.40
3a/10	Diallylamino	H	Methyl	H	A	0.5	38	118-119	$C_{10}H_{17}N_7S$	44.93	6.41	36.67	11.99
								(EtOAc)	(267.36)	45.11	6.56	36.43	12.03
3b/10	Diallylamino	H	H	Methyl	A	8	67	86-88	$C_{10}H_{17}N_7S$	44.93	6.41	36.67	11.99
							[4]	(MeOH + H_2O)	(267.36)	44.88	6.56	36.60	12.03
3a/11	Dimethylamino	H	Methyl	H	A	0.5[5]	62	169-171	$C_6H_{13}N_7S$	33.48	6.09	45.55	14.89
								(EtOAc)	(215.28)	33.55	6.21	45.48	14.80
3b/11	Dimethylamino	H	H	Methyl	A	16	49	172-174	$C_6H_{13}N_7S$	33.48	6.09	45.55	14.89
								(2-PrOH)	(215.28)	33.49	6.11	45.71	14.92
3b/12	4-Methyl-piperazin-1-yl	H	H	Methyl	A	6 [6]	48	150-152	$C_9H_{18}N_8S$	39.98	6.71	41.45	11.86
								(CH_3CN)	(270.36)	40.11	6.88	41.38	12.01
3b/13	Morpholino	H	H	Ethyl	A	8 [7]	5	128-129	$C_9H_{17}N_7OS$	39.84	6.32	36.13	11.82
								(CH_3CN)	(271.34)	39.88	6.40	36.08	11.88
3/14	Morpholino	H	Methyl	Methyl	B	16	43	128-129	$C_9H_{17}N_7OS$	39.84	6.32	36.13	11.82
								(Et_2O) [8]	(271.34)	39.78	6.43	36.08	11.96
3/15	Morpholino	Benzyl	H	H	A	4	85	141-143	$C_{14}H_{19}N_7OS$	50.43	5.74	29.41	9.62
								(MeOH)	(333.41)	50.44	5.86	29.34	9.60
3a/16	Morpholino	Benzyl	Methyl	H	A	4	63	133-134	$C_{15}H_{21}N_7OS$	51.85	6.09	28.22	9.23
								(Bz)	(347.44)	51.90	6.22	28.17	9.30
3b/16	Morpholino	Benzyl	H	Methyl	[3]		16	86-87	$C_{15}H_{21}N_7OS$	51.85	6.09	28.22	9.23
								(Hexane+ Et_2O)	(347.44)	51.78	6.05	26.32	9.20
3/17	Morpholino	Benzyl	Methyl	Methyl	B	8	45	66-68	$C_{16}H_{23}N_7OS$	53.17	6.41	27.13	8.67
								(2-PrOH) [9]	(361.47)	53.07	6.52	27.22	8.78
3/18	Methylthio	4-Cl-Benzyl	H	H	B	1	71	140-142	$C_{11}H_{13}ClN_6S_2$	40.18	3.98	25.56	19.50
								(MeOH)	(328.84)	40.22	4.12	25.61	19.47
3/19	Morpholino	4-Cl-Benzyl	H	H	B	0.5	84	169-171	$C_{14}H_{18}ClN_7OS$	45.71	4.93	26.65	8.72
								(MeOH)	(367.86)	45.77	5.06	26.53	8.70

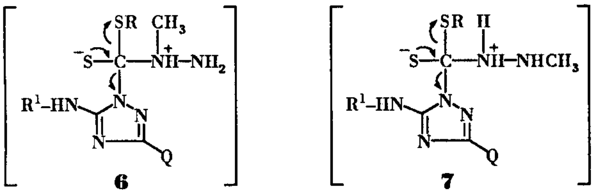
Table I (continued)

Compound No.	Q	R^1	R^2	R^3	Method	Reaction time (hours)	Yield (%)	Mp (°C) (Cryst. from)	Molecular Formula	Analysis Calcd./Found C	H	N	S
3a/20	Morpholino	4-Cl Benzyl	Methyl	H	A	5	63	152-154 (Bz + CH)	$C_{15}H_{20}ClN_7OS$ (381.88)	47.18 47.09	5.28 5.33	25.68 25.68	8.40 8.35
3/21	Morpholino	4-Dimethyl aminobenzyl	H	H	B	1	83	127-129 (MeOH)	$C_{16}H_{24}N_8OS$ (344.4)	51.05 51.11	6.43 6.55	29.76 29.71	8.52 8.48

[1] Stirred at 20° with 5 fold dimethylformamide, filtered and washed with acetonitrile. [2] Obtained after evaporation *in vacuo* to dryness and chromatography of the residue on a silica gel column. Byproduct: 6.78 g (52%) of 5-amino-3-methylthio-1*H*-1,2,4-triazole, mp 136-137° (2-PrOH), Lit [9] mp 136-137° and 6.5 g (48%) of methyl (*N*-methylhydrazinodithiocarbonate) (**4**). mp 88-89° (2-PrOH). [3] Crystallised from the mother liquor of **3a** upon standing for two days. [4] Obtained after evaporation *in vacuo* to dryness and crystallisation of the residue from the mixture of water and methanol, see also Experimental. [5] Reaction provided in 25 ml of dimethylformamide as solvent at 0°; after addition of 50 ml of water the product crystallised. [6] Obtained after evaporation *in vacuo* to dryness and recrystallisation of the residue from 2-propanol. [7] Obtained after evaporation *in vacuo* to dryness and chromatography on silica gel column. [8] Obtained after evaporation *in vacuo* to dryness taken the residue in chloroform, washing with water, drying, evaporating *in vacuo* to dryness and suspending the residue in diethyl ether . [9] Obtained after evaporation *in vacuo* to dryness taking the residue in ether, washing with water, drying, evaporating again *in vacuo* to dryness and crystallisation of the residue from 2-PrOH.

thioester moiety of **1** to yield intermediates **6** or **7**, respectively (Scheme 2). However, even the nucleophilicity of the secondary nitrogen atom of methylhydrazine (**2**, R^2 = methyl, R^3 = H) is enhanced by the +I effect of the methyl group preferring its nucleophilic attack and thus the formation of intermediate **6**, in this intermediate the steric press around the central carbon atom enables besides the splitting of the methylthio leaving group also the splitting of the 5-amino-1,2,4-triazole moiety and thus the formation of **4** and the corresponding triazole **5** besides the expected derivative **3a** (R^2 = methyl, R^3 = H) that crystallises readily from the reaction mixture. On the other hand, in a competitive reaction the unsubstituted primary amino group of methylhydrazine **2** (R^2 = methyl, R^3 = H) makes also a nucleophilic attack against the central carbon atom of the thioester moiety of **1**. The intermediate **7** thus formed is sterically less pressed, consequently it is stabilised rather by splitting of the more polar methylthio leaving group to yield **3b** (R^2 = H, R^3 = methyl) remaining dissolved in the solvent.

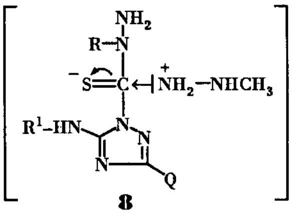
Scheme 2



6 **7**

Moreover, derivatives **3a** (R^2 = methyl, R^3 = H) once formed are not stable in the reaction mixtures. The central carbon atoms of their thiohydrazide moiety may be attacked by the primary amino group of the methylhydrazine present to yield, probably through intermediates **8** (Scheme 3), isomers **3b** (R^2 = H, R^3 = methyl) as proved by stirring the mixture of **3a/10** (Q = diallylamino, R^2 = methyl, R^3 = H) and excess of methylhydrazine (**2**, R^2 = methyl, R^3 = H) in methanol at room temperature for 12 hours to yield according to hplc a 1:1 mixture of **3a/10** (Q = diallylamino, R^2 = methyl, R^3 = H) and **3b/10** (Q = diallylamino, R^2 = H, R^3 = methyl) besides about 1.5 parts of **5** (Q = diallylamino).

Scheme 3



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The little stability of derivatives **3a** (R^2 = methyl, R^3 = H) in solution prompted us to try to convert them to their positional isomers **9** and **10**. It was known [4,5] that the acylation of the exocyclic amino group of 1-acetyl-5-amino-3-Q-1,2,4-triazoles changes the basicity of the triazolo nitrogen atoms causing rearrangement of the ring acetyl group from nitrogen 1 to nitrogen 2. Taking into account this phenomena, it was predicted that any other change of the basicity of the triazole nitrogen atoms, caused *e.g.* by protonation of the triazole ring, may cause rearrangement of the thiohydrazide moiety from nitrogen 1 to nitrogens 2 or 4, respectively. Thus thiohydrazide **3a** (Q = morpholino, R^2 = methyl, R^3 = H) was boiled in acetic acid and indeed derivatives **9** and **10** could be isolated from the reaction mixture (Scheme 4).

Table II

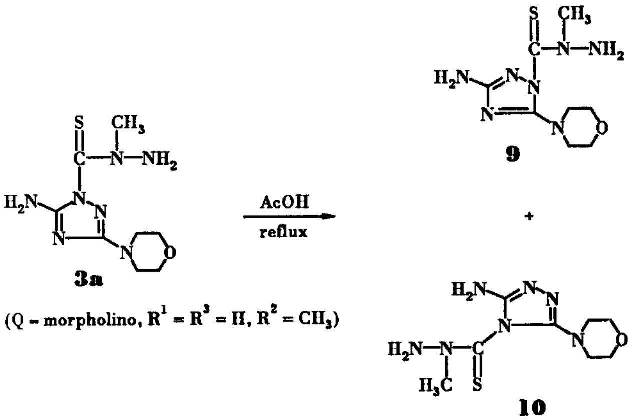
Compoud	PMR [ppm] (DMSO-d_6)							CMR [ppm] (DMSO-d_6)						
No.	δ Q	δ R^1	δ R^2	δ R^3	δ NH_2 (5)	δ NNH_2	δ NH	δ C-3	δ C-5	δ C=S	δ R^1	δ R^2	δ R^3	δ Q
3/1	2.51 s				8.0 s	[1]	[1]	160.0	156.9	167.7				13.3
3/2	3.21 m				8.1 s	[1]	[1]	161.0	156.5	167.3				45.3
	3.64 m													65.4
3/3	3.96 d				8.3 bs	[1]	7.95 b	160.5	156.5	167.2				48.8
	5.19 dd													116.9
	5.82 dt													134.3
3/4	2.89 s				8.0 bs	[1]	5.4 b (1H)	161.6	156.6	167.2				39.1
	2.96 s				7.0 bs	4.35 bs	9.4 b [2]							
3/5	1.52 m				9.0 bs	[1]	5.4 b (1H)	161.2	156.6	167.0				24.0
	3.35 t													24.8
	1.60 m				6.9 bs	4.35 bs	9.4 b [2]							45.9
3/6	2.76 s				8.3 bs	5.95 b	11.7 b	160.8	156.5	167.5				44.6
	3.08 t													45.4
	3.39 t													53.5
3a/7	5.45 s		3.37 s		6.95 s	6.5 s [2]		160.5	156.8	167.9		43.3		13.2
					5.45 s [3]									
3a/8	2.44 s		3.40 s		6.9 b	6.6 b		159.0	156.6	165.6		42.5		13.1
	2.51 s		3.63 s		5.6 b	6.35 b [2]								
3b/8	2.51 s			2.69 s	7.9 b		[1]	159.1	156.7	170.9			36.1	13.2
3a/9	3.25 t		3.43 s		6.9 bs	6.47 s		161.7	156.5	167.9		43.0		45.8
	3.64 t													65.5
3b/9	3.32 t			2.59 s	8.0 s		5.6 bs	161.2	157.0	169.2			37.0	45.7
	3.63 t						10.8 bs							65.8
3a/10	3.87 d (4H)		3.46 s		7.05 b	6.5 bs		160.5	156.8	167.9		43.2		49.3
	5.10 bs (2H)													116.4
	5.16 dd (2H)													134.3
	5.81 m (2H)													
3b/10	3.93 d (4H)			2.58 s	8.13 bs		10.75 b	160.6	156.1	168.7			36.5	49.8
	5.10 bs (2H)													116.9
	5.17 dd (2H)													133.9
	5.81 (2H)													
3a/11	2.83 s		3.46 s		6.95 bs	6.48 s								
3b/11	2.90 s			2.59 s	8.11 bs		10.5 b	161.3	157.0	168.7			37.1	37.3
3b/12	2.21 s			2.60 s	8.08 s		[1]	161.0	156.9	168.7			37.0	44.9
	2.36 t													45.5
	3.36 t													53.5
3b/13	3.41 t			1.18 t	7.2 s		5.3 bs [2]							
	3.75 t			3.02 qi			9.65 bs							
3/14	3.24 t		3.43 s	2.51 s	7.25 bs	6.95 b		161.6	157.2	173.3		43.4	36.9	45.8
	3.64 t													65.6
3/15	3.43 t	4.68 d				4.32 s	9.2 t [2]	161.7	157.4	173.8	47.4			45.8 [2]
	3.74 t	7.35 m					9.3 bs				128.0			66.3
											128.5			
											128.6			
											137.8			
3a/16	3.40 t	4.64 d	3.60 s			5.7 bs	8.05 bs	161.4	158.3	173.1	47.5	44.9		45.9 [2]
	3.75 t	7.35 m					[2]				127.2			66.2
											127.4			
											128.4			
											138.0			
3b/16	3.44 t	4.68 d		2.72 s			5.25 b	161.8	157.8	171.2	47.5		38.1	45.9 [2]
	3.75 t	7.3-7.4 m					9.20 t				127.5			66.4
							9.5 b				127.5			
											128.7			
											138.0			

Table II (continued)

Compoud No.	δ Q	PMR [ppm] (DMSO-d_6) δ R^1	δ R^2	δ R^3	Δ NH_2 (5)	Δ NNH_2	Δ NH	CMR [ppm] (DMSO-d_6) δ C-3	δ C-5	δ C=S	δ R^1	δ R^2	δ R^3	δ Q
3/17	3.40 t 3.75 t	4.64 d 7.35 m	3.55 s	2.54 bs			8.3 b [2]							
3/18	2.50 s	4.60 d 7.40 m					[1]							
3/19	3.43 t 3.74 t	4.64 d 7.3 m (NH)			4.2 s	9.18 t [2] 9.2 bs	161.8	157.5	173.9	46.8 128.9 133.5 136.5 139.0				45.8 [2] 66.5
3a/20	3.39 t 3.75 t	4.59 d 7.3 m (NH)	3.61 s		5.7 s	8.1 bs [2]	161.5	158.4	173.3	47.0 128.8 129.0 133.3 136.7	45.3			46.0 66.4
3/21	3.35 t 3.65 t	2.86 s 4.44 d 6.68 d 7.19 d 8.97 t (NH)			5.25 bs	10.7 b								

[1] Not detected. [2] Taken in deuteriochloroform. [3] δNH_2-3.

Scheme 4



(Q = morpholino, R^1 = R^3 = H, R^2 = CH_3)

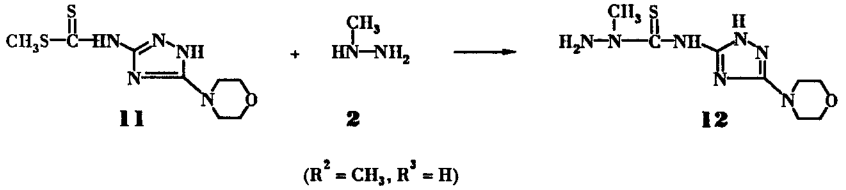
The last possible positional isomer having the thiohydrazide moiety on the exocyclic amino group **12** was obtained by reacting the corresponding exocyclic dithioester **11** [2] with methylhydrazine (**2**, R^2 = methyl, R^3 = H) (Scheme 5).

The ir spectra of isomers **3a**, **3b**, **9**, **10** and **12** (see Table II and Experimental) were all in accordance with the proposed structures but were not characteristic of them.

On the other hand the pmr spectra (Table II), analogous to those of acyl- [5], carbamoyl- [6] and thiocarbamoyl- [6] triazoles and 1,2,4-triazolylditiocarbonates [2] studied previously, made it possible to distinguish derivatives **12** having the thiohydrazide moiety on the exocyclic nitrogen atom and being characterised with two NH groups from all other **3**, **9** and **10** type derivatives having the thiohydrazide moiety attached to the triazole ring and thus being characterised with one NH_2 peak only.

However, the differentiation among derivatives having the thiohydrazide moiety in different positions of the triazole ring (**3**, **9**, and **10** type derivatives, respectively) made possible the cmr spectra only in which the chemical shifts of the triazole carbon atoms 3 and 5 were in perfect

Scheme 5



accordance with the chemical shifts of the corresponding carbon atoms of those of different alkyl- [7], acyl- [5], carbamoyl- [6] and thiocarbamoyl- [6] triazoles and 1,2,4-triazolyldithiocarbonates [2] studied previously. This fact further corroborated our rule stated previously [8] that the chemical shift of the triazole carbon atoms 3 and 5 depended mainly on the quality of the nitrogen atoms attached to them (pyridine-like or pyrrole-like) and was little influenced by the quality of the triazole ring subtituents.

An easy differentiation between isomers **3a** and **3b** offered the pmr spectra, where even no chemical coupling was observed between the R^3 methyl groups and the attached hydrazino NH group in derivatives **3b** the observed NCH$_3$ chemical shifts of the *N,N'*-dimethyl derivatives **3/14** and **3/17** made possible an unequivocal ordering of the signal appearing at about 3.5 ppm to the R^2 group of **3a** and that of appearing at about 2.6 ppm to the R^3 group of derivatives **3b**. In case of **3b/13** the CH$_2$ group of R^3 = ethyl moiety appeared as a consequence of the well developed coupling with the NH group as a quartet giving no doubt about its structure.

The above difference in the chemical shifts of the NCH$_3$ groups of derivatives **3a** and **3b** was good visible also in the cmr spectra where the corresponding NCH$_3$ groups appeared at about 43 and 37 ppm, respectively.

The chemical shifts of the triazole carbon atoms of **12** (δ C-3 = 161.9, δ C-5 = 148.4 ppm) were again in excellent agreement with those of the corresponding 5-acetylamino-3-morpholino-1*H*-1,2,4-triazole (δ C-3 = 164.0, δ C-5 = 150.7 ppm [5]) proving its 1*H* tautomeric structure in DMSO-d$_6$ solution.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 577 spectrophotometer. The ^{1}H-nmr and the ^{13}C-nmr measurements were performed using Brucker WM-250 and Brucker WP-80 SY instruments. Hplc determinations were performed using Labormim 312/1 pump, Labormim uv detector (operating at 254 nm, range 0.5), Shimadzu C-R3A Integrator (attenuation: 3, slope: 600-1300); Column; Beckmann OCTYL 25 cm/4.6 mm, inner diameter 6 μm; Eluent: acetonitrile-ammonium acetate buffer *p*H 4.5 (0.1 *M*) = 4:6, Sample: concentration 20 mg/5 ml of eluent, loop 20 μl.

General Methods for the Preparation of Carbothiohydrazydes **3**.

Method A.

The mixture of 0.1 mole of the corresponding dithiocarbonate **1** [2], 0.13 mole of the corresponding hydrazine **2** and 150 ml of methanol is stirred at room temperature for the time given in Table I. The crystals separated are filtered off and recrystallised from a solvent given in Table I.

In case of methylhydrazine (**2**, R^1 = methyl, R^2 = H) after evaporation of the mother liquors *in vacuo* to dryness and chromatography of the residue on a silica-gel column methyl (*N*-methylhydrazinodithiocarbonate) (**4**) could be isolated in 20-25% yield, that after recrystallisation from 2-propanol melted at 88-90°; ir: ν C=S= 1380 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.33 (s, 3H, SCH$_3$), 3.58 (s, 3H, NCH$_3$), 5.53 (s, 2H, NH$_2$); cmr (DMSO-d$_6$): δ ppm 19.2 (SCH$_3$), 45.7 (NCH$_3$), 198.9 (C=S).

Anal: Calcd. for $C_3H_8N_2S_2$ (MW 136.14): C, 26.44; H, 5.92; N, 20.56; S, 47.07. Found: C, 26.33; H, 6.07; N, 20.55; S, 47.06.

Continuing the chromatography the corresponding 5-amino-1,2,4-triazole derivatives **5** were isolated in 10-20% yield that were in all respects identical with those prepared previously [8,9].

Method B.

The mixture of 0.1 mole of the corresponding dithiocarbonate **1** [2], 0.13 mole of the corresponding hydrazine **2** and 150 ml of methanol is boiled with stirring for the time given in Table I. After cooling the crystals separated are filtered off and recrystallised from a solvent given in Table I. Workup of the mother liquors of reaction mixtures obtained with methylhydrazine (**2**, R^2 = methyl, R^3 = H) yielded again derivatives **4** and **5**, see above.

1-(5-Amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**3b/10**).

The mixture of 0.53 g (0.002 mole) of 1-(5-amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohyrazide (**3a/10**), 0.14 ml (0.0026 mole) of *N*-methylhydrazine and 2.5 ml of methanol was stirred at room temperature for 12 hours Hplc showed a 1:1:1.5 mixture of 1-(5-amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**3a/10**) (t$_R$ 4.6 minutes), 1-(5-amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**3b/10**) (t$_R$ 7.1 minutes) and 5-amino-3-diallylamino-1*H*-1,2,4-triazole (**5**, Q = diallylamino, R^1 = H) (t$_R$ 2.1 minutes), respectively. The solution obtained was evaporated *in vacuo* to dryness and the residue was chromatographed on a silica gel column (eluent a 9:1 mixture of chloroform and methanol) to yield 0.12 g (23%) of 1-(5-amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**3a/10**), mp 118-119° (ethyl acetate) (for spectral data see Table II), 0.15 g (28%) of 1-(5-amino-3-diallylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**3b/10**), mp 86-88° (methanol-water) (for spectral data see Table II) and 0.1 g (28%) of 5-amino-3-diallylamino-1*H*-1,2,4-triazole (**5**, Q = diallylamino, R^1 = H), mp 101-102° (acetonitrile); pmr (DMSO-d$_6$): δ, ppm 3.80 (d, 4H, NCH$_2$), 4.86 (m, 2H, CH$_2$=), 5.1 (bs, 2H, CH$_2$), 5.8 (bs, 2H, NH$_2$), 5.9 (m, 2H, CH), 11.2 (b, 1H, NH).

Anal. Calcd. for $C_8H_{13}N_5$ (MW 179.22): C, 53.61; H, 7.31; N, 39.08. Found: C, 53.58; H, 7.40; N, 39.11.

1-(5-Amino-3-morpholino-2*H*-1,2,4-triazole-2-yl)-*N*-methylcarbothiohydrazide (**9**) and 1-(5-Amino-3-morpholino-4*H*-1,2,4-triazole-4-yl)-*N*-methylcarbothiohydrazide (**10**).

1-(5-Amino-3-morpholino-1*H*-1,2,4-triazole-1-yl)-*N*-methylcarbohydrazide) (25.5 g, 0.1 mole) (**3a/9**) is boiled in 75 ml of acetic acid for 30 minutes with stirring. After cooling the separated crystals are filtered off and recrystallised from methanol to yield 10.5 g (41%) of 1-(5-amino-3-morpholino-4*H*-1,2,4-triazole-4-yl)-*N*-methylcarbothiohydrazide (**10**), mp 239-240°; ir: ν NH = 3400 and 3250, ν C=S = 1265 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 3.33 (s, 3H, NCH$_3$), 3.33 [t(J = 5 Hz), 4H, NCH$_2$], 3.66 [t(J = 5 Hz), 4H, OCH$_2$], 5.75 (s, 2H, NNH$_2$), 7.2 (s, 2H, CNH$_2$); cmr (DMSO-d$_6$): δ ppm 35.7 q (NCH$_3$), 46.2 t (NCH$_2$), 65.5 t (OCH$_2$), 151.7 m (C-3), 154.5 s (C-5), 165.5 q (C=S).

Anal. Calcd. for $C_8H_{15}N_7OS$ (MW 257.32): C, 37.34; H, 5.88; N, 38.10; S, 12.46. Found: C, 37.38; H, 5.98; N, 37.98; S, 12.44.

The combined mother liquors are evaporated to dryness *in vacuo* and the residue is recrystallised first from aqueous ethanol, then from acetonitrile to yield 6.12 g (24%) of 1-(5-amino-3-morpholino-2*H*-1,2,4-triazole-2-yl)-*N*-methylcarbothiohydrazide (**9**), mp 258-259°; ir: ν NH = 3380 and 3230, ν C=S = 1280 cm^{-1}; pmr (DMSO-d_6): δ ppm 3.34 [t(J = 4.8 Hz), 4H, NCH_2], 3.48 (s, 3H, NCH_3), 3.62 [t(J = 4.8 Hz), 4H, OCH_2], 5.75 (s, 2H, NNH_2), 6.0 (s, 2H, CNH_2); cmr (DMSO-d_6): δ ppm 35.4 q (NCH_3), 45.4 t (NCH_2), 65.7 t (OCH_2), 151.0 m (C-3), 162.4 q (C=S), 163.5 s (C-5).

Anal. Calcd. for $C_8H_{15}N_7OS$ (MW 257.32): C, 37.34; H, 5.88; N, 38.10; S, 12.46. Found: C, 37.28; H, 5.90; N, 38.12; S, 12.37.

2-Methyl-4-(3-morpholino-1*H*-1,2,4-triazol-5-yl)carbothiosemicarbazide (**12**).

The mixture of 25.9 g (0.1 mole) of methyl (3-morpholino-2*H*-1,2,4-triazol-5-yl)dithiocarbonate (**11**) [2], 6.9 ml (0.13 mole) of methylhydrazine (**2**, R^2 = methyl, R^3 = H) and 250 ml of methanol is boiled with stirring for 2 hours. After cooling the crystals precipitated are filtered off and recrystallised from methanol to yield 17.34 g (68%) of 2-methyl-4-(3-morpholino-1*H*-1,2,4-triazol-5-yl)carbothiosemicarbazide (**12**), mp 211-212°; ir: ν NH = 3240 cm^{-1}, ν C=S = 1277 cm^{-1}; pmr (DMSO-d_6): δ ppm 3.30 [t(J = 5 Hz), 4H, NCH_2], 3.50 (s, 3H, NCH_3), 3.66 [t(J = 5 Hz), 4H, OCH_2], 6.1 (s, 2H, NNH_2), 9.5 (bs, 1H, NH-exo), 12.5 (bs, 1H, NH-1); cmr (DMSO-d_6): δ ppm 42.1 (NCH_3), 46.6 (NCH_2), 65.6 (OCH_2), 148.4 (C-5), 161.9 (C-3), 177.0 (C=S).

Anal. Calcd. for $C_8H_{15}N_7OS$ (MW 257.32): C, 37.34; H, 5.88; N, 38.10; S, 12.46. Found: C, 37.21; H, 5.86; N, 38.11; S, 12.53.

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REFERENCES AND NOTES

[1] For Part **XXVII** see E. Rivó and J. Reiter, *J. Heterocyclic Chem.*, **29**, 1189 (1992).

[2] L. Pongó, J. Reiter, J. Barkóczy, P. Sohár and I. Pallagi, *J. Heterocyclic Chem.*, **27**, 1249 (1990).

[3] J. Barkóczy, J. Reiter, L. Pongó, L. Petöcz, F. Görgényi, M. Fekete, E. Szirtné-Kiszelly, M. Szécseyné-Hegedüs, I. Gacsályi and I. Gyertyán, European Patent Application EP 425,283 (HU Appl. 89/5428, 25. Oct. 1989); *Chem. Abstr.*, **115**, 136101j (1991).

[4] M. D. Coburn, E. D. Loughran and L. C. Smith, *J. Heterocyclic Chem.*, **7**, 1149 (1970).

[5] J. Reiter, L. Pongó and P. Dvortsák, *J. Heterocyclic Chem.*, **24**, 127 (1987).

[6] J. Reiter, L. Pongó and P. Dvortsák, *J. Heterocyclic Chem.*, **24**, 1685 (1987).

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

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

[9] J. Reiter, T. Somorai, Gy. Jerkovich and P. Dvortsák, *J. Heterocyclic Chem.*, **19**, 1157 (1982).