On Triazoles XLV [1]. Synthesis of 5,7-Diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines

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Dedicated to Professor András Messmer on the occasion of his 80th birthday

The reaction of differently substituted 5-amino-1,2,4-triazoles (**5**) with isothiourea derivatives (**3**) to yield isomeric 5,7-diamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**6** and **7**), previously described as not proceeding in melt, was performed in different solvents as well as in the melt at 150-160°. It was proved that the above reaction had rather general validity. The structure of isomers **6** and **7** were proved spectroscopically. The structure of **6/5** (Q = ethylamino) was corroborated with single crystal X-ray diffraction determination, as well.

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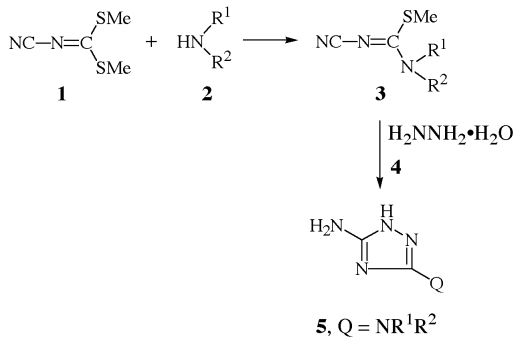
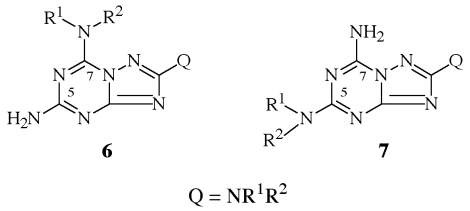
The synthesis of 5-amino-3-(substitutedamino)-1,2,4-triazoles (**5**, Q = NR^1R^2) by the reaction of dimethyl *N*-cyanimidodithiocarbonate (**1**) with primary or secondary amines (**2**, R^1, R^2 = hydrogen, alkyl, aralkyl, aryl) through the isothiourea derivatives (**3**) (which can be either isolated or not isolated using a one pot procedure) [2-3] and hydrazine hydrate (**4**) is well known in the literature [4-5](Scheme 1).

Scheme 1

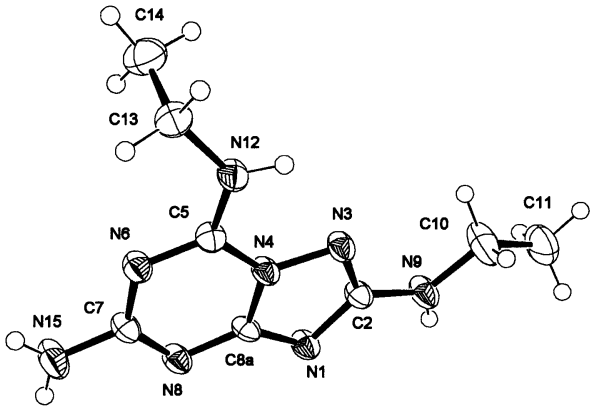


Scheme 2



As some of our tricyclic cycloalka- and heterocyclocalka-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives possessed excellent cardiovascular activity [6] large quantities of derivatives (**5,** Q = NR^1R^2) as their starting materials were required to enable their synthesis for biological screening. During the large scale preparation of 5-amino-3-(ethylamino and *n*-octylamino)-1,2,4-triazoles (**5**, Q = ethylamino and *n*-octylamino, respectively) a small amount (3 and 4 %, respectively) of byproducts (**6** or **7**, Q = ethylamino and *n*-octylamino, respectively, Scheme 2) could be isolated from the mother liquors. The ms and nmr data of products recorded corroborated their 5,7-diamino-1,2,4-triazolo-[1,5-*a*][1,3,5]triazine structure **6** or **7** but owing to the unusual symmetry of the isomeric molecules could not differentiate between them. To verify their structure X-ray diffraction analysis of the ethyl derivative was performed proving its structure **6/5** (Q = ethylamino, Scheme 3, Table I) [7]. The full analogy of the cmr data measured for the 1,2,4-triazolo[1,5-*a*][1,3,5]triazine skeleton of the ethyl and *n*-octyl derivatives, respectively, proved also the structure of derivative **6/7** (Q = *n*-octylamino)(Scheme 2, Table I).

Scheme 3



Perspective view of **6/5**. Atomic thermal ellipsoids are on 50% probability level.

Recently, Caulkett and coworkers [8] happened to synthesise analogous 5-amino-7-alkylamino-1,2,4-triazolo[1,5-*a*][1,3,5]triazine derivatives **12** (Scheme 4)

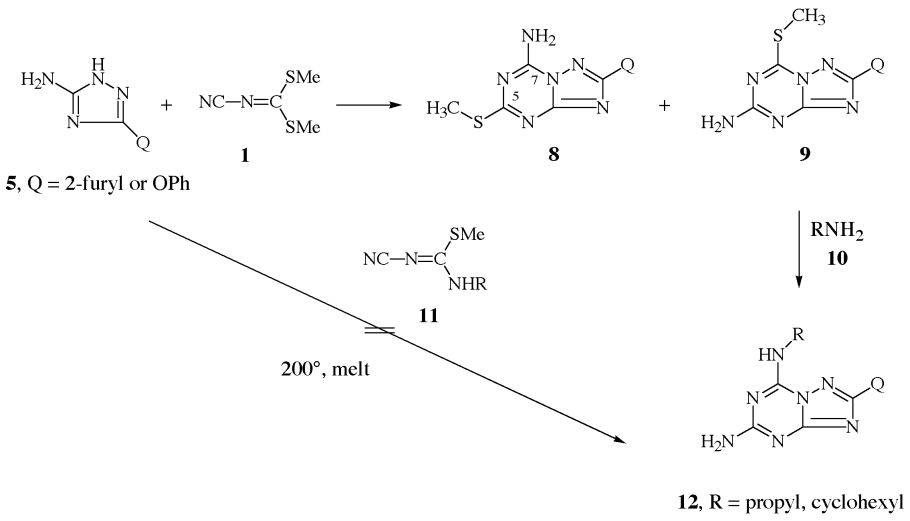
Table I

Physical and Analytical Data of Compounds **6**

Compound	Q	NR^1R^2	Reaction Time (hours)	Yield (%)	Mp (°C) (Solvent)	Molecular Formula (MW)	Analysis Calcd/Found				MS	Note
							C	H	N	S		
6/1	H	3-Dimethylaminopropylamino	38	33	189-191	$C_9H_{16}N_8$	45.75	6.83	47.42		EI	
					(CH_3CN)	(236.28)	45.67	6.88	47.28		236	
6/2	H	Benzylamino	72	35	261-263	$C_{11}H_{11}N_7$	54.76	4.60	40.64		EI	
					(CH_3CN/EtOH)	(241.26)	54.55	4.62	40.55		241	
6/3	Methylthio	Morpholin-4-yl	66	30	225-228	$C_9H_{13}N_7OS$	40.44	4.90	36.68	11.99	EI	
					(EtOH)	(267.31)	40.48	4.98	36.57	12.04	267	
6/4	Methylthio	Ethylamino	96	32 + 7 [a]	229-231	$C_7H_{11}N_7S$	37.32	4.92	43.52	14.23	EI	
			148	48 + 2 [a]	(CH_3CN/EtOH)	(225.28)	37.41	4.98	43.41	14.25	225	
6/5	Ethylamino	Ethylamino	51	35	280-285	$C_8H_{14}N_8$	43.23	6.35	50.42		EI	[b]
					(CH_3CN/H_2O)	(222.25)	43.28	6.44	50.37		222	
6/6	Benzylamino	Benzylamino	48	37	192-195	$C_{18}H_{18}N_8$	62.41	5.24	32.35		ES	
					(CH_3CN/EtOH)	(346.40)	62.36	5.30	32.30		347	
6/7	*n*-Octylamino	*n*-Octylamino	40	28	196-197	$C_{20}H_{38}N_8$	61.50	9.81	28.69		EI	[c]
					(2-PrOH)	(390.58)	61.55	9.99	28.62		390	
6/8	2-Dimethylaminoethylamino	2-Dimethylaminoethylamino	48	22	199-203	$C_{12}H_{24}N_{10}$	46.73	7.84	45.42		EI	
					(CH_3CN/EtOH)	(308.38)	46.88	7.95	45.37		308	
6/9	3-Dimethylaminopropylamino	3-Dimethylaminopropylamino	25	34	199-203	$C_{14}H_{28}N_{10}$	49.98	8.39	41.63		ES	
					(2-PrOH)	(336.45)	50.12	8.51	41.44		337	
6/10	Morpholin-4-yl	Morpholin-4-yl	70	33	315-324 (dec)	$C_{12}H_{18}N_8O_2$	47.05	5.92	36.58		EI	
					(EtOH/H_2O)	(306.33)	46.99	6.01	36.52		306	

[a] Second crop isolated by chromatography of the mother liquor; [b] Identical with that of **6/5** obtained as byproduct of **5/5**; [c] Identical with that of **6/7** obtained as byproduct of **5/7**

Scheme 4



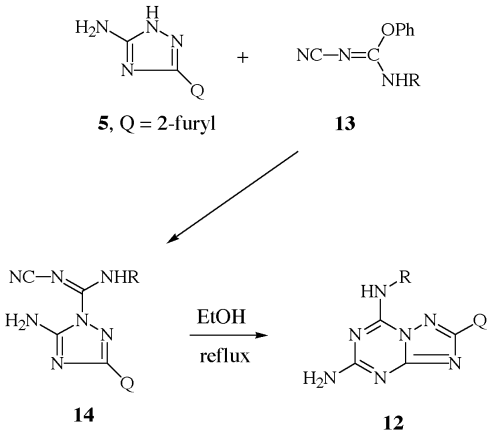
starting from the corresponding 5-amino-3-substituted-1,2,4-triazole derivatives **5** and dimethyl *N*-cyanimidodithiocarbonate (**1**) to yield a mixture of isomeric derivatives **8** and **9**. After their separation the reactive methylthio group of **9** was transformed with the corresponding amines (**10**) leading to derivatives **12**. However, even though it seemed to be straightforward, the corresponding derivative **12** could not be obtained by the reaction of the triazole **5** (Q = 2-furyl) and the corresponding type **3** isothiourea **11**, even by performing the reaction at 200° in melt [8](Scheme 4).

On the other hand, the analogous isourea derivative **13** [R = 2-(4-hydroxyphenyl)ethyl] reacted readily at room temperature with **5** (Q = 2-furyl) in acetonitrile to give a 1-*N*-substituted-5-amino-1,2,4-triazole **14** [Q = 2-furyl, R = 2-(4-hydroxyphenyl)ethyl] that proved to be the intermediate of the reaction leading to **12** [Q = 2-furyl, R = 2-(4-hydroxyphenyl)ethyl] as shown by its refluxing in ethanol [8](Scheme 5).

Even though it was stated [8], that the type **3** isothioureas **11** did not react with the type **5** 5-amino-1,2,4-triazole (**5,** Q = 2-furyl) in melt we came to the decision that our type **6** derivatives could only have formed during the synthesis of triazoles **5** in ethanol by the route mentioned above, *i.e.* by the reaction of the triazoles **5** once formed with the isothioureas (**3**) most probably through the not isolated type **15** intermediates (Scheme 6).

For this reason we tried to react derivatives **3** with derivatives **5** using different solvents and temperatures. The reaction - even though it was rather sluggish requiring long reaction times - proceeded acceptably in many high boiling solvents, such as *n*-amylalcohol, benzylalcohol, dimethylformamide, but surprisingly, from the reaction mixtures obtained by long refluxing of the reactants in *n*-butanol products **6** crystallised in pure state in 22-48 % yield (Scheme 6, Table I, for their spectral data see Table II).

Scheme 5



Scheme 6

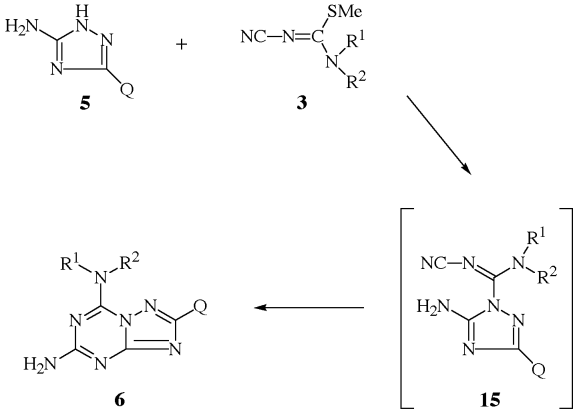


Table II
Pmr and cmr Spectral Data of Compounds **6**

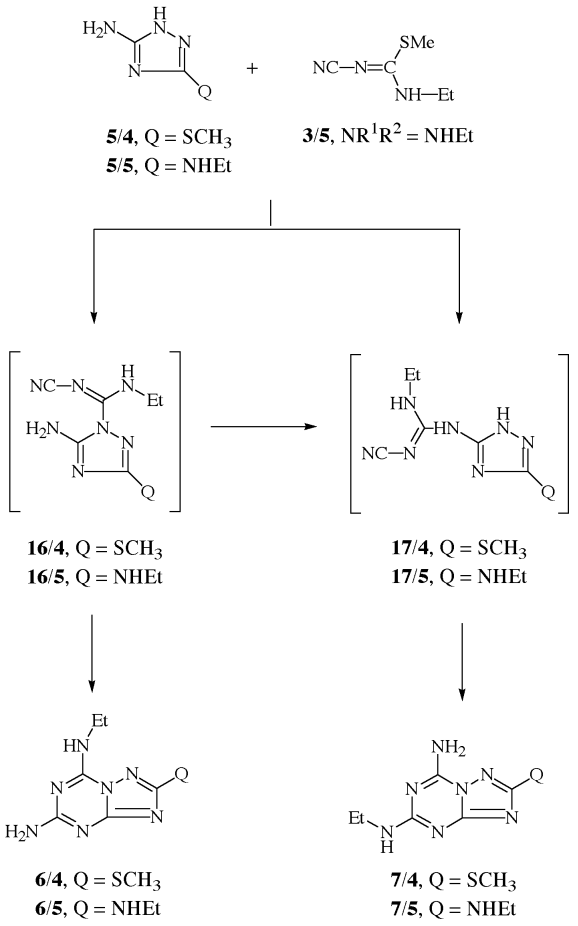
	pmr (DMSO-d_6), δ, ppm				cmr (DMSO-d_6), δ, ppm					
Compounds	NH_2	Q	NH	$R^1 + R^2$	C-2	C-7	C-5	C-3a	Q	$R^1 + R^2$
6/1	6.97 bs	8.06 s	8.61 s	1.74 (qi, 2H) 2.14 (s, 6H) 2.28 (t, 2H) 3.45 (q, 2H)	154.2	149.2	162.7	158.8	-	26.5 39.2 ($NHCH_2$) 45.3 (NMe_2) 57.1 (NCH_2)
6/2	7.03 bs	8.10 s	9.07 (t, J = 5.4 Hz)	4.65 (d, J = 5.4 Hz) 7.25 - 7.4 (m, 5H)	154.4	149.5	162.7	159.0	-	43.3 127.2 (*p*), 127.5 128.5, 138.6 (*s*)
6/3	7.04 bs	2.53 s	-	3.73 (t, 4H, OCH_2) 4.13 (bs, 4H, NCH_2)	165.0	148.4	161.8	161.3	13.2	46.7 (NCH_2) 65.9 (OCH_2)
6/4 [a]	7.01 bs	2.58 s	8.31 bs	1.18 (t, 3H) 3.44 (m, 2H)	165.2	148.2	162.6	159.3	13.4	14.6 (CH_3) 35.1 (CH_2)
6/5 [a]	6.68 bs	1.13 (t, 3H) 3.20 (qi, 2H)	6.32 (t, NH-2) 7.68 (t, NH-7)	1.15 (t, 3H) 3.41 (qi, 2H)	165.6	148.2	162.3	158.4	15.2 37.0	15.0 (CH_3) 34.9 (CH_2)
6/6	6.77 bs	4.44 (d, J = 6.3 Hz) 7.2-7.4 (m, 5H)*	7.00 (t, J = 6.3 Hz, NH-2) 8.29 (t, J = 6.0 Hz, NH-7)	4.58 (d, J = 6.0 Hz) 7.2-7.4 (m, 5H)*	165.9	148.5	162.3	158.7	45.7 140.7 (*s*) 126.7, 127.7 (*p*) 127.3, 127.5, 128.3, 128.4 (*o* + *m*)	43.1 139.1 (*s*)
6/7	6.59 bs	0.86 (t, 3H)* 1.25 (m, 10H)* 1.55 (m, 2H)* 3.16 (q, 2H)	6.25 (t, NH-2) 7.53 (t, NH-7)	0.86 (t, 3H)* 1.25 (m, 10H)* 1.55 (m, 2H)* 3.36 (q, 2H)						
	5.15 bs [b]	0.9 (m, 3H)* 1.28 (m, 10H)* 1.63 (m, 2H)* 3.30 (q, 2H)	4.52 (t, NH-2) 5.89 (t, NH-7)	0.9 (m, 3H)* 1.28 (m, 10H)* 1.63 (m, 2H)* 3.50 (q, 2H)	164.8 [c]	148.6	162.4	157.8	31.8 42.9 14.1 (two peaks) 22.7 (two peaks) 26.8-29.6 (8 peaks)	31.9 41.0
6/8	6.70 bs	2.16 (s, 6H) 2.40 (t, 6H) 3.25 (q, 2H)	6.15 (t, NH-2) 7.35 (t, NH-7)	2.18 (s, 6H) 2.45 (t, 2H) 3.46 (q, 2H)	165.6	148.3	162.3	158.4	37.8 45.3* 57.9	40.4 ($NHCH_2$) 45.4* (NMe_2) 58.5 (NCH_2)
6/9	6.68 bs	1.67 (m, 2H) 2.11 (s, 6H) 2.25 (t, 2H) 3.19 (q, 2H)	6.37 (t, NH-2) 7.93 (t, NH-7)	1.71 (m, 2H) 2.14 (s, 6H) 2.27 (t, 2H) 3.41 (q, 2H)	165.7	148.3	162.3	158.3	27.3 45.4 40.8 57.2	26.6 39.1 ($NHCH_2$) 45.3 (NMe_2) 57.2 (NCH_2)
6/10	6.83 bs	3.35 (m, 4H, NCH_2) 3.66 (t, 4H, OCH_2)	-	3.70 (t, 4H, OCH_2) 4.11 (bs, 4H, NCH_2)	165.5	148.5	161.6	160.7	45.7 65.8	46.5 66.0

[a] Assignment checked by 2D-NMR; [b] Taken in deuteriochloroform; [c] Taken in a mixture of deuteriochloroform and deuteriomethanol.

To study the scope of the above reaction it was performed with differently substituted isothioureas **3**, such as the mono-*N*-substituted derivatives **3** (R^1 = ethyl, *n*-octyl, benzyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl, respectively, R^2 = H), the di-*N*-substituted derivatives **3** (NR^1R^2 = morpholin-4-yl) as well as different 5-amino-1,2,4-triazoles such as **5** (Q = H), **5** (Q = methylthio), and 5-amino-3-monosubstitutedamino-1,2,4-triazoles such as **5** (Q = ethylamino, *n*-octylamino, benzylamino, 2-dimethylaminoethylamino, 3-dimethylaminopropylamino) and 5-amino-3-disubstitutedamino-1,2,4-triazoles such as **5** (Q = morpholin-4-yl), respectively, (Table I) giving in each case the expected type **6** derivatives. These experiments showed the rather general validity of the above reaction.

It is worth mentioning that in the reaction of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**5/4**, Q = methylthio) and *N*-cyano-*N'*-ethyl-*S*-methylisothiourea (**3/5**, NR^1R^2 = ethylamino) besides the expected derivative **6/4** (Q = methylthio) the isomeric **7/4** (Q = methylthio) was also formed that could be isolated by column chromatography of the mother liquor evaporated to dryness (Scheme 7). The formation of **7/4** (Q = methylthio) could be deduced from the intermediate **17/4** (Q = methylthio) formed either directly from **5/4** (Q = methylthio) and **3/5** (NR^1R^2 = ethylamino) or by thermal rearrangement of the intermediate **16/4** (Q = methylthio). An analogous rearrangement of 1-acyl, 1-carbamoyl and 1-thiocarbamoyl-5-amino-1,2,4-triazoles was observed previously [9-10].

Scheme 7



After the success of the above reactions we tried to perform them also in melt. Surprisingly, from the reaction mixture of **5/4** (Q = methylthio) and **3/5** (NR^1R^2 = ethylamino) 69 % of **6/4** (Q = methylthio) and 3.7 % of **7/4** (Q = methylthio) could be isolated by chromatography. Analogously, from the reaction mixture of **5/5** (Q = ethylamino) and **3/5** (NR^1R^2 = ethylamino) 52 % of **6/5** (Q = ethylamino) and 1.8 % of **7/5** (Q = ethylamino) was obtained.

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 882 spectrophotometer. The pmr and the cmr measurements were performed on Bruker WM-250 and Varian Unity Inova 400 (400 MHz) instruments. To confirm the assignments in some cases standard Varian HSQC and HMBC 2D-nmr programs were used. The ms spectra were recorded on a Kratos MS25RFA instrument using direct inlet probe in EI or CI mode, as well as on a VG Quattro instrument (ES).

5-Amino-3-ethylamino-1*H*-1,2,4-triazole (**5/5**, Q = ethylamino) and 5-Amino-2,7-bis(ethylamino)-1,2,4-triazolo[1,5-*a*]-[1,3,5]triazine (**6/5**, Q = ethylamino).

To a stirred hot suspension of 83.1 g (0.58 mole) of *N*-cyano-*N'*-ethyl-*S*-methylisothiourea (**3/5**, NR^1R^2 = ethylamino) [12] in 200 ml of 2-propanol 35.0 g (34 ml, 0.7 mole) of 100 % hydrazine hydrate was added dropwise within 1.5 hours (during the reaction methylthiol was evolved that was trapped in sodium hydroxyde solution). The reaction was completed by refluxing for a further 2 hours. After cooling 300 ml of diethyl ether was added to the reaction mixture, the crystals that precipitated were isolated by filtration and washed with a 1:1 mixture of ether and 2-propanol to yield 51.0 g (69 %) of 5-amino-3-ethylamino-1*H*-1,2,4-triazole (**5/5**, Q = ethylamino), mp 152-154°. An analytical sample was recrystallised from a mixture of CH_3CN and 2-PrOH, mp 156-157.5° (Lit. [11] mp 116-118°, Lit. [13] mp 120-123°; [14]). The mother liquor was evaporated *in vacuo* to dryness and the residue dry column flash chromatographed on Kieselgel 60 H, eluent chloroform-methanol 100:1 to yield 2.2 g (3 %) of 5-amino-2,7-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/5**, Q = ethylamino), mp 280-285° (for its spectral data see Table II). Continuing the chromatography with a 9:1 mixture of chloroform and methanol a further 13.3 g (18 %) crop of (**5/5**) was obtained, mp 153-155°.

5-Amino-3-(*n*-octyl)amino-1*H*-1,2,4-triazole (**5/7**, Q = *n*-octylamino) and 5-Amino-2,7-bis(*n*-octylamino)-1,2,4-triazolo-[1,5-*a*][1,3,5]triazine (**6/7**, Q = *n*-octylamino).

To a stirred hot suspension of 84.2 g (0.37 mole) of *N*-cyano-*N'*-(*n*-octyl)-*S*-methylisothiourea (**3/7**, NR^1R^2 = *n*-octylamino) [15] in 200 ml of 2-propanol 22.2 g (21.5 ml, 0.44 mole) of 100 % hydrazine hydrate was added dropwise within 1.5 hours (during the reaction methylthiol was evolved that was trapped in sodium hydroxyde solution). The reaction was completed by refluxing for a further 2 hours. After cooling 300 ml of diethyl ether was added to the reaction mixture, the crystals precipitated were isolated by filtration and washed with a 1:1 mixture of ether and 2-propanol to yield 51.5 g (66 %) of 5-amino-3-(*n*-octyl)amino-1*H*-1,2,4-triazole (**5/7**, Q = *n*-octylamino), mp 135-137°. An analytical sample was recrystallised from acetonitrile, mp 138.5-139.5°; ms (ES): 212 (MH^+); pmr (DMSO-d_6): δ, ppm 0.86 (t, J = 6.5 Hz, 3H, CH_3), 1.25 (bs, 10H, CH_2-3',4',5',6',7'), 1.45 (m, 2H, CH_2-2'), 2.98 (q, J = 6.5 Hz, 2H, $NHCH_2$), 5.2 (bs, 3H, NH and NH_2), 10.65 (bs, 1H, triazole NH); cmr (DMSO-d_6): δ, ppm 14.1 (CH_3), 22.2, 26.7, 28.9, 29.0, 29.6, 31.4 (CH_2), 43.0 ($NHCH_2$), 160 (bm, triazole C_3 and C_5) (a mixture of 1*H* and 2*H* tautomeric forms).

The mother liquor was evaporated *in vacuo* to dryness and triturated with ether to yield after filtration 3.4 g of crude 5-amino-2,7-bis(*n*-octylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]-triazine (**6/7**, Q = *n*-octylamino), mp 194-197°. After recrystallisation from 2-propanol 3.0 g (4 %) of pure **6/7** was obtained mp 196-196.5° (for its spectral data see Table II).

N-Cyano-*N'*-(2-dimethylaminoethyl)-*S*-methylisothiourea (**3/8**, NR^1R^2 = 2-dimethylaminoethylamino).

To a suspension of 14.62 g (0.1 mole) of dimethyl *N*-cyanimidodithiocarbonate (**1**) (Fluka) in 150 ml of diethyl ether the solution of 9.70 g (0.11 mole) of *N*,*N*-dimethylaminoethylamine (Fluka) in 50 ml of diethyl ether was added dropwise with stirring

at room temperature within 20 minutes. (The methylthiol liberated was trapped in sodium hydroxide solution.) The thick suspension obtained was stirred at room temperature overnight. The crystals precipitated were isolated by filtration and washed with diethyl ether to yield 17.2 g (92 %) of *N*-cyano-*N'*-(2-dimethylaminoethyl)-*S*-methylisothiourea (**3/8**, NR^1R^2 = 2-dimethylaminoethylamino), mp 98-99°. An analytical sample was recrystallised from a mixture of diisopropyl ether and ethyl acetate, mp 99.5-100.5°; ir ν (CN): 2173 cm^{-1}; ms (ES): 187 (MH^+); pmr (deuteriochloroform): δ, ppm 2.26 (s, 6H, NCH_3), 2.52 (t, J = 6.2 Hz, 2H, NCH_2), 2.57 (s, 3H, SCH_3), 3.45 (bs, 2H, $NHCH_2$), 7.0 (bs, 1H, NH); cmr (deuteriochloroform): δ, ppm 14.1 (SCH_3), 40.4 ($NHCH_2$), 44.8 (NCH_3), 56.2 (NCH_2), 115.9 (CN), 169.7 (C=N).

Anal. Calcd. for $C_7H_{14}N_4S$ (MW 186.28): C, 45.14; H, 7.58; N, 30.08; S, 17.21. Found: C, 45.08; H, 7.64; N, 29.94; S, 17.30.

5-Amino-3-(2-dimethylaminoethyl)amino-1*H*-1,2,4-triazole (**5/8**, Q = 2-dimethylaminoethylamino).

To a stirred suspension of 9.32 g (0.05 mole) of *N*-cyano-*N'*-(2-dimethylaminoethyl)-*S*-methylisothiourea (**3/8**, NR^1R^2 = 2-dimethylaminoethylamino) in 50 ml of acetonitrile 2.40 g (0.075 mole) of anhydrous hydrazine was added and the reaction mixture stirred at room temperature for 27 hours (during the reaction methylthiol was evolved that was trapped in sodium hydroxyde solution). The crystals that precipitated were isolated by filtration and washed with acetonitrile to yield 8.3 g (97 %) of 5-amino-3-(2-dimethylaminoethyl)amino-1*H*-1,2,4-triazole (**5/8**, Q = 2-dimethylaminoethylamino), mp 159-160°. An analytical sample was recrystallised from a mixture of CH_3CN and EtOH, mp 159.5-161°; ms (ES): 171 (MH^+); pmr (DMSO-d_6): δ, ppm 2.14 (s, 6H, NCH_3), 2.35 (t, J = 6.7 Hz, 2H, NCH_2), 3.09 (q, J = 6.7 Hz, 2H, $NHCH_2$), 4.5-6.5 (bs, 3H, NH and NH_2), 10.75 (bs, 1H, triazole NH); cmr (DMSO-d_6): δ, ppm 41.0 ($NHCH_2$), 45.4 (NCH_3), 58.7 (NCH_2), 160 (bm, triazole C_3 and C_5) (a mixture of 1*H* and 2*H* tautomeric forms).

Anal. Calcd. for $C_6H_{14}N_6$ (MW 170.22): C, 42.34; H, 8.28; N, 49.37. Found: C, 42.24; H, 8.42; N, 49.28.

N-Cyano-*N'*-(3-dimethylaminopropyl)-*S*-methylisothiourea (**3/9**, NR^1R^2 = 3-dimethylaminopropylamino).

To a suspension of 14.62 g (0.1 mole) of dimethyl *N*-cyanimidodithiocarbonate (**1**) (Fluka) in 150 ml of diethyl ether the solution of 11.24 g (0.11 mole) of *N,N*-dimethyl-1,3-propanediamine (Fluka) in 50 ml of diethyl ether was added dropwise with stirring at room temperature within 20 minutes. (The methylthiol liberated was trapped in sodium hydroxide solution.) The thick suspension obtained was stirred at room temperature overnight. The precipitated crystals were isolated by filtration and washed with diethyl ether to yield 18.1 g (90 %) of *N*-cyano-*N'*-(3-dimethylaminopropyl)-*S*-methylisothiourea (**3/9**, NR^1R^2 = 3-dimethylaminopropylamino), mp 90-91°. An analytical sample was recrystallised from a mixture of diisopropyl ether and ethyl acetate, mp 90-91°; ir ν (CN): 2176 cm^{-1}; ms (ES): 201 (MH^+); pmr (deuteriochloroform): δ, ppm 1.73 (qui, J = 5.5 Hz, 2H, CCH_2C), 2.28 (s, 6H, NCH_3), 2.44 (s, 3H, SCH_3), 2.54 (t, J = 5.4 Hz, 2H, NCH_2), 3.50 (t, 2H, $NHCH_2$), 9.4 (bs, 1H, NH); cmr (deuteriochloroform): δ, ppm 13.4 (SCH_3), 23.6 (CCH_2C), 44.5 ($NHCH_2$), 44.5 (NCH_3), 58.4 (NCH_2), 115.5 (CN), 169.7 (C=N).

Anal. Calcd. For $C_8H_{16}N_4S$ (MW 200.31): C, 47.97; H, 8.05; N, 27.97; S, 16.01. Found: C, 48.11; H, 8.30; N, 27.86; S, 15.99.

5-Amino-3-(3-dimethylaminopropyl)amino-1*H*-1,2,4-triazole (**5/9**, Q = 3-dimethylaminopropylamino).

To a stirred suspension of 16.02 g (0.08 mole) of *N*-cyano-*N'*-(3-dimethylaminopropyl)-*S*-methylisothiourea (**3/9**, NR^1R^2 = 3-dimethylaminopropylamino) in 80 ml of acetonitrile 3.84 g (0.12 mole) of anhydrous hydrazine was added and the reaction mixture stirred at room temperature for 23 hours (during the reaction methylthiol was evolved that was trapped in sodium hydroxyde solution). The crystals that precipitated were isolated by filtration and washed with acetonitrile to yield 12.7 g (86 %) of 5-amino-3-(3-dimethylaminopropyl)amino-1*H*-1,2,4-triazole (**5/9**, Q = 3-dimethylaminopropylamino), mp 107-109°. An analytical sample was recrystallised from CH_3CN, mp 105.5-107.5°; ms (ES): 185 (MH^+); pmr (DMSO-d_6): δ, ppm 1.62 (qui, J = 7.0 Hz, 2H, CCH_2C), 2.13 (s, 6H, NCH_3), 2.24 (t, J = 7.0 Hz, 2H, NCH_2), 3.04 (q, J = 6.5 Hz, 2H, $NHCH_2$), 5.3 (bs, 2H, NH_2), 5.6 (bs, 1H, NH), 10.8 (bs, 1H, triazole NH); cmr (DMSO-d_6): δ, ppm 27.4 (CCH_2C), 41.4 ($NHCH_2$), 45.1 (NCH_3), 57.1 (NCH_2), 158.4 (C-3), 160.0 (C-5)

Anal. Calcd. For $C_7H_{16}N_6$ (MW 184.25): C, 45.63; H, 8.75; N, 45.61. Found: C, 45.55; H, 8.88; N, 45.61.

General Method for the Direct Synthesis of Derivatives **6**

A solution of 0.01 mole of the appropriate isothiourea derivative **3** and 0.01 mole of the appropriate 5-amino-1,2,4-triazole **5** in 10 ml of *n*-butanol was refluxed for the time given in Table I. After cooling the product that precipitated was isolated by filtration and washed with acetonitrile. For preparative conditions and physical data of products see Table I, for their spectral data see Table II.

5-Amino-7-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*]-[1,3,5]triazine (**6/4**, Q = methylthio) and 7-Amino-5-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**7/4**, Q = methylthio) – in *n*-Butanol.

A mixture of 9.76 g (0.075 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**5/4**, Q = methylthio) [16] and 10.75 g (0.075 mole) of *N*-cyano-*N'*-ethyl-*S*-methylisothiourea (**3/5,** NR^1R^2 = ethylamino) [12] and 75 ml of *n*-butanol was refluxed with stirring for 96 hours. After cooling the product that crystallised was isolated by filtration and washed with acetonitrile to yield 6.6 g (39 %) of raw 5-amino-7-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/4**, Q = methylthio) (mp 222-231°), that after recrystallisation from 160 ml of a 1:1 mixture of acetonitrile and ethanol yielded 5.4 g (32 %) of pure **6/4** (Table I), mp 229-231°. (For its spectral data see Table II).

The combined mother liquors were evaporated *in vacuo* to dryness and the residue was twice dry column flash chromatographed on Kieselgel 60 H (Merck). The elution with dichloromethane resulted in 2.6 g (24 %) of unreacted isothiourea **3/5** (NR^1R^2 = ethylamino). Continuing the chromatography with 100:1 and 100:2 mixtures of dichloromethane and methanol resulted in a mixture of **6/4** (Q = methylthio) and **7/4** (Q = methylthio), that was chromatographed again using a 1:1 mixture of cyclohexane and ethyl acetate. This way 0.64 g (3.8 %) of 7-amino-5-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*]-[1,3,5]triazine (**7/4**) was obtained that after recrystallisation from acetonitrile melted at 203-205°; ms (EI): 225 (M^+); pmr (DMSO-d_6): δ, ppm 1.09 (t, J = 7.0 Hz, 3H, CCH_3), 2.56 (s, 3H,

SCH_3), 3.26 (qui, J = 6.4 Hz , 2H, $NHCH_2$), 7.35 (t, J = 5.5 Hz, 1H, NH), 7.95 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 13.35 (SCH_3), 14.7 (CH_3), 35.5 ($NHCH_2$), 149.4 (C-7), 159.4 (C-3a), 161.0 (C-5), 165.2 (C-2).

Anal. Calcd. for $C_7H_{11}N_7S$ (MW 225.28): C, 37.32; H, 4.92; N, 43.52; S, 14.23. Found: C, 37.30; H, 5.03; N, 43.48; S, 14.19.

Continuing the chromatography with pure ethyl acetate a second 1.26 g (7.5 %) crop of **6/4** (Q = methylthio) was obtained, mp 226-228° (acetonitrile/ethanol).

5-Amino-7-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/4**, Q = methylthio) and 7-Amino-5-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**7/4**, Q = methylthio) – in Melt.

A mixture of 3.90 g (0.03 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**5/4**, Q = methylthio) [16] and 4.32 g (0.03 mole) of *N*-cyano-*N'*-ethyl-*S*-methyl-isothiourea (**3/5**, NR^1R^2 = ethylamino) [12] was melted at 150° for 6 hours. After cooling 30 ml of acetonitrile was added to the melt obtained, the product that crystallised was isolated by filtration and washed with acetonitrile to yield 4.75 g of raw 5-amino-7-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/4**, Q = methylthio) that was dry column flash chromatographed on Kieselgel 60 H (Merck), eluent a 97:3 mixture of dichloromethane and methanol. After collecting and evaporating the appropriate fractions and triturating the residue with acetonitrile 4.30 g (63.5 %) of pure 5-amino-7-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/4**, Q = methylthio) was obtained, mp 222-227° that was identical (ir, pmr) with that **6/4** obtained above.

Evaporating the mother liquor of raw **6/4** to dryness and dry column flash chromatography of the residue on Kieselgel 60 H using the method described in the previous experiment 0.25 g (3.7 %) of 7-amino-5-ethylamino-2-methylthio-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**7/4**, Q = methylthio) was obtained that after recrystallisation from acetonitrile melted at 203-205°. The product is identical (ir, pmr) with that of **7/4** obtained in the previous experiment.

Continuing the chromatography with pure ethyl acetate a second 0.38 g (5.5 %) crop of **6/4** (Q = methylthio) was obtained.

5-Amino-2,7-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/5**, Q = ethylamino) and 7-Amino-2,5-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**7/5**, Q = ethylamino) – in Melt.

A mixture of 2.54 g (0.02 mole) of 5-amino-3-ethylamino-1*H*-1,2,4-triazole (**5/5**, Q = ethylamino) and 2.86 g (0.02 mole) of *N*-cyano-*N'*-ethyl-*S*-methyl-isothiourea (**3/5**, NR^1R^2 = ethylamino) [12] was melted at 160° for 1 hour. After cooling 20 ml of acetonitrile was added to the melt obtained, the product that crystallised was isolated by filtration and washed with acetonitrile to yield 3.17 g of raw 5-amino-2,7-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/5**, Q = ethylamino) that was dry column flash chromatographed on Kieselgel 60 H (Merck), eluent a 95:5 mixture of dichloromethane and methanol. After collecting and evaporating the appropriate fractions 2.32 g (52 %) of pure 5-amino-2,7-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**6/5**, Q = ethylamino) was obtained, mp 270-281° that was identical (ir, pmr) with that of **6/5** obtained above.

Evaporating the mother liquor of raw **6/5** to dryness and dry column flash chromatography of the residue on Kieselgel 60 H using ethyl acetate as eluent 0.08 g (1.8 %) of 7-amino-2,5-bis(ethylamino)-1,2,4-triazolo[1,5-*a*][1,3,5]triazine (**7/5**, Q = ethylamino) was obtained that after washing with ether melted at 202-205°. ms (EI): 222 (M^+); pmr (DMSO-d_6): δ, ppm 1.09 (t, J = 7.2 Hz, 3H, CCH_3-5), 1.13 (t, J = 7.1 Hz, 3H, CCH_3-2), 3.26 (m, 4H, $NHCH_2$-2,5), 6.29 (t, J = 5.7 Hz, 1H, NH-2), 7.03 (t, 1H, NH-5), 7.44 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 14.9 (CH_3-5), 15.2 (CH_3-2), 35.4 ($NHCH_2$-5), 36.9 ($NHCH_2$-2), 149.4 (C-7), 158.6 (C-3a), 160.9 (C-5), 165.6 (C-2).

Anal. Calcd. for $C_8H_{14}N_8$ (MW 222.25): C, 43.23; H, 6.35; N, 50.42. Found: C, 43.30; H, 6.45; N, 50.38.

Crystal Structure Analysis of **6/5** [7].

Crystal data: C_8 H_{14} N_8, Fwt.: 222.27, monoclinic, space group $P\ 2_1/n$, a = 7.240(2)Å, b = 13.315(2)Å, c = 11.009(1)Å, β = 90.42(1)°, V = 1061.3(3) $Å^3$, T = 293(2)K, Z = 4, F(000) = 472, Dx =1.391Mg/m^3, μ = 0.097mm^{-1}. crystal size: 0.40 x 0.22 x 0.10 mm. Intensities of 4677 reflections (4407 unique, 2191 > 2σ(I)) were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation, λ = 0.71070 Å) at 293(2)K in the range 2.40° ≤ θ ≤ 34.22° using ω/θ scans. No absorption correction was applied. The structure was solved by direct methods and refined in anisotropic approximation by full-matrix least-squares refinement on F^2 for all non-hydrogen atoms to R1 = 0.075 and wR2 = 0.234 for I>2σ(I) (R1 = 0.1836 and wR2 = 0.312 for all intensity data, goodness-of-fit = 1.007; the maximum and mean shift/esd 0.136 and 0.005). Number of parameters = 147. The maximum and minimum residual electron density in the final difference map was 0.534 and -0.438e/ $Å^3$. Hydrogen atomic positions were located from assumed geometries, but were not refined.

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[12] Compound **3/5** (NR^1R^2 = ethylamino) was synthesised according to [2]. Lit. [11] mp 160°, our mp 163-164° (2-PrOH); ms (EI): 143 (M^+); ir: ν (CN): 2171 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.10 (t, J = 7.1 Hz, 3H, CH_3), 2.56 (s, 3H, SCH_3), 3.31 (q, J = 7.1 Hz, 2H, CH_2), 8.34 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 13.6 (SCH_3), 14.0 (CH_3), 38.2 (CH_2), 115.6 (CN), 169.6 (C=N).

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[14] We have repeated the experiment described in [11] leading to **5/5** (Q = ethylamino) but obtained for **5/5** a mp 155-156° with spectral data: ms (EI): 127 (M^+); pmr (DMSO-d_6): δ, ppm 1.07 (t, J = 7.1 Hz, 3H, CH_3), 3.04 (qi, J = 6.5 Hz, 2H, CH_2), 5.3 (bs, 2H, NH_2), 5.6 (bs, 1H, NH), 10.8 (bs, 1H, triazole NH); cmr (DMSO-d_6): δ, ppm 15.4 (CH_3), 37.6 (CH_2), 156.1 (C-3), 162.4 (C-5).

[15] Compound **3/7** (NR^1R^2 = *n*-octylamino) was prepared according to [2], mp 115-116° (2-PrOH); ms (ES): 228 (MH^+); ir: ν (CN): 2170 cm^{-1}; pmr (DMSO-d_6): δ, ppm 0.86 (t, J = 6.5 Hz, 3H, CH_3), 1.25 (bs, 10H, CH_2-3',4',5',6',7'), 1.51 (qui, J = 6.5 Hz, 2H, CH_2-2'), 2.56 (s, 3H, SCH_3), 3.26 (t, J = 7.0 Hz, 2H, $NHCH_2$), 8.34 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 14.05 (CH_3), 14.17 (SCH_3), 22.2, 26.3, 28.2, 28.72, 28.74, 31.4 (CH_2), 43.3 ($NHCH_2$), 116.1 (CN), 169.7 (C=N).

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