On Triazoles. XXIX [1]. The Reaction of Triazolyl Thiohydrazides with Isocyanates and Isothiocyanates

József Reiter* and József Barkóczy

EGIS Pharmaceuticals Ltd., H-1475 Budapest,
P.O. Box 100, Hungary

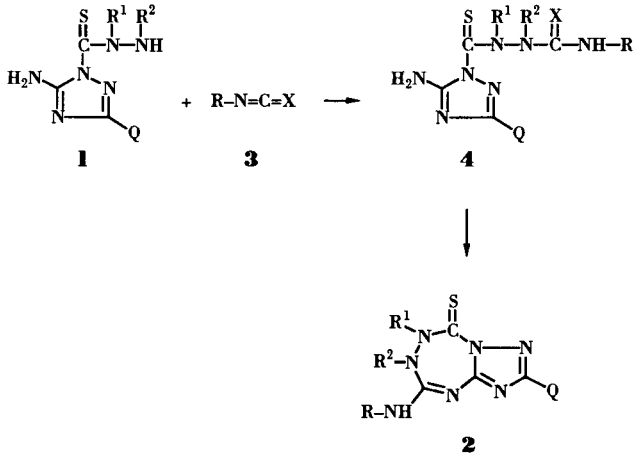
Received June 30, 1992

Different *N*-methylsubstituted, *N'*-methylsubstituted and *N,N'*-unsubstituted triazol-1-ylcarbothiohydrazides were reacted with isocyanates and isothiocyanates to yield the corresponding carbamoyl and thiocarbamoyl derivatives **4**. The thiocarbamoyl derivatives could be cyclised by heating in dimethylformamide or 10% sodium hydroxide solution, reacting them with dicyclohexylcarbodiimide or thier alkylation to the corresponding 1,3,4-thiadiazoles **12** and **16**, and derivatives **5** formed by splitting the triazole moiety. Cleaved derivatives **9** and **11** were also formed in the reaction of thiocarbamoyl derivatives **4** with carbon disulfide in the absence or presence of methyl iodide, respectively. Spectroscopic evidence is given for the structure of products obtained.

J. Heterocyclic Chem., **30**, 333 (1993).

In the previous paper of this series [1] we have reported on the synthesis of different 1,2,4-triazolylthiohydrazide derivatives, among others the **1** (R^1 = methyl, R^2 = H), **1** (R^1 = H, R^2 = methyl) and **1** (R^1 = R^2 = H) type ones. They were reacted with isocyanates (**3**, X = O) and isothiocyanates (**3**, X = S) expecting the formation of the corresponding carbamoyl and thiocarbamoyl derivatives **4** (X = O and S, respectively) that were hoped to ring close to the corresponding [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepines (**2**) (Scheme 1).

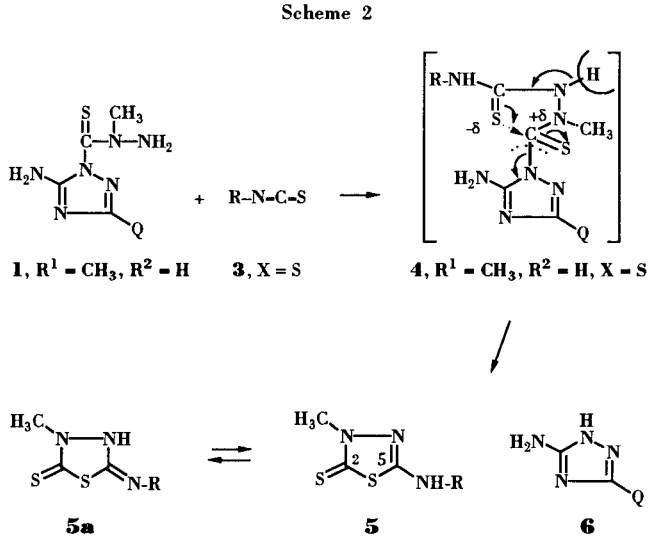
Scheme 1



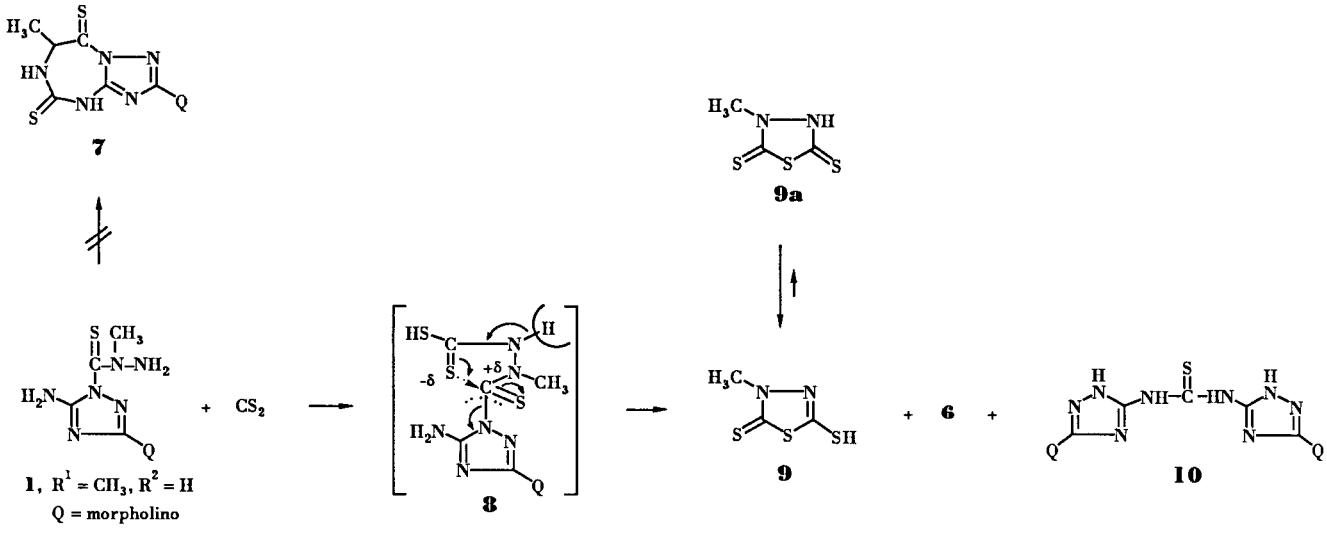
The reaction of **1** (R^1 = methyl, R^2 = H, Q = methylthio and morpholino, respectively) with phenyl isocyanate (**3**, X = O, R = phenyl) afforded the expected carbamoyl derivatives **4** (X = O, R = phenyl, R^1 = methyl, R^2 = H, Q = methylthio and morpholino, respectively). However, attempts to their cyclisation to the corresponding **2** type [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine derivatives (**2**) failed.

Unexpectedly, from the reaction mixtures of **1** (R^1 = methyl, R^2 = H, Q = methylthio and morpholino, respectively) and butyl or phenyl isothiocyanate (**3**, X = S, R = *n*-butyl and phenyl, respectively) instead of the corresponding thiocarbamoyl derivatives **4** (X = S, R^1 = methyl, R^2 = H, Q = methylthio and morpholino, R = *n*-butyl and phenyl, respectively) 2,3-dihydro-3-methyl-5-(*n*-butylamino)-1,3,4-thiadiazole-2-thione (**5**, R = *n*-butyl) and 2,3,4,5-tetrahydro-3-methyl-5-phenylimino-1,3,4-thiadiazole-2-thione (**5a**, R = phenyl), respectively, were isolated besides the known [2,3] 5-amino-3-(methylthio and morpholino)-1*H*-1,2,4-triazoles (**6**, Q = methylthio and morpholino, respectively) (Scheme 2). This may be explained by a nucleophilic attack of the negatively charged sulfur atom of the newly constructed thiocarbamoyl moiety of the unstable intermediate **4** on the carbon atom of the thiohydrazide moiety to yield after cleavage of the triazole ring the corresponding derivatives **5** and **5a**, respectively.

Scheme 2



Scheme 3

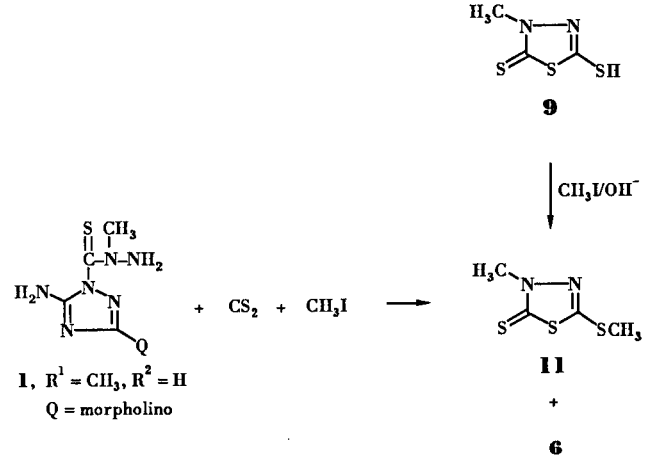


The tautomeric form **5** of the *n*-butyl derivative proves the primary coupling to be between the exocyclic NH group and the R = butyl moiety attached shown in the pmr (see Experimental). This is in accordance with a previous observation [4] that the "exo" benzylsubstituted 2-aminothiazoles exist in the **5** type "amino" tautomeric form.

However, the corresponding phenyl derivative should exist at least in DMSO-d_6 solution in the tautomeric form **5a** (R = phenyl), as shown by its very different NH chemical shift from that of **5** (R = *n*-butyl) in the pmr (δ NH = 10.2 s and 7.69 t, respectively) and the unusually low chemical shift of the *para*-phenyl carbon atom (δ *p*-PhC = 122.2 ppm) in excellent agreement with that of observed previously [5] for the 2-(2,6-dimethylphenyl)iminothiazolidine (δ *p*-PhC = 122.6 ppm).

A similar cleavage of the triazole moiety was observed when derivative **1** (R^1 = methyl, R^2 = H, X = S, Q = morpholino) was reacted with carbon disulfide either alone to yield **9** (Scheme 3) or in the presence of methyl iodide to yield **11** (Scheme 4), respectively. This reaction could be again easily explained by assuming a nucleophilic attack of the sulfur atom of the intermediate **8** on the carbon atom of the thiohydrazide moiety to yield - after cleavage of the corresponding triazole derivative **6** - the thiadiazolidine derivative **9**, which is followed in case of methyl iodide present by the *S*-alkylation to yield **11** (Schemes 3 and 4). The by-product of the former reaction is the bis(1,2,4-triazolylthiourea) derivative **10** formed most probably from the cleaved triazole **6** and carbon disulfide present. As expected derivative **11** could by easily prepared by methylation of the isolated **9** as well (Scheme 4).

Scheme 4

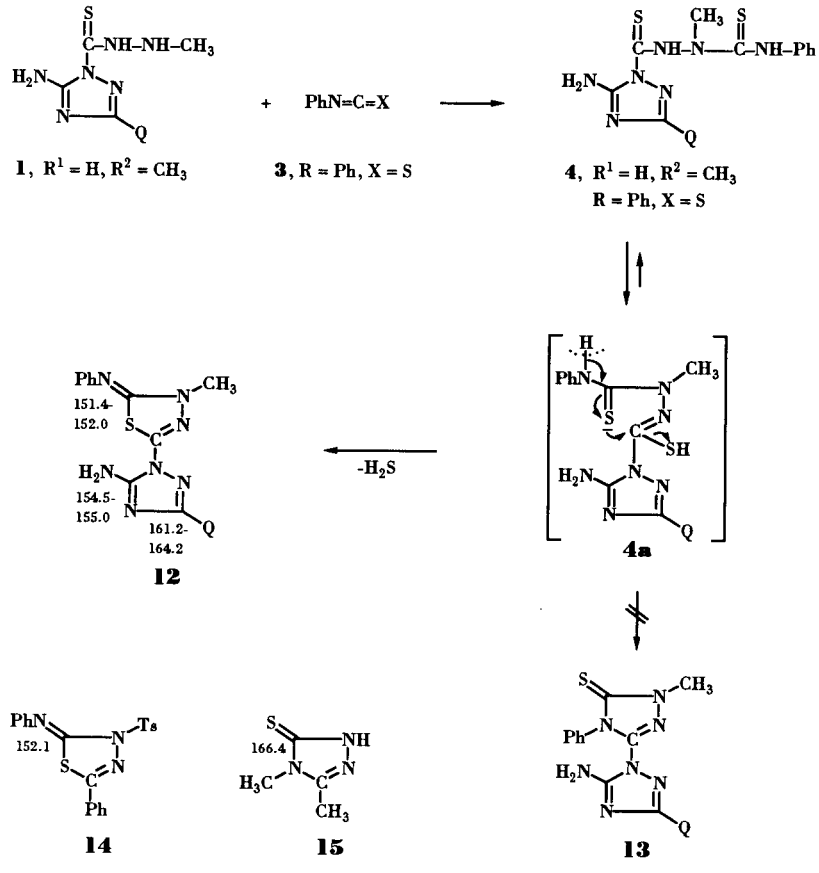


Derivative **9** may again exist in the tautomeric form **9a**. However, the close analogy of the chemical shifts of the triazole carbon atoms of derivatives **9** and **11** (δ C-2 = 153.1 and 156.0, respectively; δ C-5 = 186.5 and 185.0 ppm, respectively) supports the thiol form **9** in DMSO-d_6 solution.

The reaction of the isomeric **1** (R^1 = H, R^2 = CH_3, Q = methylthio, morpholino and dimethylamino, respectively) with phenyl isothiocyanate (**3**, R = phenyl, X = S) afforded at room temperature the expected phenylthiocarbamoyl derivatives **4** (R^1 = H, R^2 = CH_3, R = phenyl, Q = methylthio, morpholino and dimethylamino, respectively) (Scheme 5). The thermally unstable derivatives **4** (R^1 = H, R^2 = CH_3, R = phenyl, Q = methylthio, morpholino and dimethylamino, respectively) could by easily cyclised - probably through their tautomeric form **4a** - to the thiadiazoles **12** (Q = methylthio, morpholino and dimethylamino, respectively) by their short heating in dimethylformamide (Scheme 5).

It should be mentioned that the loss of hydrogen sulfide from derivatives **4** (R^1 = H, R^2 = CH_3, R = Ph, X = S)

Scheme 5



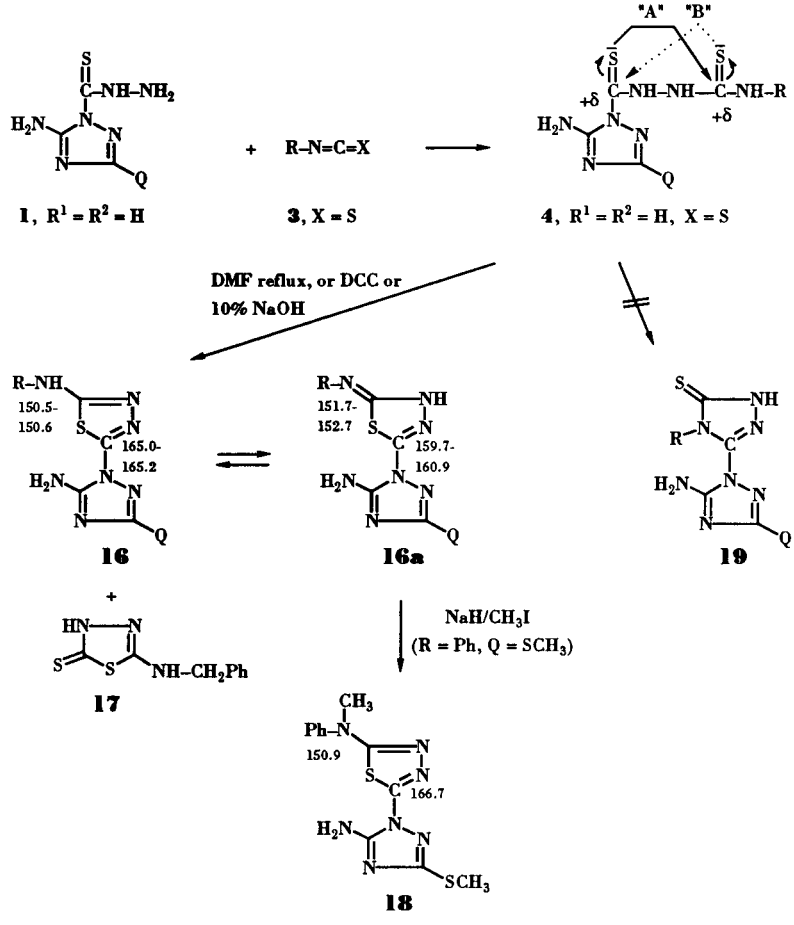
may - in principal - also lead to the formation of derivatives **13**, thus the structure of derivatives **12** formed had to be confirmed. The chemical shifts of the triazole carbon atoms 3′ and 5′ of derivatives **12** (161.2-164.2 and 154.5-155.0 ppm, respectively) were in accordance with that of expected [1,6] confirming that during the reaction no isomerisation of the carbothiohydrazide moiety to any of positions 2 or 4 of the triazole ring occurred [1]. The decision between structures **12** and **13** made possible the comparison of the chemical shifts of the thiadiazole carbon atoms 5 of derivatives **12** (δ C-5 = 151.4-152.0 ppm) with those of the corresponding carbon atoms of model compounds **14** [7] and **15** [8] (δ C-5 = 152.1 and 166.4 ppm, respectively) (Scheme 5) to prove structure **12** unequivocally.

The reaction of the "non alkylated" carbothiohydrazides **1** (R^1 = R^2 = H, Q = methylthio, morpholino and dimethylamino, respectively) provided at room temperature in methanol or dimethylformamide as solvent led again to the thermally unstable thiocarbamoyl derivatives **4** (R^1 = R^2 = H, X = S, R = ethyl, benzyl and phenyl, Q = methylthio, morpholino, and dimethylamino, respectively) (Scheme 6). These were cyclised either in boiling dimethylformamide, or by reaction with dicyclohexylcarbodiimide, or by heating them in 10% sodium hydroxide to the corresponding thiadiazoles **16**.

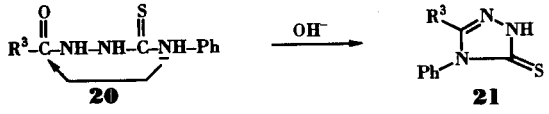
Derivatives **16** may also exist in the tautomeric form **16a** (Scheme 6). The 5-alkylamino tautomeric structure **16** of derivatives (R = ethyl and benzyl, respectively) in DMSO-d_6 solution corroborate the primary coupling between the NH and R (ethyl and benzyl) groups in the pmr [see: **16** (R = ethyl): δ CH_2CH_3 = 3.30 m, δ NH = 7.75 t; **16** (R = benzyl): δ CH_2Ph = 4.49 d, δ NH = 8.26 t]. However, derivatives **16** (R = phenyl) have to exist in DMSO-d_6 solution in the 5-imino tautomeric form **16a** as proved by their different NH proton shifts (δ NH = 10.2, 10.2 and 10.3 ppm, respectively) appearing as a broad singlet and the downfield shift of the para-phenyl carbon atoms (δ *p*-PhC = 121.9, 121.9 and 123.9 ppm, respectively) [5] that changes to the "normal" value after *N*-methylation to **18** (δ *p*-PhC = 127.1 ppm).

It should be mentioned that in contrast to the known [9,10,11] ring closure of acyl thiosemicarbazides **20** under basic conditions to yield triazolylthiones **21** (Scheme 7) we did not observe during the cyclisation of derivatives **4** (R^1 = R^2 = H, X = S) in 10% sodium hydroxide solution the

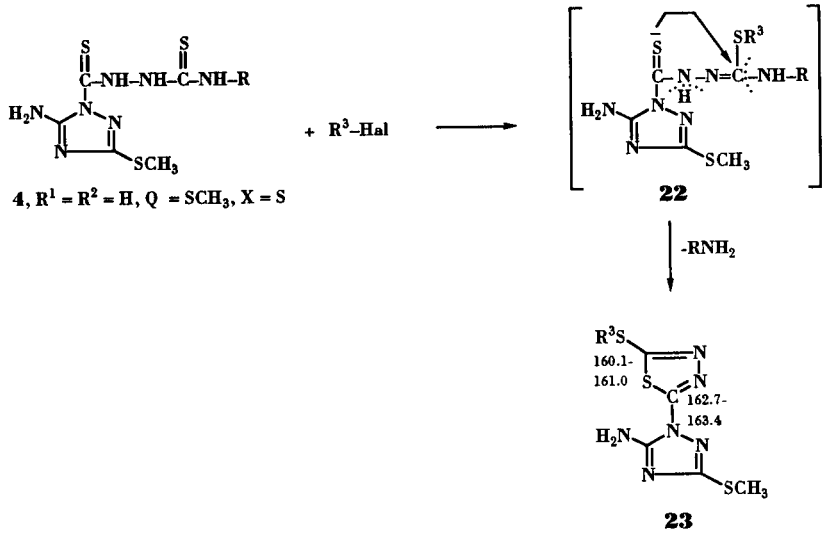
Scheme 6



Scheme 7



Scheme 8



formation of the corresponding triazolylthione derivatives **19** (Scheme 6).

The alkylation of the "non alkylated" derivatives **4** (R^1 = R^2 = H, R = ethyl, benzyl and phenyl, Q = methylthio) with methyl iodide and benzyl bromide afforded either in methanol or dimethylformamide the corresponding 5-alkylthiothiadiazole derivatives **23** (Scheme 8). Their structure was corroborated by the analogy of the chemical shifts of their triazole 3′ and 5′ carbon atoms as well as the thiadiazole carbon atom 2 with those of derivatives **16** and **18** (δ C-3′ = 161.2-163.0 and 160.8-164.4 ppm, respectively; δ C-5′ = 154.9-155.0 and 154.5-155.1 ppm, respectively; δ C-2 = 162.7-163.4 and 165.0-166.7 ppm, respectively).

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.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N*′-phenylcarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = O).

A mixture of 2.04 g (0.01 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, R^1 = R^2 = H, Q = methylthio) [1], 2.4 g (0.02 mole) of phenyl isocyanate (**3**, R = phenyl, X = O) and 50 ml of methanol was stirred at room temperature for 16 hours. The crystals which precipitated were filtered off and washed thoroughly with methanol to yield 2.91 g (90%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N*′-phenylcarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = O), mp 178-180°; ir: ν NH_2 = 3320 and 3265 cm^{-1}, ν C=O = 1689 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.59 (s, 3H, SCH_3), 7.01 [dt (J = 6.5 and 0.8 Hz), 1H, *p*-PhH], 7.30 (t, 2H, *m*-PhH), 7.50 [dd (J = 8.5 and 0.8 Hz), 2H, *o*-PhH], 8.4 (bs, 2H, NH_2), 8.65 (s, 1H, NH), 9.0 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3), 118.7 (*o*-PhC), 122.8 (*p*-PhC), 128.7 (*m*-PhC), 139.4 (*s*-PhC), 154.1 (C=O), 157.9 (C-5), 160.5 (C-3), 174.7 (C=S).

Anal. Calcd. for $C_{11}H_{13}N_7OS_2$ (MW. 323.39): C, 40.85; H, 4.05; N, 30.32; S, 19.83. Found: C, 41.02; H, 4.20; N, 30.28; S, 19.80.

1-(5-Amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methyl-*N*′-phenylcarbamoylcarbothiohydrazide (**4**, R^1 = methyl, R^2 = H, R = phenyl, Q = morpholino, X = O).

A mixture of 1.0 g (0.0039 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = morpholino) [1], 0.6 g (0.005 mole) of phenyl isocyanate (**3**, R = phenyl, X = O) and 60 ml of benzene was refluxed with stirring for 8 hours. After cooling the crystals which precipitated were filtered off to yield 1.35 g (92%) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methyl-*N*′-phenylcarbamoylcarbothiohydrazide (**4**, R^1 = methyl, R^2 = H, R = phenyl, Q = morpholino, X = O), that after recrystallization from acetonitrile melted at 168-170°; ir: ν NH_2 = 3380 and 3305 cm^{-1}, ν C=O = 1661 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.22 (t, 4H, NCH_2), 3.54 (b, 7H, NCH_3 + OCH_2), 7.00 (t, 1H, *p*-PhH), 7.28 (t, 2H, *m*-PhH), 7.42 (d, 2H, *o*-PhH), 7.56 (bs, 2H, NH_2), 9.11 (s, 1H, NH), 9.16 (s, 1H, NH); cmr (DMSO-d_6): δ, ppm 44.8 (NCH_3), 45.6 (NCH_2), 65.5 (OCH_2), 118.4 (*o*-PhC), 122.2 (*p*-PhC), 128.7 (*m*-PhC), 139.1 (*s*-PhC), 153.5 (C=O), 157.7 (C-5), 161.1 (C-3), 178.2 (C=S).

Anal. Calcd. for $C_{15}H_{20}N_8O_2S$ (MW. 376.44): C, 47.86; H, 5.36; N, 29.77; S, 8.52. Found: C, 47.80; H, 5.40; N, 29.68; S, 8.48.

2-(*n*-Butylamino)-4-methyl-4,5-dihydro-1,3,4-thiadiazole-5-thione (**5**, R = *n*-butyl).

A mixture of 0.77 g (0.003 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = morpholino) [1], 25 ml of benzene and 0.35 g (0.003 mole) of *n*-butyl isothiocyanate (**3**, R = *n*-butyl, X = S) was refluxed for 5 hours followed by its evaporation *in vacuo* to dryness. The residue was chromatographed on a silica gel column (eluent a 2:1 mixture of benzene and ethyl acetate) to yield after recrystallisation from 2-propanol 0.18 g (30%) of 2-(*n*-butylamino)-4-methyl-4,5-dihydro-1,3,4-thiadiazole-5-thione (**5**, R = *n*-butyl), mp 88-90°; ir: ν C=S = 1263 cm^{-1}; pmr (DMSO-d_6): δ, ppm 0.86 [t (J = 7 Hz), 3H, CH_3], 1.32 [sx (J = 7 Hz), 2H, CH_2-3], 1.5 [qi (J = 7 Hz), 2H, CH_2-2], 3.14 [q (J = 5 Hz), 2H, $NHCH_2$], 3.61 (s, 3H, NCH_3), 7.69 [t (J = 5 Hz), 1H, NH]; cmr (DMSO-d_6): δ, ppm 13.3 (CH_3), 19.3 (CH_2-3), 30.2 (CH_2-2), 38.7 (NCH_3), 43.1 ($NHCH_2$), 156.3 (C-5), 177.2 (C-2).

Anal. Calcd. for $C_7H_{13}N_3S_2$ (MW. 203.32): C, 41.35; H, 6.44; N, 20.67; S, 31.54. Found: C, 41.31; H, 6.55; N, 20.73; S, 31.48.

Continuing the chromatography 0.31 g (61%) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**6**, Q = morpholino) was isolated, mp 165-167° (2-PrOH) {Lit [3] mp 166-167° (2-PrOH)}.

2-(Phenylimino)-4-methyl-2,3,4,5-tetrahydro-1,3,4-thiadiazole-5(3*H*)-thione (**5a**, R = phenyl) from **1** (R^1 = methyl, R^2 = H, Q = morpholino).

A mixture of 2.57 g (0.01 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = morpholino) [1], 30 ml of methanol and 1.4 ml (0.012 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 5 hours. The crystals which precipitated were filtered off and recrystallised from methanol to yield 1.48 g (66%) of 2-(phenylimino)-4-methyl-2,3,4,5-tetrahydro-1,3,4-thiadiazole-5(3*H*)-thione (**5a**, R = phenyl), mp 183-184°; ir: ν C=S = 1265 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.73 (s, 3H, NCH_3), 7.02 [t (J = 7.2 Hz), 1H, *p*-PhH], 7.32 [t (J = 7.5 Hz), 2H, *m*-PhH], 7.43 [d (J = 7.5 Hz), 2H, *o*-PhH], 10.2 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 38.0 (NCH_3), 122.2 (*p*-PhC), 127.6 (*o*-PhC), 128.7 (*m*-PhC), 139.5 (*s*-PhC), 153.1 (C-5), 178.1 (C-2).

Anal. Calcd. for $C_9H_9N_3S_2$ (MW. 223.31): C, 48.41; H, 4.06; N, 18.82; S, 28.71. Found: C, 48.34; H, 4.15; N, 18.78; S, 28.70.

The mother liquor was evaporated to dryness and the residue was crystallised twice from 2-propanol to yield 0.95 g (56%) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**6**, Q = morpholino), mp 166-167° {Lit [3] mp 166-167° (2-PrOH)}.

2-(Phenylimino)-4-methyl-2,3,4,5-tetrahydro-1,3,4-thiadiazole-5(3*H*)-thione (**5a**, R = phenyl) from **1** (R^1 = methyl, R^2 = H, Q = methylthio).

A mixture of 1.09 g (0.005 mole) of 1-(5-amino-3-methylthio-1*H*-

1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = methylthio) [1], 20 ml of benzene and 0.6 ml (0.005 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was refluxed with stirring for 1 hour. After cooling the crystals which precipitated were filtered off and recrystallised from a 2:1 mixture of methanol and water to yield 0.74 g (66%) of 2-(phenylimino)-4-methyl-2,3,4,5-tetrahydro-1,3,4-thiadiazole-5(3*H*)-thione (**5a**, R = phenyl), mp 180-183°, that was identical (ir, mixed mp) with that of **5a** (R = phenyl) obtained above. The mother liquor was evaporated to dryness and the residue was crystallised first from ethyl acetate then from 2-propanol to yield 0.40 g (62%) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**6**, Q = methylthio), mp 135-137° {Lit [2] mp 136-137° (2-PrOH)}.

2-Mercapto-4-methyl-4,5-dihydro-1,3,4-thiadiazole-5-thione (**9**) and 1,3-Bis(3-morpholino-1,2,4-triazole-5-yl)thiourea (**10**).

A mixture of 2.57 g (0.01 mole) 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = morpholino) [1] 12 ml of pyridine and 4 ml of carbon disulfide was refluxed with stirring for 8 hours. After cooling the crystals which precipitated were filtered off and recrystallised from dioxane to yield 0.94 g (49%) of 1,3-bis(3-morpholino-1,2,4-triazole-5-yl)thiourea (**10**, Q = morpholino), mp 269-271° (Lit [12], mp 268-270°).

To the mother liquor 50 ml of water was added, the crystals which precipitated were filtered off and recrystallised from acetonitrile to yield 0.51 g (31%) of 2-mercapto-4-methyl-4,5-dihydro-1,3,4-thiadiazole-5-thione (**9**), mp 106-108°; ir: ν C=S = 1265 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.73 (s, 3H, CH_3); cmr (DMSO-d_6): δ, ppm 37.9 (CH_3), 153.1 (C-2), 186.5 (C-5).

Anal. Calcd. for $C_3H_4N_2S_3$ (MW. 164.26): C, 21.94; H, 2.45; N, 17.05; S, 58.55. Found: C, 22.03; H, 2.63; N, 16.99; S, 58.42.

4-Methyl-2-methylthio-4,5-dihydro-1,3,4-thiadiazole-5-thione (**11**) - By Reaction of **1** (R^1 = methyl, R^2 = H, Q = morpholino) with Carbon Disulfide and Methyl Iodide.

To a solution of 2.57 g (0.01 mole) 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, R^1 = methyl, R^2 = H, Q = morpholino) [1] in 7 ml of dimethylformamide, 4 ml of carbon disulfide and a solution of 0.62 g (0.011 mole) of potassium hydroxide in 3.5 ml of water were successively added with stirring keeping the temperature of the reaction mixture below 5°. The reaction mixture was then stirred at 30° for 2 hours and 0.7 ml (0.011 mole) of methyl iodide was added to it below 20° with stirring and slight cooling. The reaction mixture was then stirred for further 30 minutes, 20 ml of water was added to it, stirred again for 1 hour, the crystals which precipitated were filtered off and recrystallised from 2-propanol to yield 1.16 g (65%) of 4-methyl-2-methylthio-4,5-dihydro-1,3,4-thiadiazole-5-thione (**11**), mp 81-83°; ir: ν C=S = 1260 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.63 (s, 3H, SCH_3), 3.84 (s, 3H, NCH_3); cmr (DMSO-d_6): δ, ppm 15.4 (SCH_3), 38.5 (NCH_3), 156.0 (C-2), 185.0 (C-5).

Anal. Calcd. for $C_4H_6N_2S_3$ (MW. 178.29): C, 26.95; H, 3.39; N, 15.71; S, 53.95. Found: C, 27.02; H, 3.54; N, 15.68; S, 53.87.

The dimethylformamide-water containing mother liquor was evaporated *in vacuo* to dryness and the residue was recrystallised twice from 2-propanol to yield 1.15 g (68%) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**6**, Q = morpholino), mp 165-167° {Lit [3] mp 166-167° (2-PrOH)}.

4-Methyl-2-methylthio-4,5-dihydro-1,3,4-thiadiazole-5-thione (**11**) - By Methylation of **9**.

To the solution of 0.115 g (0.005 mole) of metallic sodium in 10 ml of methanol 0.82 g (0.005 mole) of 2-mercapto-4-methyl-4,5-dihydro-1,3,4-thiadiazole-5-thione (**9**) was added and the solution which was obtained refluxed for 1 hour. After cooling 0.35 ml (0.0055 mole) of methyl iodide was added to the reaction mixture, stirred at room temperature for 2 hours and evaporated *in vacuo* to dryness. The residue was dissolved in a small amount of water and made alkaline (*p*H = 8-9) with 10% sodium hydroxide solution. After standing for 1 hour the crystals which precipitated were filtered off and recrystallised from 2-propanol to yield 0.69 g (78%) of 4-methyl-2-methylthio-4,5-dihydro-1,3,4-thiadiazole-5-thione (**11**), mp 82-83°. The product is identical (ir, mixed mp) with that of **11** obtained in the previous experiment.

1-(5-Amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = morpholino, X = S).

A mixture of 2.57 g (0.01 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**1**, R^1 = H, R^2 = methyl, Q = morpholino) [1], 400 ml of methanol and 1.42 g (1.26 ml = 0.0105 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 4 hours. The crystals which precipitated were filtered off and washed thoroughly with methanol to yield 3.6 g (92%) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = morpholino, X = S), mp 112-115°; pmr (DMSO-d_6): δ, ppm 3.35 (t, 4H, NCH_2), 3.53 (s, 3H, NCH_3), 3.60 (t, 4H, OCH_2), 7.27 (bs, 5H, PhH), 8.4 (bs, 2H, NH_2), 9.7 (bs, 1H, NH), 11.3 (bs, 1H, NH).

Anal. Calcd. for $C_{15}H_{20}N_8OS_2$ (MW. 392.50): C, 45.90; H, 5.14; N, 28.55; S, 16.34. Found: C, 45.88; H, 5.21; N, 28.50; S, 16.36.

2-(5-Amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-4-methyl-1,3,4-thiadiazole (**12**, Q = morpholino).

A solution of 1.00 g (0.0025 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = morpholino, X = S) in 40 ml of a 1:1 mixture of dimethylformamide and water was refluxed for 5 minutes. After cooling the crystals which precipitated were filtered off to yield 0.43 g (48%) of 2-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-4-methyl-1,3,4-thiadiazole (**12**, Q = morpholino), mp 207-208°; ir: ν NH_2 = 3440 and 3315 cm^{-1}; pmr (deuteriochloroform): δ, ppm 3.33 (t, 4H, NCH_2), 3.65 (s, 3H, NCH_3), 3.73 (t, 4H, OCH_2), 5.9 (s, 2H, NH_2), 7.05 [dt (J = 6.5 and 0.8 Hz), 1H, *p*-PhH], 7.08 (dd, 2H, *o*-PhH), 7.34 (t, 2H, *m*-PhH); cmr (deuteriochloroform): δ, ppm 35.9 (NCH_3), 46.2 (NCH_2), 66.4 (OCH_2), 121.0 (*o*-PhC), 123.8 (*p*-PhC), 129.7 (*m*-PhC), 141.6 (*s*-PhC), 151.9 (C-5), 153.4 (C-2), 155.0 (C-5'), 163.7 (C-3'); cmr (DMSO-d_6): δ, ppm 35.8 (NCH_3), 45.7 (NCH_2), 65.6 (OCH_2), 120.1 (*o*-PhC), 123.5 (*p*-PhC), 129.8 (*m*-PhC), 139.8 (*s*-PhC), 151.7 (C-5), 154.1* (C-2), 154.5* (C-5'), 163.6 (C-3').

Anal. Calcd. for $C_{15}H_{18}N_8OS$ (MW. 358.42): C, 50.27; H, 5.06; N, 31.26; S, 8.94. Found: C, 50.30; H, 5.12; N, 31.21; S, 8.90.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = methylthio, X = S).

To a solution of 1.20 g (0.005 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**1**, R^1 = H, R^2 = methyl, Q = methylthio) [1] in 50 ml of dimethylformamide

1.39 g (1.23 ml = 0.0095 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was added and the mixture was stirred at room temperature for 1 hour. To the solution obtained 8 ml of water was added with cooling at 0°. The crystals which precipitated were filtered off and recrystallised from ethyl acetate to yield 1.14 g (59%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = methylthio, X = S), mp 146-149°; pmr (DMSO-d_6): δ, ppm 2.56 (s, 3H, SCH_3), 3.35 (s, 3H, NCH_3), 7.35-7.55 (m, 5H, PhH), 8.4 (bs, 2H, NH_2), 10.2 (bs, 1H, NH), 11.25 (bs, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_7S_3$ (MW. 363.56): C, 40.78; H, 4.28; N, 27.74; S, 27.21. Found: C, 40.82; H, 4.44; N, 27.65; S, 27.30.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4-methyl-4,5-dihydro-1,3,4-thiadiazole (**12**, Q = methylthio).

A solution of 0.35 g (0.001 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = methylthio, X = S) in 1 ml of dimethylformamide was refluxed for 5 minutes. To the still hot solution 2 ml of water was added and allowed to crystallise. After cooling the crystals which precipitated were filtered off to yield 0.28 g (88%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4-methyl-4,5-dihydro-1,3,4-thiadiazole (**12**, Q = methylthio) that after recrystallisation from methanol melted at 219-220°; ir: ν NH_2 = 3435 and 3300 cm^{-1}; ν C=S = 1267 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.48 (s, 3H, SCH_3), 3.68 (s, 3H, NCH_3), 6.3 (bs, 2H, NH_2), 7.04 (d, 2H, *o*-PhH), 7.11 (t, 1H, *p*-PhH), 7.35 (t, 2H, *m*-PhH); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3), 35.8 (NCH_3), 120.6 (*o*-PhC), 123.6 (*p*-PhC), 129.8 (*m*-PhC), 139.0 (*s*-PhC), 151.4 (C-5), 154.2* (C-2), 154.8* (C-5'), 161.2 (C-3').

Anal. Calcd. for $C_{12}H_{13}N_7S_2$ (MW. 319.41): C, 45.13; H, 4.10; N, 30.70; S, 20.07. Found: C, 45.10; H, 4.22; N, 30.65; S, 19.89.

1-(5-Amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = dimethylamino, X = S).

A mixture of 0.43 g (0.002 mole) of 1-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methylcarbothiohydrazide (**1**, R^1 = H, R^2 = methyl, Q = dimethylamino) [1], 80 ml of methanol and 0.34 g (0.0025 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 2 hours. The crystals which precipitated were filtered off and recrystallised from ethyl acetate to yield 0.46 g (66%) of 1-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = dimethylamino, X = S), mp 144-146°; pmr (DMSO-d_6): δ, ppm 2.95 (s, 6H, NCH_3), 3.54 (s, 3H, NCH_3), 7.30 (bs, 5H, PhH), 8.4 (bs, 2H, NH_2), 9.7 (bs, 1H, NH), 11.3 (bs, 1H, NH).

Anal. Calcd. for $C_{13}H_{18}N_8S_2$ (MW. 350.46): C, 44.55; H, 5.18; N, 31.97; S, 18.30. Found: C, 44.63; H, 5.34; N, 32.08; S, 18.21.

2-(5-Amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4-methyl-4,5-dihydro-1,3,4-thiadiazole (**12**, Q = dimethylamino).

A solution of 0.35 g (0.001 mole) of 1-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-methyl-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = H, R^2 = methyl, R = phenyl, Q = dimethylamino, X = S) in 1 ml of dimethylformamide was refluxed for 5 minutes. To the still hot solution 2 ml of water was added and allowed to crystallise. After cooling the crystals which precipitated were filtered off to yield 0.21 g (66%) of 2-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4-methyl-4,5-dihydro-1,3,4-thiadiazole (**12**, Q = dimethylamino) that after recrystallisation from the mixture of dimethylformamide and water melted at 238-240°; ir: ν NH_2 = 3420 and 3310 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.81 (s, 6H, NCH_3), 3.58 (s, 3H, NCH_3), 7.2 (bs, 2H, NH_2), 6.95-7.65 (m, 5H, PhH); cmr (DMSO-d_6): δ, ppm 36.0 (NCH_3), 37.5 (NCH_3), 120.8 (*o*-PhC), 123.6 (*m*-PhC), 129.8 (*p*-PhC), 140.0 (*s*-PhC), 152.0 (C-5), 154.3* (C-2), 155.0* (C-5'), 164.2 (C-3'); ms: M^+ = 316.

Anal. Calcd. for $C_{13}H_{16}N_8S$ (MW. 316.39): C, 49.35; H, 5.10; N, 35.42; S, 10.13. Found: C, 49.32; H, 5.18; N, 35.38; S, 10.17.

1-(5-Amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = morpholino, X = S).

A mixture of 0.97 g (0.004 mole) of 1-(5-amino-3-morpholino-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, R^1 = R^2 = H, Q = morpholino) [1], 25 ml of methanol and 0.54 g (0.004 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 5 hours. The crystals which precipitated were filtered off and washed thoroughly with methanol to yield 0.98 g (65%) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = morpholino, X = S), mp 160-162°; pmr (DMSO-d_6): δ, ppm 3.38 (t, 4H, NCH_2), 3.64 (t, 4H, OCH_2), 7.13-7.55 (m, 5H, PhH), 8.05 (bs, 1H, NH), 8.3 (bs, 2H, NH_2), 8.6 (bs, 1H, NH), 9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{14}H_{18}N_8OS_2$ (MW. 378.47): C, 44.43; H, 4.79; N, 29.61; S, 16.94. Found: C, 44.51; H, 4.96; N, 29.57; S, 17.03.

2-(5-Amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = morpholino, R = phenyl).

A solution of 0.19 g (0.0005 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) in 1 ml of dimethylformamide was refluxed for 5 minutes. To the still hot solution 2 ml of water was added and allowed to crystallise. After cooling the crystals which precipitated were filtered off to yield 0.11 g (57%) of 2-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = morpholino, R = phenyl) that after recrystallisation from the mixture of dimethylformamide and water melted at 303-306°; ir: ν NH_2 = 3400 and 3300 cm^{-1}, ν C=N = 1659, 1589 and 1564 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.25 (t, 4H, NCH_2), 3.67 (t, 4H, OCH_2), 7.35 (bs, 2H, NH_2), 6.99-7.66 (m, 5H, PhH), 10.2 (bs, 1H, NH); cmr (DMSO-d_6): 45.8 (NCH_2), 65.7 (OCH_2), 117.4 (*o*-PhC), 121.9 (*p*-PhC), 129.2 (*m*-PhC), 140.5 (*s*-PhC), 152.7 (C-5), 154.5 (C-5'), 159.8 (C-2), 163.8 (C-3'); ms: M^+ = 344.

Anal. Calcd. for $C_{14}H_{16}N_8OS$ (MW. 344.40): C, 48.83; H, 4.68; N, 32.54; S, 9.31. Found: C, 48.99; H, 4.86; N, 32.50; S, 9.28.

1-(5-Amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = dimethylamino, X = S).

A mixture of 1.02 g (0.005 mole) of 1-(5-amino-3-dimethylamino-1,2,4-triazol-1-yl)-carbothiohydrazide (**1**, R^1 = R^2 = H, Q = dimethylamino) [1], 25 ml of methanol and 0.88 g (0.0065 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 5 hours. The crystals which precipitated were filtered off and washed thoroughly with methanol to yield 0.98 g

(57%) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = dimethylamino, X = S), mp 142-145°; pmr (DMSO-d_6): δ, ppm 2.95 (s, 6H, NCH_3), 7.14-7.60 (m, 5H, PhH), 8.05 (bs, 1H, NH), 8.4 (bs, 2H, NH_2), 8.6 (bs, 1H, NH), 9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{12}H_{16}N_8S_2$ (MW. 336.44): C, 42.84; H, 4.79; N, 33.31; S, 19.06. Found: C, 42.86; H, 4.88; N, 33.18; S, 19.01.

2-(5-Amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = dimethylamino, R = phenyl).

A solution of 0.17 g (0.0005 mole) of 1-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S) in 1 ml of dimethylformamide was refluxed for 5 minutes. To the still hot solution 2 ml of water was added and allowed to crystallise. After cooling the crystals which precipitated were filtered off to yield 0.12 g (79%) of 2-(5-amino-3-dimethylamino-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = dimethylamino, R = phenyl) that after recrystallisation from the mixture of dimethylformamide and water melted at 325-328°; ir: ν NH_2 = 3380 and 3305 cm^{-1}, ν C=N = 1655, 1591 and 1560 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.88 (s, 6H, NCH_3), 7.4 (bs, 2H, NH_2), 6.95-7.65 (m, 5H, PhH), 10.2 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 37.1 (NCH_3), 117.3 (*o*-PhC), 121.9 (*p*-PhC), 129.2 (*m*-PhC), 140.6 (*s*-PhC), 152.7 (C-5), 154.5 (C-5'), 159.7 (C-2), 164.4 (C-3'); ms: M^+ = 302.

Anal. Calcd. for $C_{12}H_{14}N_8S$ (MW. 302.36): C, 47.67; H, 4.67; N, 37.06; S, 10.60. Found: C, 47.48; H, 4.65; N, 36.99; S, 10.51.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S).

A mixture of 0.41 g (0.002 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, R¹ = R² = H, Q = methylthio) [1], 80 ml of methanol and 0.34 g (0.0025 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was stirred at room temperature for 2 hours. The crystals which precipitated were filtered off and recrystallised from ethyl acetate to yield 0.46 g (68%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S), mp 164-166°; pmr (DMSO-d_6): δ, ppm 2.55 (s, 3H, SCH_3), 7.3-7.5 (m, 5H, PhH), 8.0 (bs, 1H, NH), 8.4 (bs, 2H, NH_2), 8.6 (bs, 1H, NH), 9.8 (bs, 1H, NH).

Anal. Calcd. for $C_{11}H_{13}N_7S_3$ (MW. 339.45): C, 38.92; H, 3.86; N, 28.88; S, 28.33. Found: C, 39.04; H, 3.92; N, 28.97; S, 28.35.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S).

To a solution of 0.41 g (0.002 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, R¹ = R² = H, Q = methylthio) in 10 ml of dimethylformamide 0.41 g (0.003 mole) of phenyl isothiocyanate (**3**, R = phenyl, X = S) was added and stirred at room temperature for 16 hours. 20 ml of water was added to the reaction mixture, the crystals which precipitated were filtered off and recrystallised from ethyl acetate to yield 0.44 g (65%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S), mp 162-165°. The product is identical (mixed mp, ir) with that of **4** (R¹ = R² = H, R = phenyl, Q = methylthio, X = S) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl).

A solution of 0.34 g (0.001 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S) in 1 ml of dimethylformamide was refluxed for 5 minutes. To the still hot solution 2 ml of water was added and allowed to crystallise. After cooling the crystals which precipitated were filtered off to yield 0.22 g (72%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl) that after recrystallisation from dioxane melted at 323-325°; ir: ν NH_2 = 3405 and 3300 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.50 (s, 3H, SCH_3), 7.1-7.6 (m, 5H, PhH), 7.5 (s, 2H, NH_2), 10.3 (s, 1H, NH); cmr (DMSO-d_6): δ, ppm 13.3 (SCH_3), 119.3 (*o*-PhC), 123.9 (*p*-PhC), 130.9 (*m*-PhC), 142.1 (*s*-PhC), 151.7 (C-5), 155.0 (C-5'), 160.9* (C-2), 161.4* (C-3').

Anal. Calcd. for $C_{11}H_{11}N_7S_2$ (MW. 305.38): C, 43.26; H, 3.63; N, 32.11; S, 21.00. Found: C, 43.33; H, 3.88; N, 32.14; S, 20.94.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl).

A mixture of 3.39 g (0.01 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S) 75 ml of dry benzene and 3.1 g (0.015 mole) of dicyclohexylcarbodiimide was refluxed for 1 hour. After cooling the crystals which precipitated were filtered off and recrystallised from dioxane to yield 1.98 g (65%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl), mp 322-324°. The product is identical (mixed mp, ir) with that of **16a** (Q = methylthio, R = phenyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl).

A mixture of 3.39 g (0.01 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = phenyl, Q = methylthio, X = S) and 30 ml of 10% sodium hydroxide was stirred at room temperature for 7 days. The crystals which precipitated were filtered off washed with water and recrystallised from dioxane to yield 1.55 g (51%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl), mp 322-325°. The product is identical (mixed mp, ir) with that of **16a** (Q = methylthio, R = phenyl) obtained above.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = benzyl, Q = methylthio, X = S).

A mixture of 4.08 g (0.02 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, R¹ = R² = H, Q = methylthio), 100 ml of methanol and 7.46 g (6.6 ml = 0.05 mole) of benzyl isothiocyanate (**3**, R = benzyl, X = S) was stirred at room temperature for 3 days. The crystals which precipitated were filtered off and recrystallised from acetonitrile to yield 5.33 g (75%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, R¹ = R² = H, R = benzyl, Q = methylthio, X = S), mp 166-169°; pmr (DMSO-d_6):

δ, ppm 2.55 (s, 3H, SCH_3), 4.30 (d, 2H, $NHCH_2$), 7.15-7.55 (m, 5H, PhH), 8.05 (bs, 1H, NH), 8.4 (bs, 2H, NH_2), 8.6 (bs, 1H, NH), 9.6 (t, 1H, NH).

Anal. Calcd. for $C_{12}H_{15}N_7S_3$ (MW. 353.49): C, 40.78; H, 4.28; N, 27.74; S, 27.21. Found: C, 40.66; H, 4.21; N, 27.80; S, 27.23.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl) and 5-Benzylamino-2,3-dihydro-1,3,4-thiadiazole-2(3*H*)-thione (**17**).

A solution of 0.35 g (0.001 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = benzyl, Q = methylthio, X = S) in 2 ml of dimethylformamide was refluxed for 5 minutes, then 2 ml of water was added to the still hot solution. After cooling the crystals which precipitated were filtered off to yield after recrystallisation from ethanol 0.17 g (53%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl), mp 242-244°; ir: ν NH_2 = 3390 and 3300 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.47 (s, 3H, SCH_3), 4.49 [d (J = 5.7 Hz), 2H, CH_2Ph], 7.3 (s, 2H, NH_2), 7.25-7.40 (m, 5H, PhH), 8.26 (t, 1H, NH); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3), 49.5 (CH_2), 128.8 (*p*-PhC), 129.2 (*o*-PhC), 130.0 (*m*-PhC), 142.4 (*s*-PhC), 150.6 (C-5), 155.0 (C-3'), 160.8 (C-5'), 165.0 (C-2).

Anal. Calcd. for $C_{12}H_{13}N_7S_2$ (MW. 319.40): C, 45.13; H, 4.10; N, 30.70; S, 20.07. Found: C, 45.10; H, 4.21; N, 30.65; S, 20.13.

To the dimethylformamide-containing mother liquor 10 ml of water was added which initiated crystallisation again to yield after filtration 0.07 g (31%) of 5-benzylamino-2,3-dihydro-1,3,4-thiadiazole-2(3*H*)-thione (**17**), mp 139-141°; ir: ν NH = 3295 and 3260 cm^{-1}, ν C=N = 1553 cm^{-1}; pmr (DMSO-d_6): δ, ppm 4.34 [d (J = 5.7 Hz), 2H, CH_2], 7.3 (m, 5H, PhH), 8.04 [t (J = 5.7 Hz), 1H, NH], 13.3 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 47.0 (CH_2), 127.1 (*p*-PhC), 127.3 (*o*-PhC), 128.2 (*m*-PhC), 138.0 (*s*-PhC), 160.7 (C-5), 181.0 (C=S); ms: M^+ = 223.

Anal. Calcd. for $C_9H_9N_3S_2$ (MW. 223.32): C, 48.41; H, 4.06; N, 18.82; S, 28.71. Found: C, 48.44; H, 4.11; N, 18.95; S, 28.75.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl).

A mixture of 1.06 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = benzyl, Q = methylthio, X = S), 40 ml of benzene and 0.93 g (0.0045 mole) of dicyclohexylcarbodiimide was refluxed for 2 hours. The reaction mixture was evaporated *in vacuo* to dryness and the residue (2.04 g) was chromatographed on a silica gel column (eluent a 9:1 mixture of chloroform and methanol) to yield 0.47 g (49%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl) that after recrystallisation from ethanol melted at 242-243°. The product is identical (mixed mp, ir) with that of **16** (Q = methylthio, R = benzyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl).

A mixture of 1.06 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = benzyl, Q = methylthio, X = S) and 10 ml of 10% sodium hydroxide was stirred at room temperature for 16 hours. The crystals which precipitated were filtered off to yield 0.40 g (42%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = benzyl) that after recrystallisation from ethanol melted at 241-243°. The product is identical (mixed mp, ir) with that of **16** (Q = methylthio, R = benzyl) obtained above.

1-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-ethylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = ethyl, Q = methylthio, X = S) and 2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl).

A mixture of 6.12 g (0.03 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)carbothiohydrazide (**1**, $R^1 = R^2 = H$, Q = methylthio) [1], 150 ml of dimethylformamide and 5.23 g (5.25 ml = 0.06 mole) of ethyl isothiocyanate (**3**, R = ethyl, X = S) was stirred at room temperature for 16 hours; 250 ml of water was added to the reaction mixture. The crystals which precipitated were filtered off and washed with methanol to yield 5.25 g (60%) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-ethylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = ethyl, Q = methylthio, X = S), mp 155-157°; pmr (DMSO-d_6): δ, ppm 1.10 (t, 3H, CH_3), 2.56 (s, 3H, SCH_3), 3.42 (qi, 2H, CH_2), 7.80 (t, 1H, NH), 8.4 (bs, 2H, NH_2), 8.6 (bs, 1H, NH), 9.8 (bs, 1H, NH).

Anal. Calcd. for $C_7H_{13}N_7S_3$ (MW. 291.41): C, 28.85; H, 4.50; N, 33.65; S, 33.01. Found: C, 28.92; H, 4.67; N, 33.60; S, 33.08.

The mother liquor crystallised again upon standing for some days to yield 1.01 g (13%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl) that after recrystallisation from ethanol melted at 268-270°; ir: ν NH + NH_2 = 3400 and 3280 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.19 [t (J = 7 Hz), 3H, CH_3], 2.48 (s, 3H, SCH_3), 3.30 (m, 2H, CH_2), 7.4 (bs, 1H, NH_2), 7.75 [t (J = 6 Hz), 1H, NH]; cmr (DMSO-d_6): δ, ppm 13.5 (SCH_3), 14.5 (CH_3), 39.5 (CH_2), 150.5 (C-5), 155.1 (C-5'), 161.2 (C-3'), 165.2 (C-2).

Anal. Calcd. for $C_7H_{11}N_7S_2$ (MW. 257.33): C, 32.67; H, 4.31; N, 38.10; S, 24.92. Found: C, 32.70; H, 4.43; N, 30.01; S, 25.04.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl).

A mixture of 0.87 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-ethylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = ethyl, Q = methylthio, X = S) 40 ml of benzene and 0.93 g (0.0045 mole) of dicyclohexylcarbodiimide was refluxed with stirring for 1 hour. After cooling the crystals which precipitated were filtered off to yield 0.45 g (58%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl) that after recrystallisation from ethanol melted at 268-270°. The product is identical (mixed mp, ir) with that of **16** (Q = methylthio, R = ethyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl).

A mixture of 1.75 g (0.006 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-ethylthiocarbamoylcarbothiohydrazide (**4**, $R^1 = R^2 = H$, R = ethyl, Q = methylthio, X = S) and 20 ml of 10% sodium hydroxide was stirred at room temperature for 16 hours. The crystals which precipitated were filtered off to yield 0.73 g (47%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-ethylamino-1,3,4-thiadiazole (**16**, Q = methylthio, R = ethyl) that after recrystallisation from ethanol melted at 268-270°. The product is identical (mixed mp, ir) with that of **16** (Q = methylthio, R = ethyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-(*N*-phenyl-*N*-methyl)amino-1,3,4-thiadiazole (**18**).

To a solution of 0.91 g (0.003 mole) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-phenylimino-4,5-dihydro-1,3,4-thiadiazole (**16a**, Q = methylthio, R = phenyl) in 4 ml of dry dimethylformamide 0.12 g (0.0039 mole) of sodium hydride (80% solution in parraffin oil, Aldrich) was added and the mixture was stirred at room temperature for 1 hour. Then 0.32 ml (0.005 mole) of methyl iodide was added to the reaction mixture by dropping it with stirring and cooling below 15°. Cooling was discontinued and the reaction mixture was stirred at room temperature for 1 hour. The mixture thus obtained was quenched with 8 ml of water, the crystals which precipitated were collected and recrystallised twice from methanol to yield 0.43 g (45%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-(*N*-phenyl-*N*-methyl)-amino-1,3,4-thiadiazole (**18**), mp 224-226°; ir: ν NH_2 = 3395 and 3300 cm^{-1}, ν C=S = 1274 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.45 (s, 3H, SCH_3), 3.53 (s, 3H, NCH_3), 7.50 (bs, 2H, NH_2), 7.37-7.55 (m, 1H, *p*-PhH), 7.55-7.60 (m, 4H, *o*- and *m*-PhH); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3), 39.9 (NCH_3), 124.3 (*o*-PhC), 127.1 (*p*-PhC), 130.1 (*m*-PhC), 146.3 (*s*-PhC), 150.9 (C-5), 155.1 (C-5'), 161.3 (C-3'), 166.7 (C-2).

Anal. Calcd. for $C_{12}H_{13}N_7S_2$ (MW. 319.40): C, 45.13; H, 4.10; N, 30.70; S, 20.07. Found: C, 45.16; H, 4.22; N, 30.68; S, 20.11.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) - from **4** (R^1 = R^2 = H, R = ethyl, Q = methylthio, X = S).

The mixture of 1.02 g (0.0035 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-ethylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = ethyl, Q = methylthio, X = S) 20 ml of methanol and 1.42 g (0.62 ml = 0.01 mole) of methyl iodide was refluxed for 2 hours. After cooling the crystals which precipitated were filtered off to yield 0.65 g (71%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) that after recrystallisation from acetonitrile melted at 189-190°; ir: ν NH_2 = 3400 and 3290 cm^{-1}, ν C=N = 1662, 1561 and 1518 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.50 (s, 3H, SCH_3-3'), 2.77 (s, 3H, SCH_3-5), 7.65 (bs, 2H, NH_2); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3-3'), 16.4 (SCH_3-5), 155.0 (C-5'), 160.1 (C-5), 162.7* (C-2), 163.0* (C-3'); ms: M^+ = 260.

Anal. Calcd. for $C_6H_8N_6S_3$ (MW. 260.37): C, 27.68; H, 3.10; N, 32.28; S, 36.94. Found: C, 27.77; H, 3.26; N, 32.21; S, 36.89.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) - from **4** (R^1 = R^2 = H, R = benzyl, Q = methylthio, X = S).

The mixture of 1.06 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-benzylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = benzyl, Q = methylthio, X = S) 20 ml of methanol and 1.42 g (0.62 ml = 0.01 mole) of methyl iodide was refluxed for 2 hours. After cooling the crystals which precipitated were filtered off to yield 0.52 g (57%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) that after recrystallisation from acetonitrile melted at 188-190°. The product is identical (mixed mp, ir) with that of **23** (R^3 = methyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) - from **4** (R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) in methanol.

The mixture of 1.02 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) 20 ml of methanol and 1.42 g (0.62 ml = 0.01 mole) of methyl iodide was refluxed for 2 hours. After cooling the crystals which precipitated were filtered off to yield 0.58 g (74%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) that after recrystallisation from acetonitrile melted at 189-190°. The product is identical (mixed mp, ir) with that of **23** (R^3 = methyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) - from **4** (R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) in dimethylformamide.

The mixture of 1.02 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) 15 ml of dimethylformamide and 1.42 g (0.62 ml = 0.01 mole) of methyl iodide was stirred at room temperature for 5 hours; 50 ml of water was added to the reaction mixture and the crystals which precipitated were filtered off to yield 0.55 g (71%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-methylthio-1,3,4-thiadiazole (**23**, R^3 = methyl) that after recrystallisation from acetonitrile melted at 188-189°. The product is identical (mixed mp, ir) with that of **23** (R^3 = methyl) obtained above.

2-(5-Amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylthio-1,3,4-thiadiazole (**23**, R^3 = benzyl) - from **4** (R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S).

The mixture of 1.02 g (0.003 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N'*-phenylthiocarbamoylcarbothiohydrazide (**4**, R^1 = R^2 = H, R = phenyl, Q = methylthio, X = S) 10 ml of dimethylformamide and 0.86 g (0.6 ml = 0.005 mole) of benzyl bromide was stirred at room temperature for 16 hours. The crystals which precipitated were filtered off and washed with acetonitrile to yield 0.73 g (72%) of 2-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-5-benzylthio-1,3,4-thiadiazole (**23**, R^3 = benzyl) that after recrystallisation from acetonitrile melted at 163-165°; ir: ν NH_2 = 3405 and 3300 cm^{-1}, ν C=N = 1650, 1563 and 1512 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.52 (s, 3H, SCH_3), 4.50 (s, 2H, SCH_2), 6.83 (s, 2H, NH_2), 7.2-7.4 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 38.6 (SCH_2), 128.0 (*p*-PhC), 128.8 (*o*-PhC), 129.1 (*m*-PhC), 135.5 (*s*-PhC), 154.9 (C-5'), 161.0* (C-5), 161.2* (C-3'), 163.4 (C-2).

Anal. Calcd. for $C_{12}H_{12}N_6S_3$ (MW. 336.45): C, 42.84; H, 3.60; N, 24.98; S, 28.59. Found: C, 42.88; H, 3.82; N, 25.04; S, 28.66.

Acknowledgement.

The authors wish to express their thanks to Mrs. Sándorné Sólyom and Miss Mónika Sipos for recording the ir spectra, to Mrs. Béláné Csákváry and Mr. Attila Fürjes for recording the nmr spectra, to Mr. János Brlik for recording the ms spectra, to Mrs. Lászlóné Zalavári for performing the elemental analysis and to Mrs. Lászloné Nyikos, Mrs. Tamásné Nyaras, and Miss Ildikó Szebelédi for technical assistance.

REFERENCES AND NOTES

[1] For Part XXVIII see: J. Barkóczy and J. Reiter, *J. Heterocyclic Chem.*, **29**, 1677 (1992).

[2] J. Reiter, T. Somorai, Gy. Jerkovich and P. Dvortsák, *J. Hetero-*

cyclic Chem., **19**, 1157 (1982).

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

[4] J. Reiter, L. Toldy, I. Schäfer, E. Szondy, J. Borsi and I. Lukovits, *Eur. J. Med. Chem.-Chim. Ther.*, **15**, 41 (1980).

[5] P. Sohár, G. Fehér and L. Toldy, *Org. Magn. Reson.*, **11**, 9 (1978).

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

[7] G. L'abbe, G. Verhelst, L. Huybrechts and S. Toppet, *J. Heterocyclic Chem.*, **14**, 515 (1977).

[8] M. Veverka, *Collect. Czech. Chem. Commun.*, **52**, 113 (1987).

[9] M. Gál, E. Tihanyi and P. Dvortsák, *Acta Chim. Hung.*, **123**, 55 (1986).

[10] S. Sunder, N. P. Peet and R. J. Barbuch, *J. Heterocyclic Chem.*, **18**, 1601 (1981).

[11] V. J. Ram and H. N. Pandey, *Bull. Soc. Chim. Belg.*, **86**, 399 (1977).

[12] J. Reiter, L. Pongó and I. Pallagi, *J. Heterocyclic Chem.*, **27**, 1689 (1990).