On Triazoles XXXI [1]. The Reaction of 1,2,4-Triazolylcarbothiohydrazides with Homo- and Heterocyclic Ketones. An Unexpected Reaction Leading to 4,5-Polyalkylene Thiazoles

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The reaction of 1,2,4-triazolylcarbothiohydrazides with homo- and heterocyclic ketones to yield 8-spiro-[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thiones **7** (n = 4, 5, 6, 7 and 11), **8** and **9**, respectively, all representing novel ring systems was studied. Providing the reaction at higher temperature a novel reaction was observed to yield 4,5-polyalkylene thiazoles for which a mechanism is proposed.

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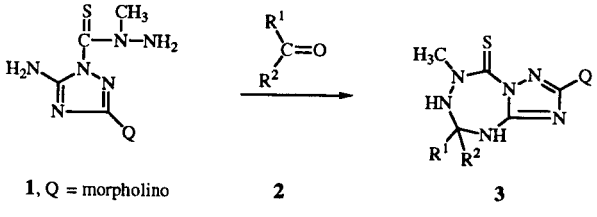
In a previous paper of this series [1] we have described the reaction of different 1-(5-amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazides **1** with aldehydes **2** (R^1 = H, $R^2 \neq$ H) and aliphatic ketones **2** (R^1 and $R^2 \neq$ H) to yield **3** type [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thiones (Scheme 1).

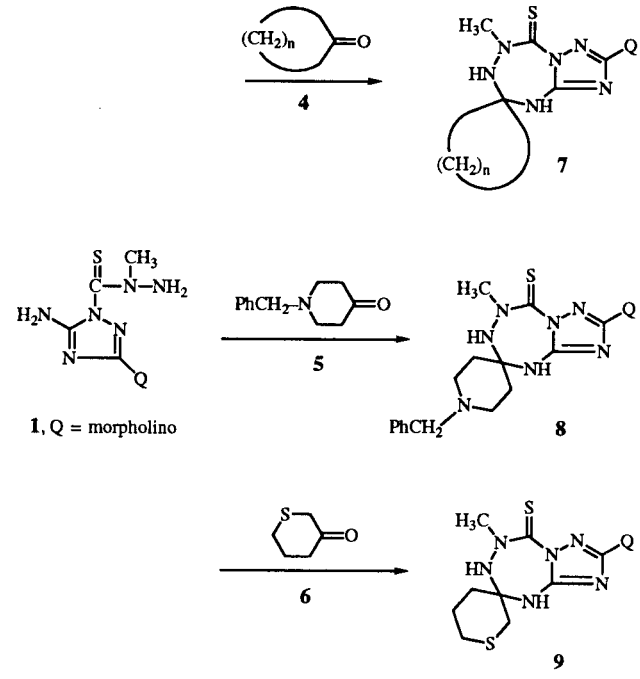
Scheme 1



1, Q = morpholino **2** **3**

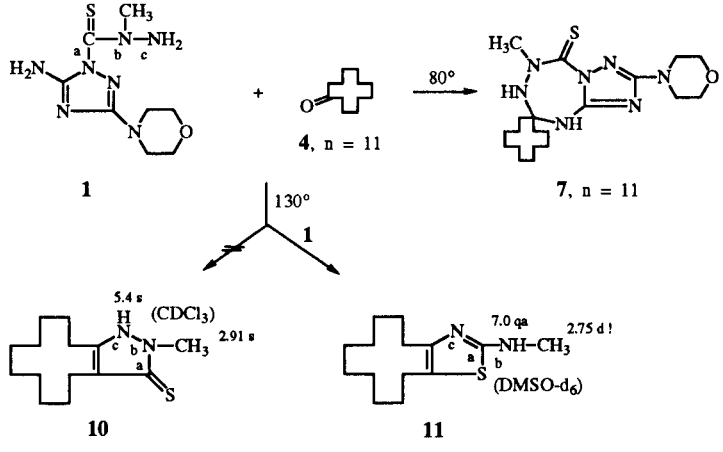
Repeating the above reaction with homo- **4** (n = 4, 5, 6, 7 and 11) or heterocyclic ketones **5** and **6** the analogues 8-spiro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thiones **7**, (n = 4, 5, 6, 7 and 11), **8** and **9**, respectively (Scheme 2) were obtained all representing novel ring systems. The proof of the structure of the products obtained was based on their full analogy with those of derivatives **3** obtained

Scheme 2



1, Q = morpholino **4** **5** **6** **7** **8** **9**

Scheme 3



1 **4**, n = 11 **7**, n = 11 **10** **11**

Table I

Compound No.	Q	n	Conditions of Preparation Yield (%)	Mp (°C) (Crystallized	Molecular Formula (MW)	Analysis Calcd./Found C	H	N	S
7/1	Morpholino	4	62	219-222 (EtOH + H_2O)	$C_{13}H_{21}N_7OS$ (323.43)	48.28 48.13	6.54 6.65	30.31 30.44	9.91 9.87
7/2	Methylthio	4	78	202-205 (Dioxane)	$C_{10}H_{16}N_6S_2$ (284.41)	42.23 42.26	5.67 5.76	29.55 29.68	22.55 22.46
7/3	Morpholino	5	77	223-225 (DMF + H_2O)	$C_{14}H_{23}N_7OS$ (337.45)	49.83 49.78	6.87 6.95	29.05 28.98	9.50 9.55
7/4	Methylthio	5	93	225-227 (DMF)	$C_{11}H_{18}N_6S_2$ (298.44)	44.27 44.25	6.08 6.22	28.16 28.08	21.49 21.55
7/5	Morpholino	6	65	209-211 (EtOH)	$C_{15}H_{25}N_7OS$ (351.48)	51.26 51.33	7.17 7.32	27.90 28.04	9.12 8.97
7/6	Morpholino	7	71	204-206 (MeOH)	$C_{16}H_{27}N_7OS$ (365.51)	52.58 52.41	7.45 7.50	26.82 26.78	8.77 8.83
7/7	Morpholino	11	63	203-205 (EtOH)	$C_{20}H_{35}N_7OS$ (421.62)	56.98 57.11	8.37 8.51	23.25 32.18	7.60 7.58
8	Morpholino	–	52	227-229 (DMF + H_2O)	$C_{20}H_{28}N_8OS$ (428.57)	56.05 56.11	6.59 6.73	26.15 26.07	7.48 7.51
±9	Morpholino	–	49	226-228 (MeOH)	$C_{13}H_{21}N_7OS_2$ (355.49)	43.93 44.02	5.95 6.11	27.58 27.55	18.04 17.98

previously [1]. Thus the [1,2,4]triazolo[1,5-*d*]tetrazepine-5-thione ring was characterised by two different NH groups appearing in the pmr spectra at 6.9-7.1 and 7.8-8.4 ppm, respectively (Table II) in DMSO-d_6 solution and the "spiro" carbon atom 8 appearing in DMSO-d_6 solution depending on the size of the "spiro" ring between 76.3 and 86.6 ppm in the cmr (Table II). The [1,5-*d*] connection of the [1,2,4]triazole and [1,2,4,6]tetrazepinethione rings was characterised by the chemical shifts of the C-2, C-9a and C-5 carbon atoms that appeared at 161.0-163.9, 152.0-152.9 and 178.6-180.1 ppm, respectively (Table II).

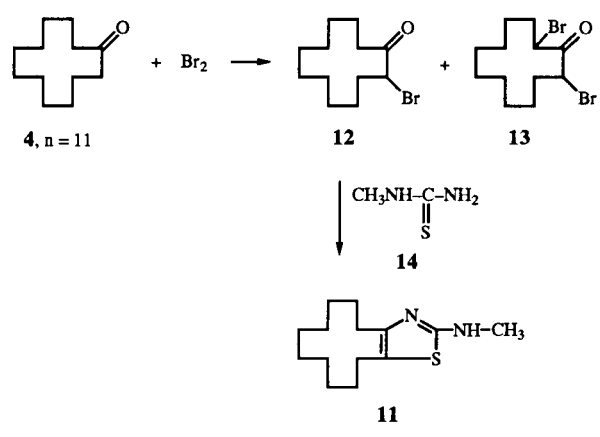
Unexpectidely, when providing the reaction of **1** (Q = morpholino) with cyclododecanone (**4**, n = 11) at 130° instead of **7** (n = 11) obtained previously in boiling ethanol as the solvent a cleaved product of the molecular formula $C_{14}H_{24}N_2S$ was formed as proved by its analytical and ms data (Scheme 3). In the pmr spectrum taken in deuteriochloroform two singlets were observed at 2.91 and 5.4 ppm corresponding to NCH_3 and NH groups, respectively, thus structure **10** was proposed for this product the formation of which could be well deduced from the Shiff base formed as an intermediate by splitting the triazole ring and ring closure of the thiocarbonyl group to the neighbouring carbon atom of the cyclododecane ring.

Quite surprisingly when the pmr spectrum was recorded in DMSO-d_6 solution the above two signals split into a methyl doublet and NH quartet indicating that these two moieties should be attached to each other excluding the possibility of structure **10** and indicating rather structure **11**. However, if the structure **11** is correct then during the reaction an unusual rearrangement had to have occurred as the original a-b-c sequence of the carbon-nitrogen-nitrogen atoms in **1** changed into the sequence c-a-b, *i.e.* a nitrogen-carbon-nitrogen. As on the basis of the cmr spectrum it was not possible to distinguish between structures **10** and **11**, an independent synthesis of **11** was decided.

Thus cyclododecanone (**4**, n = 11) was brominated to the mixture of the mono- **12** and dibromo- **13** derivatives which were separated and the monobromo derivative **12** was reacted with *N*-methylthiourea (**14**) to yield **11** with an unequivocal structure (Scheme 3). The material obtained was in all respects identical with that obtained in the previous reaction.

The following mechanism was proposed for the formation of **11** (Scheme 5). Cyclododecanone (**4**, n = 11) reacted with **1** (Q = morpholino) to yield the Shiff base **14** which may cyclise to form **7** (n = 11). On the other hand **14** may undergo as a consequence of the electron withdrawing effect of the thiocarbonyl and triazole moieties the electrone shift shown on Scheme 5 to yield after the splitting of the 5-amino-3-morpholino-1*H*-1,2,4-triazole (**15**) moiety the diaziridine intermediate **16**. The sulfur atom of **16** may start a nucleophilic attack against the en-

Scheme 4



4, n = 11 **12** **13**

14

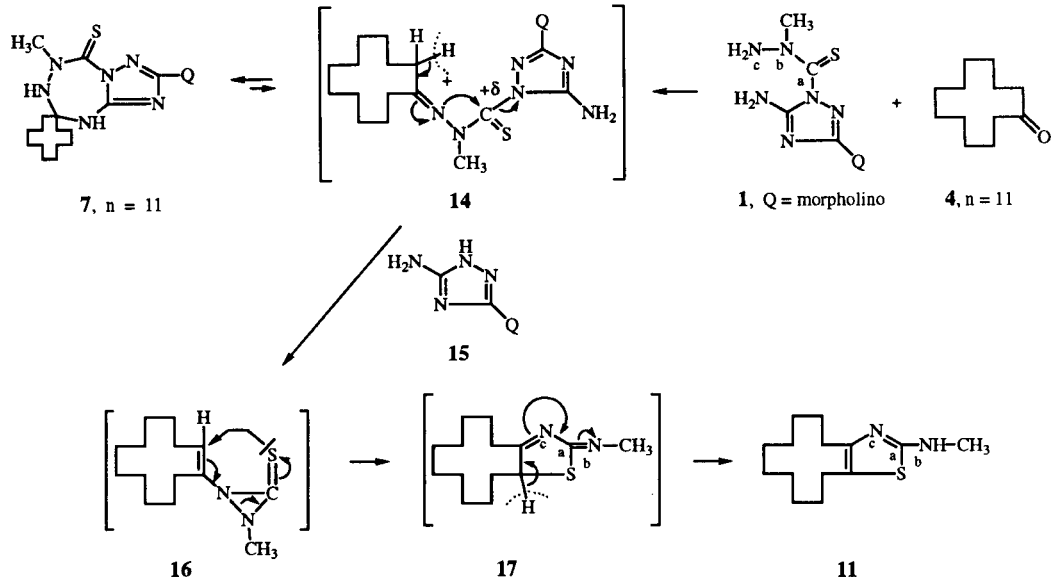
11

Table II

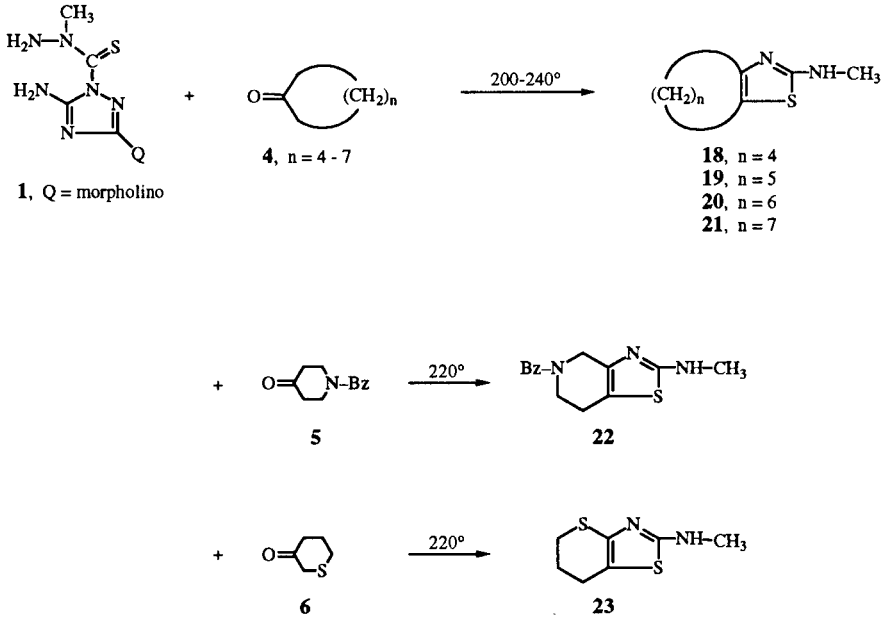
Compound No.	IR [cm^{-1}] ν C=S	PMR δ CH_3	PMR δ NH (7)	PMR δ NH (9)	PMR δ Q	PMR δ $(CH_2)_n$	CMR δ C-8	CMR δ C-2/ δ C-9a	CMR δ Q	CMR δ CH_3/ δ C=S	CMR δ $(CH_2)_n$
7/1	1275	3.51 s (3H)	7.0 s (1H)	8.2 s (1H)	3.25 t (4H) (J = 5 Hz) 3.65t (4H) (J = 5 Hz)	1.7 m (8H)	86.4	163.2 152.5	45.9 65.7	46.6 179.1	37.3 (C-α) 22.3 (C-β)
7/2	1275	3.55 s (3H)	7.1 s (1H)	8.4 s (1H)	2.47 s (3H)	1.7 m (8H)	86.6	161.2 152.9	13.3	46.9 178.6	37.4 (C-α) 22.3 (C-β)
7/3	1283	3.51 s (3H)	6.9 s (1H)	7.9 s (1H)	3.25 t (4H) (J = 4.7 Hz) 3.65 t (4H) (J = 4.7 Hz)	1.2 m (1H) 1.55 m (7H) 1.78 m (2H)	78.6	163.2 152.6	45.8 65.6	46.1 179.5	36.1 (C-α) 24.8 (C-β) 22.2 (C-γ)
7/4	1277	3.55 s (3H)	7.1 a (1H)	8.1 s (1H)	2.47 s (3H)	1.15 m (1H) 1.55 m (7H) 1.75 m (2H)	78.7	161.0 152.8	13.0	46.1 178.8	35.9 (C-α) 24.6 (C-β) 22.0 (C-γ)
7/5	1279 [1]	3.59 s (3H)	5.7 s (1H)	5.2 s (1H)	3.44 t (4H) (J = 5 Hz) 3l75 t (4H) (J = 5 Hz)	1.5-2.1 m [1] (12H)	84.3	163.9 152.0	46.1 66.5	47.0 180.1	39.6 (C-α) 29.5 (C-β) 22.0 (C-γ)
7/6	1279	3.49 s (3H)	6.9 s (1H)	8.1 s (1H)	3.24 t (4H) (J = 4.8 Hz) 3.64 t (4H) (J = 4.8 Hz)	1.4-1.9 m (14H)	81.3	163.1 152.3	45.8 65.7	46.7 179.1	33.7 (C-α) 27.6 (C-β) 25.4 (C-ε) 24.0 (C-γ) 21.2 (C-δ)
7/7	1279	3.49 s (3H)	6.9 s (1H)	7.8 s (1H)	3.25 t (4H) (J = 5 Hz) 3.64 t (4H) (J = 5 Hz)	1.35-1.8 m (22H)	82.0	163.1 152.5	45.8 65.7	47.0 179.2	33.0 (C-α) 26.0 (C-β) 25.5 (C-ξ) 22.3 (C-γ) 22.0 (C-δ) 19.3 (C-ε)
8	1279	3.50 s (3H)	6.95 s (1H)	7.95 s (1H)	3.25 t (4H) (J = 4.7 Hz) 3.75 t ·4H) (j = 4.7 Hz)	1.8 m (4H) [2] 2.25 m (2H) [3] 2.65 m (2H) [3] 3.46 s (2H [4] 7.3 (5H)	77.1	163.2 152.4	45.8 65.6	46.2 179.6	35.5 [2] 49.5 [4] 61.8 [3] 126.8 128.1 128.7 138.5
±9	1278	3.59 s (3H)	7.1 s (1H)	8.0 s (1H)	3.27 t (4H) (J = 5 Hz) 3.67 t (4H) (J = 5 Hz)	2.74 s (2H) [5] 1.35-2.6 m (6H)	76.3 [8]	163.1 152.1	45.8 65.6	45.9 179.0	26.3 [6] 28.5 [7] 37.0 [9] 37.6 [10]

[1] Taken in deuteriochloroform. [2] Piperidine C-CH_2. [3] Piperidint NCH_2. [4] CH_2Ph. [5] C-CH_2S. [6] Thiacyclohexane C-5. [7] Thiacyclohexane C-6. [8] Thiacyclohexane $(CH_2)_3$. [9] Thiacyclohexane C-4. [10] Thiacyclohexane C-2.

Scheme 5



Scheme 6



aminic carbon atom of the cyclododecanone ring to yield after the shift of the electron pairs indicated on the Scheme 5 intermediate **17** which is stabilized in the tautomeric form **11**.

Considering the above mechanism at least at severe conditions, *i.e.* at high temperature besides the spiro derivatives **7** (**8**, **9**) the corresponding cleaved ones **11** (**18-23**) have to be formed too. Thus the reactions were repeated at 220-240° (Scheme 6) and according to the mass spectra the reaction mixtures really contained besides the spiro derivatives **7** (**8**, **9**) the corresponding derivatives **18-23**, respectively. In case of **21** (Q = morpholino) it was also isolated from the reaction mixture in pure form.

On the other hand if at least at high temperature exists a tautomeric equilibria between the spiro derivatives **7** (**8**, **9**) and the corresponding **14** type Shiff bases as was shown previously [1] (Scheme 5) then heating the spiro derivatives should also lead to the cleaved derivatives **11** (**18-23**), respectively. Thus small samples of derivatives **7**, n = 4-11, **8** and **9** were heated for 5 minutes to 250° and the mass spectra of the melts obtained were again recorded. Again in each case the formation of the corresponding cleaved derivatives **11**, **18-23**, respectively was observed corroborating at least in part the mechanism proposed for their formation. The ms evaluation of the reaction mixtures will be reported in detail elsewhere [2].

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using a 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 mass spectra were recorded on a Kratos MS25RFA instrument using direct inlet probe.

General Method for the Preparation of 6-Methyl-2-Q-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione-8-spiro-1'-cyclopentanes and -cyclohexanes **7/1-7/4**.

The mixture of 0.01 mole of the corresponding 1-(5-amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**) [3] and 0.06 mole of the corresponding cyclopentanone or cyclohexanone was stirred at 140° for 5 hours. After cooling 25 ml of ethanol was added to the reaction mixture it was stirred at room temperature for 1 hour and precipitated crystals were filtered and recrystallised from a solvent given in Table I. For spectral data see Table II.

General Method for the Preparation of 6-Methyl-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione-8-spiro-1'-cycloheptane, -1'-cyclooctane, -1'-cyclododecane, -[4'-(*N*-benzylpiperidine)] and -(3'-thiacyclohexane) **7/5-7/7**, **8** and **9**.

The solution of 0.01 mole of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, Q = morpholino) [3] and 0.015 mole of the corresponding cycloalkanone in 25 ml of ethanol was refluxed for 16 hours. After cooling the precipitated crystals were filtered and recrystallised from a solvent given in Table I. For spectral data see Table II.

4,5,6,7,8,9,10,11,12,13-Decahydro-2-methylaminocyclododeca-[1,2-*d*]thiazole (**11**).

The mixture of 2.55 g (0.01 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, Q = morpholino) [3] and 9.1 g (0.05 mole) of cyclododecanone (**4**, n = 11) was stirred at 140° for 5 hours. After cooling 20 ml of acetonitrile was added to the reaction mixture, it was stirred at room temperature for 15 minutes, the precipitated crystals were filtered and

recrystallised from ethanol to yield 1.79 g (71%) of 4,5,6,7,8,9,10,11,12,13-decahydro-2-methylaminocyclododeca[1,2-*d*]thiazole (**11**), mp 146-148°; ir: ν NH = 3216 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.2-1.8 (m, 16H, CH_2-5 - CH_2-12), 2.50 [t (J = 6.5 Hz), 2H, CH_2-13], 2.65 [t (J = 6.5 Hz), 2H, CH_2-4], 2.91 (s, 3H, CH_3), 6.0 (s, 1H, NH); pmr (DMSO-d_6): δ, ppm 1.4-1.8 (m, 16H, CH_2-5 - CH_2-12), 2.48 [t (J = 6.5 Hz), 2H, CH_2-13], 2.64 [t (J = 6.5 Hz), 2H, CH_2-4], 2.73 [d (J = 4.6 Hz), 3H, CH_3], 7.1 [qa (J = 4.6 Hz), 1H, NH]; cmr (DMSO-d_6): δ, ppm 23.6, 23.8, 24.5, 25.6, 25.9, 26.1, 26.2, 27.1 (C-5 - C-12), 28.1 (C-13), 31.0 (C-4), 32.6 (CH_3), 120.6 (C-13a), 148.8 (C-3a), 168.4 (C-2); ms: M^+ = 252.

Anal. Calcd. for $C_{14}H_{24}N_2S$ (MW 252.43): C, 66.62; H, 9.58; N, 11.10; S, 12.70. Found: C, 66.65; H, 9.73; N, 11.08; S, 12.68.

The mother liquor was evaporated to dryness *in vacuo* and chromatographed on a silica gel column (eluent a 2:1 mixtue of benzene and ethyl acetate) to yield 1.05 g (62%) of 5-amino-3-morpholino-1*H*-1,2,4-triazole, mp 167-168° (2-PrOH), Lit [4] mp 167-168°.

2-Bromocyclododecanone (**12**) and 2,12-Dibromocyclododecanone (**13**).

To the solution of 18.2 g (0.1 mole) of cyclododecanone (**4**, n = 11) in 15 ml of 99.5% acetic acid 5.1 ml (0.1 mole) of bromine was added with stirring and cooling keeping the temperature of the reaction mixture below 25°. The stirring was continued at laboratory temperature for 1 hour, the precipitated crystals were filtered off and washed with 10 ml of a 1:1 mixture of 2-propanol and water. The dry crystals were recrystallised from diethyl ether to yield 1.6 g (12%) of 2,12-dibromocyclododecanone (**13**), mp 124-125°; ir: ν C=O = 1726 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.1-1.55 (m, 14H, CH_2-4 - CH_2-10), 2.1-2.3 (m, 4H, CH_2-3 and CH_2-11), 4.97 [dd (J = 8.9 Hz and 3.4 Hz), 2H, CH-2 and CH-12].

Anal. Calcd. for $C_{12}H_{20}Br_2O$ (MW 340.11): C, 42.38; H, 5.93; Br, 46.99. Found: C, 42.44; H, 6.02; Br, 46.73.

The mother liquor crystallised again upon standing for two days. The precipitated crystals were filtered and recrystallised from a 1:1 mixture of 2-propanol and water to yield 10.2 g (39%) of 2-bromocyclododecanone (**12**), mp 46-47°; ir: ν C=O = 1718 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.0-2.9 [m, 20H, $(CH_2)_n$], 4.82 [dd (J = 9 Hz and 3.5 Hz), 1H, CH].

Anal. Calcd. for $C_{12}H_{21}BrO$ (MW 261.21): C, 55.18; H, 8.10; Br, 30.59. Found: C, 55.06; H, 8.21; Br, 30.55.

4,5,6,7,8,9,10,11,12,13-Decahydro-2-methylaminocyclododeca-[1,2-*d*]thiazole (**11**) from 2-Bromocyclododecanone (**12**) and *N*-Methylthiourea (**14**).

To the solution of 2.61 g (0.01 mole) of 2-bromocyclododecanone (**12**) in 5 ml of methanol the solution of 1.8 g (0.02 mole) of *N*-methylthiourea (**14**) in 25 ml of methanol was added and the reaction mixture refluxed for 24 hours. After cooling the reaction mixture was evaporated *in vacuo* to dryness and the residue was chromatographed on a silica-gel column (Mesh 0.063-0.2 mm), eluent a mixture of chloroform and methanol with continuously increasing amount of methanol. The fractions obtaining the main product were collected, evaporated to dryness and recrystallised from ethanol to yield 0.88 g (35%) of 4,5,6,7,8,9,10,11,12,13-decahydro-2-methylaminocyclododeca[1,2-*d*]thiazole (**11**), mp 146-148°. The product was in all respects (ir, mixed mp) identical with that of obtained above.

4,5,6,7,8,9-Hexahydro-2-methylaminocycloocta[1,2-*d*]thiazole (**21**).

The 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**, Q = morpholino) [3] and 4.0 ml of cyclooctanone (**4**, n = 7) was stirred at 150° for 4 hours. After cooling the reaction mixture was evaporated *in vacuo* to dryness and the residue (2 g) was triturated with acetonitrile to yield 1.20 g (66%) of 4,5,6,7,8,9-hexahydro-2-methylaminocycloocta[1,2-*d*]thiazole (**21**), mp 128-130°; ir: ν NH = 3210 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.35 (m, 4H, CH_2-6 and CH_2-7), 1.54 (m, 4H, CH_2-5 and CH_2-8), 2.52 [t (J = 5.4 Hz), 2H, CH_2-9], 2.61 [t (J = 6.1 Hz), 2H, CH_2-4], 2.73 [d (J = 4.1 Hz), 3H, CH_3], 7.1 (m, 1H, NH); cmr (DMSO-d_6): δ, ppm 23.5, 25.1, 25.6, 27.6 (CH_2-5 - CH_2-8), 29.0 (C-9), 30.6 (C-4), 30.8 (CH_3), 115.7 (C-9a), 147.8 (C-3a), 166.1 (C-2); ms: M^+ = 196.

Anal. Calcd. for $C_{10}H_{16}N_2S$ (MW 196.32): C, 61.18; H, 8.21; N, 14.27; S, 16.33. Found: C, 61.32; H, 8.44; N, 14.23; S, 16.28.

The mother liquor was evaporated to dryness and chromatographed on a silica gel column (eluent a 2:1 mixture of benzene and ethyl acetate) to yield 0.5 g (76%) of 5-amino-3-morpholino-1*H*-1,2,4-triazole, mp 166-167° (2-PrOH), lit [4] mp 167-168°.

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