On Triazoles. XXXII [1]. The Reaction of 5-Amino-1*H*-1,2,4-triazolylcarbothiohydrazides with β- and γ-Oxo-esters

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Dedicated to the memory of Professor Roland K. Robins

5-Amino-1*H*-1,2,4-triazolylcarbothiohydrazides gave β and γ-oxo-esters in boiling ethanol [1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepine-5-thiones **3**. Analogously ethyl 2-oxocyclohexanecarboxylate provided a mixture of two diastereomeric spiro derivatives **5** and **6**. At 130°, 2-acetonyl-5-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**) was formed. Ring closure of **3e** (R^1 = CH_3, R^2 = CH_2CH_2COOEt, Q = morpholino) lead to the isomeric pyrrolo[2,1-*g*][1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-8(11*H*)-one (**12**) and pyrrolo[1,2-*f*][1,2,4]triazolo-[1,5-*d*][1,2,4,6]tetrazepin-10(7*H*)-one (**13**) derivatives representing two new ring systems.

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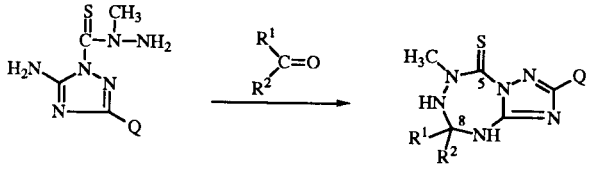
In the previous papers of this series [1,2] we have described the reaction of different 1-(5-amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazides **1** with linear (**2a**, R^1 = CH_3, R^2 = C_2H_5) [2], cyclic [**2b**, $R^1 + R^2 = (CH_2)_{4\text{-}11}$] [1] and heterocyclic [**2c**, $R^1 + R^2 = (CH_2)_2N(Ph)(CH_2)_2$ and $CH_2S(CH_2)_3$] [1] ketones to yield the corresponding **3a** type [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5-thiones (R^1 = CH_3, R^2 = C_2H_5), and their **3b** [$R^1 + R^2 = (CH_2)_{4\text{-}11}$] and **3c** [$R^1 + R^2 = (CH_2)_2N(Ph)(CH_2)_2$ and $CH_2S(CH_2)_3$] type spiro analogues, respectively (Scheme 1).

Scheme 1



1 **2** **3**

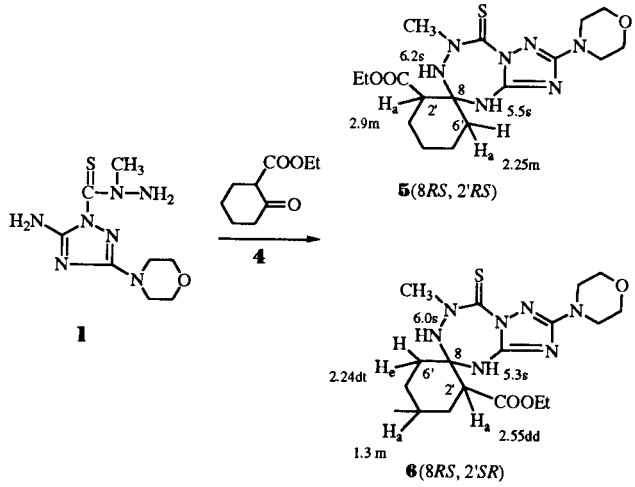
a, $R^1 = CH_3$, $R^2 = C_2H_5$
b, $R^1 + R^2 = (CH_2)_{4\text{-}11}$
c, $R^1 + R^2 = (CH_2)_2N(Ph)(CH_2)_2$, $CH_2S(CH_2)_3$
d, $R^1 = CH_3$, $R^2 = CH_2COOCH_3$
e, $R^1 = CH_3$, $R^2 = CH_2CH_2COOC_2H_5$

It was known [3] that the β-oxo-esters may react with diamines either by their keto group or ester group or both to yield different products. Consequently, it was of interest to study which products would by formed from 1-(5-amino-3-Q-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazides **1** and different β- and γ-oxo esters.

Thus the reaction of **1** (Q = methylthio and morpholino, respectively) was repeated with methyl acetoacetate (**2d**, R^1 = CH_3, R^2 = CH_2COOCH_3) and ethyl levulinate (**2e**, R^1 = CH_3, R^2 = $CH_2CH_2COOC_2H_5$) in boiling ethanol as the solvent. In all cases the corresponding racemic **3d** (R^1 = CH_3, R^2 = CH_2COOCH_3) and **3e** (R^1 = CH_3, R^2 = $CH_2CH_2COOC_2H_5$) type [1,2,4]triazolo[1,5-*d*][1,2,4,6]-tetrazepine-5-thiones, respectively, were formed. Their spectral data were fully analogues with those of **3a** (R^1 = CH_3, R^2 = C_2H_5, Q = methylthio) [2] giving an unequivocal proof for their structure. Thus in their pmr spectra taken in DMSO-d_6 solution the NH groups 7 and 9 appeared at δ = 7.1-7.2 ppm and δ = 8.05-8.2 ppm, respectively (compare with **3a**, δ NH-7 and 9 = 7.1 ppm and 8.2 ppm, respectively [2]) and the newly built in carbon atoms 8 appeared in the cmr spectra at δ = 77.1-77.9 ppm (compare with **3a**, δ C-8 = 79.1 ppm [2]).

An indirect but very descriptive proof for the formation

Scheme 2

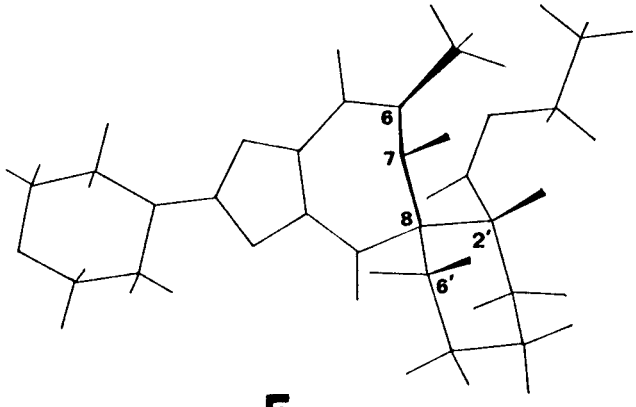


1 **4** **5**(8*RS*, 2'*RS*) **6**(8*RS*, 2'*SR*)

of the [1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine ring system gave the repeating of the above reaction with a cyclic β-oxo-ester, namely the ethyl 2-oxocyclohexanecarboxylate (**4**) (Scheme 2). In this case owing to fact that the spiro ring formed is not symmetrical and a further asymmetric center was introduced to the molecule two diastereomers **5** and **6** could be isolated. They were differentiated by DNOE investigations.

In the spectra taken in deuteriochloroform solution irradiation of the 6.2 ppm NH group of **5** afforded 1.5% NOE to N-CH_3 together with 5.8% and 7.1% NOE enhancements to axial cyclohexane protons 2′ and 6′, respectively (see the steric picture of **5** computed by PCGEOM Molecular Grafics Program [4] in Scheme 3). In accordance with the above experiment, on irradiation of the axial proton 2′ of the cyclohexane ring NOE enhancements to the NH proton appearing at 6.2 ppm and to the *N*-methyl protons were observed and the irradiation of the *N*-methyl protons afforded NOE to the axial proton 2′ of the cyclohexane ring.

Scheme 3

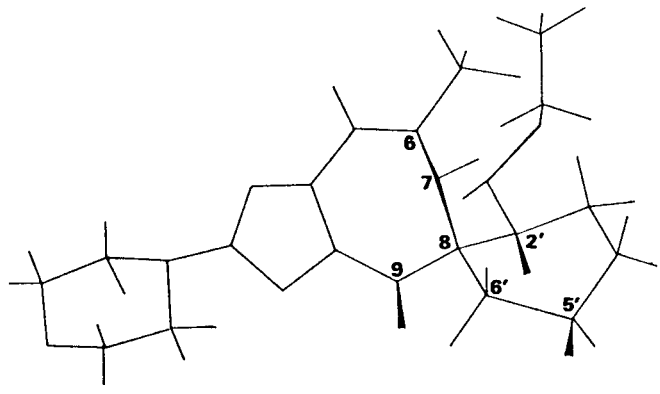


5

On the other hand in the case of **6** (see its steric picture computed by PCGEOM Molecular Graphics Program [4] in Scheme 4) on irradiation of the 5.3 ppm NH proton a 10% and 5.3% NOE enhancements were observed to the axial cyclohexane 2′ and axial cyclohexane 5′ protons appearing at 2.55 and 1.3 ppm, respectively. When the axial cyclohexane 2′ proton was irradiated an 8% NOE to the cyclohexane 5′ proton was observed. When the *N*-methyl protons appearing at 3.65 ppm were irradiated a NOE to the equatorial cyclohexane 6′ proton appearing at 2.24 ppm was observed. When the 6.6 ppm NH proton was irradiated a NOE to the *N*-methyl protons appeared. At last, when the equatorial cyclohexane proton 6′ was irradiated a NOE to the axial cyclohexane proton 5′ occurred.

All these data pointed out that in diastereomer **5** the ethoxycarbonyl group is sterically close to NH-7 proving its 8*RS*,2′*RS* structure, while in the case of **6** the ethoxycarbonyl group is close to NH-9 giving an undoubt proof

Scheme 4



6

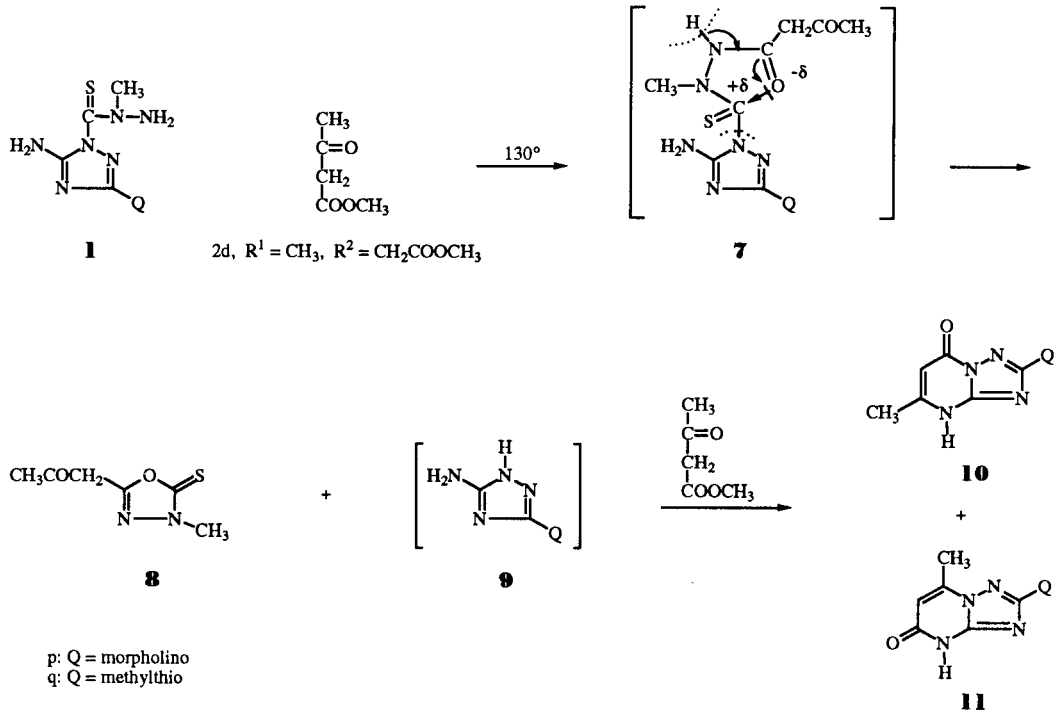
for its 8*RS*,2′*SR* structure.

Repeating the reactions of **1** (Q = methylthio and morpholino, respectively) with methyl acetoacetate (**2d**, R^1 = CH_3, R^2 = CH_2COOCH_3) in the boiling oxo-ester used as the solvent (Scheme 5) instead of **3d** (R^1 = CH_3, R^2 = CH_2COOCH_3) obtained at 80°, 2-acetonyl-4-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**) was formed beside the known [5] 7-methyl-2-Q-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10**) and 5-methyl-2-Q-[1,2,4]triazolo[1,5-*a*]pyrimidin-7(8*H*)-one (**11**) derivatives.

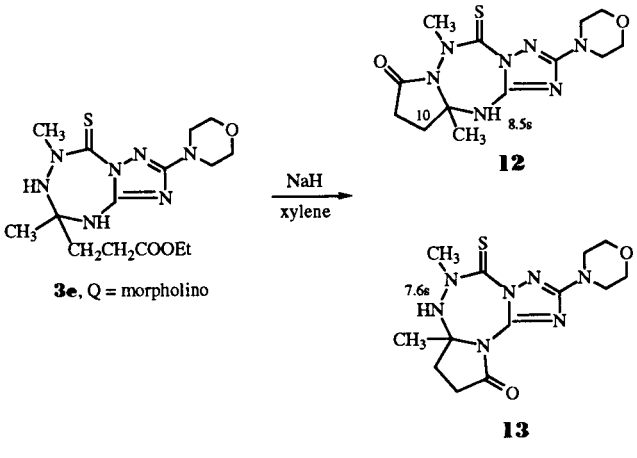
The formation of the abvove derivatives can be easily explained by assuming that the methyl acetoacetate reacted with the thiohydrazide unit at high temperature by its ester group to yield the amide **7** (Scheme 5) in which a nucleophilic attack against the positively charged carbon atom of the thiocarbonyl moiety was made by the amide carbonyl group to yield after splitting off the triazole **9** moiety the oxadiazole **8**. Later on the 5-amino-3-Q-1*H*-1,2,4-triazole (**9**) formed underwent a condensation with the methyl acetoacetate used as the solvent to yield the corresponding 7-methyl-2-Q-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10**) and 5-methyl-2-Q-[1,2,4]triazolo[1,5-*a*]-pyrimidin-7(8*H*)-one **11** derivatives, respectively.

Subjecting derivative **3e** (R^1 = CH_3, R^2 = CH_2CH_2-COOEt, Q = morpholino) to ring closure by refluxing it in xylene in the presence of sodium hydride derivatives **12** and **13** were obtained both representing novel ring systems. Their ir, pmr and cmr spectral data were again in accordance with the proposed structures but made not possible to distinguish between them. Again the DNOE experiments were performed. Thus the irradiation of the NH protons of derivative **12** appearing in DMSO-d_6 solution at 8.5 ppm afforded NOE enhancements to the CCH_3 and CH_2-10 protons, while on irradiating the NH protons of **13** appearing in DMSO-d_6 solution at 7.6 ppm an increase of the intensities of the NCH_3 and CCH_3 protons was observed helping an unequivocal differentiation between them.

Scheme 5



Scheme 6



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 Bruker WM-250 and Bruker WP-80 SY instruments. The ms spectra were recorded on a Kratos MS25RFA instrument using a direct inlet probe.

±6,8-Dimethyl-8-methoxycarbonylmethyl-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3d**, Q = morpholino).

The 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**, Q = morpholino) [6], 25 ml of ethanol and 1.74 g (1.62 ml = 0.015 mole) of methyl acetoacetate (**2d**) was refluxed with stirring for 16 hours. After cooling the crystals which precipitated were filtered off and recrystallised from 2-propanol to yield 2.27 g (64%) of ±6,8-dimethyl-8-methoxycarbonylmethyl-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3d**, Q = morpholino), mp 201-203°; ir: ν NH = 3345 and 3205 cm^{-1}, ν C=O = 1725 cm^{-1}, ν C=S = 1275 cm^{-1}; pmr (DMSO-d$_6$): δ, ppm 1.40 (s, 3H, CCH_3), 2.75 (bs, 2H, CH_2), 3.25 (m, 4H, NCH_2), 3.51 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 3.64 (m, 4H, OCH_2), 7.15 (s, 1H, NH-7), 8.05 (s, 1H, NH-9); cmr (DMSO-d$_6$): δ, ppm 25.4 (CCH_3), 43.8 (CH_2), 45.8 (NCH_2), 46.1 (NCH_3), 51.6 (OCH_3), 65.6 (OCH_2), 77.2 (C-8), 152.2 (C-9a), 163.2 (C-2), 169.4 (C=O), 179.2 (C=S).

Anal. Calcd. for $C_{13}H_{21}N_7SO_3$ (MW 355.41): C, 43.93; H, 5.96; N, 27.59; S, 9.02. Found: C, 44.02; H, 6.12; N, 27.55; S, 8.96.

±6,8-Dimethyl-8-methoxycarbonylmethyl-2-methylthio-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3d**, Q = methylthio).

The mixture of 2.20 g (0.01 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, Q = methylthio) [6], 25 ml of ethanol and 1.74 g (1.62 ml = 0.015 mole) of methyl acetoacetate (**2d**) was refluxed with stirring for 16 hours. After cooling the crystals which precipitated were filtered off and recrystallised from acetonitrile to yield 2.34 g (74%) of ±6,8-dimethyl-8-methoxycarbonylmethyl-2-methylthio-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3d**, Q

= morpholino), mp 198-200°; ir: ν NH = 3340 and 3210 cm^{-1}, ν C=O = 1730 cm^{-1}, ν C=S = 1270 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.42 (s, 3H, CCH_3), 2.48 (s, 3H, SCH_3), 2.80 (bs, 2H, CH_2), 3.54 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 7.2 (bs, 1H, NH-7), 8.2 (s, 1H, NH-9); cmr (DMSO-d_6): δ, ppm 13.7 (q, SCH_3), 26.0 (q, CCH_3), 44.2 (t, CH_2), 46.8 (q, NCH_3), 52.2 (q, OCH_3), 77.9 (m, C-8), 152.1 (s, C-9a), 162.0 (q, ^3J(C,H) = 4.8 Hz, C-2), 170.0 (m, C=O), 179.0 (q, ^3J(C,H) = 3 Hz, C=S).

Anal. Calcd. for $C_{10}H_{16}N_6S_2O_2$ (MW 316.40): C, 37.96; H, 5.10; N, 26.56; S, 20.27. Found: C, 37.83; H, 5.08; N, 26.60; S, 20.18.

±6,8-Dimethyl-8-(2-ethoxycarbonylethyl)-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3e**, Q = morpholino).

The 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**, Q = morpholino) [6], 25 ml of ethanol and 2.16 g (2.13 ml = 0.015 mole) of ethyl levulinate (**2e**) was refluxed with stirring for 16 hours. After cooling the crystals which precipitated were filtered off and recrystallised from 2-propanol to yield 2.25 g (61%) of ±6,8-dimethyl-8-(2-ethoxycarbonylethyl)-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3e**, Q = morpholino), mp 176-178°; ir: ν NH = 3330 and 3210 cm^{-1}, ν C=O = 1724 cm^{-1}, ν C=S = 1273 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.18 [t (J = 7 Hz), 3H, ester CH_3], 1.26 (s, 3H, CCH_3), 1.92 (m, 2H, CCH_2), 2.40 (m, 2H, $COCH_2$), 3.25 (m, 4H, NCH_2), 3.50 (s, 3H, NCH_3), 3.65 (m, 4H, OCH_2), 4.05 [q (J = 7 Hz), 2H, ester CH_2], 7.1 (s, 1H, NH-7), 8.1 (s, 1H, NH-9); cmr (DMSO-d_6): δ, ppm 14.0 (CH_3-ester), 24.7 (CCH_3), 34.8 ($COCH_2$), 28.7 (CCH_2), 45.8 (NCH_2), 46.3 (NCH_3), 59.9 (OCH_2-ester), 65.6 (OCH_2), 77.1 (C-8), 152.5 (C-9a), 163.1 (C-2), 172.3 (C=O), 178.9 (C=S).

Anal. Calcd. for $C_{15}H_{25}N_7SO_3$ (MW 383.47): C, 46.98; H, 6.57; N, 25.57; S, 8.36. Found: C, 47.12; H, 6.83; N, 25.62; S, 8.24.

Preparation of the Diastereomeric Mixture of ±8*RS*,2'*RS* and ±8*RS*,2'*SR* 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'-(2-ethoxycarbonylcyclohexane) (**5** and **6**, respectively).

The mixture of 10.36 g (0.04 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, Q = morpholino) [6], 200 ml of methanol and 10 ml (0.055 mole) of ethyl 2-oxocyclohexanecarboxylate (**4**) was stirred at room temperature for 72 hours. The crystals which precipitated were filtered off and recrystallised from acetonitrile to yield 6.37 g (39%) of ±8*RS*,2'*RS* 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'-(2-ethoxycarbonylcyclohexane) (diastereomer **5**), mp 222-224°; ir: ν NH = 3290 and 3150 cm^{-1}, ν C=O = 1720 cm^{-1}, ν C=S = 1270 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.27 [t (J = 7.1 Hz), 3H, ester CH_3], 1.45-1.70 (m, 4H, 2 x H-4' and 2 x H-5'), 1.8 (m, 2H, 2 x H-3'), 2.1 (m, 1H, H_e-6'), 2.25 (m, 1H, H_a-6'), 2.9 (m, 1H, H_a-2'), 3.44 [t (J = 4.9 Hz), 4H, NCH_2], 3.62 (s, 3H, NCH_3), 3.74 [t (J = 4.9 Hz), 4H, OCH_2], 4.17 [q (J = 7.1 Hz), 2H, ester CH_2], 6.2 (s, 1H, NH-7), 5.5 (s, 1H, NH-9); irradiated at 6.2 ppm NOE enhancements to 3.62 ppm (1.5%), 2.9 ppm (5.8%) and 2.25 ppm (7.1%); irradiated at 2.9 ppm NOE enhancements to 6.2 ppm (1.2%) and 3.62 ppm (2%); irradiated at 3.62 ppm NOE enhancement to 2.9 ppm (0.5%); cmr (DMSO-d_6): δ, ppm 13.8 (ester CH_3), 21.2 (C-4'), 23.3 (C-5'), 26.0 (C-3'), 36.2 (C-6'), 45.8 (NCH_2), 46.3 (NCH_3), 49.3 (C-2'), 60.4 (ester CH_2). 65.6 (OCH_2), 78.1 (C-8), 152.5 (C-9a), 163.1 (C-2), 171.8 (C=O), 178.5 (C=S).

Anal. Calcd. for $C_{17}H_{27}N_7SO_3$ (MW 409.51): C, 49.86; H, 6.65; N, 23.94; S, 7.83. Found: C, 50.01; H, 6.73; N, 24.03; S, 7.66.

The mother liquors were evaporated to dryness and the residue recrystallised from 2-propanol to yield 7.35 g (45%) of ±8*RS*,2'*SR* 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'-(2-ethoxycarbonylcyclohexane) (diastereomer **6**), mp 180-182°; ir: ν NH = 3280 and 3200 cm^{-1}, ν C=O = 1720 cm^{-1}, ν C=S = 1270 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.23 [t (J = 7.2 Hz), 3H, CH_3 ester], 1.3 (m, 1H, H_a-5'), 1.7-1.95 (m, 6H, 2 x H-3', 2 x H-4', H_e-5', H_a-6'), 2.24 (dt, 1H, H_e-6'), 2.55 (dd, 1H, H_a-2'), 3.42 [t (J = 5 Hz), 4H, NCH_2], 3.65 (s, 3H, NCH_3), 3.73 [t (J = 5 Hz), 4H, OCH_2], 4.07 [q (J = 7.2 Hz), 2H, CH_2 ester], 5.3 (s, 1H, NH-9), 6.6 (s, 1H, NH-7); irradiated at 5.3 ppm NOE enhancements to 2.55 ppm (10%) and 1.3 ppm (5.3%); irradiated at 2.55 ppm NOE enhancement to 1.3 ppm (8%); irradiated at 3.65 ppm NOE enhancement to 2.24 ppm (0.5%); irradiated at 6.2 ppm NOE enhancement to 3.65 ppm (1.5%); irradiated at 2.24 ppm NOE enhancement to 1.3 ppm (18%); cmr (DMSO-d_6): δ, ppm 13.7 (ester CH_3), 21.8 (C-4'), 23.8 (C-5'), 26.5 (C-3'), 35.7 (C-6'), 45.8 (NCH_2), 46.4 (NCH_3), 51.8 (C-2'), 60.6 (ester CH_2), 65.5 (OCH_2), 78.8 (C-8), 152.7 (C-9a), 163.3 (C-2), 172.8 (C=O), 179.9 (C=S).

Anal. Calcd. for $C_{17}H_{27}N_7SO_3$ (MW 409.51): C, 49.86; H, 6.65; N, 23.94; S, 7.83. Found: C, 49.77; H, 6.71; N, 23.88; N, 7.86.

2-Acetonyl-4-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**), 7-Methyl-2-morpholino[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10p**) and 5-Methyl-2-morpholino[1,2,4]triazolo[1,5-*a*]pyrimidin-7(8*H*)-one (**11p**).

The mixture of 1.29 g (0.005 mole) of 1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1p**, Q = morpholino) [6] and 12 ml of methyl acetoacetate (**2d**) was refluxed with stirring for 2 hours. After cooling the crystals which precipitated were filtered off and subjected to column chromatography (silica-gel, eluent a mixture of chloroform and ethanol) to yield 0.73 g (63%) of 7-methyl-2-morpholino[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10p**), mp 335-337° (ethanol), lit [5] mp 336-338° and 0.22 g (19%) of 5-methyl-2-morpholino[1,2,4]triazolo[1,5-*a*]-pyrimidin-7(8*H*)-one (**11p**), mp 265-266° (ethanol), lit [5] mp 248-250°.

The methyl acetoacetate containing mother liquor was evaporated *in vacuo* to dryness and the residue was crystallised from ethanol to yield 0.49 g (63%) of 2-acetonyl-4-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**), mp 83-85°; ir: ν C=O = 1735 cm^{-1}, ν C=S = 1290 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.32 (s, 3H, CCH_3), 3.69 (s, 3H, NCH_3), 3.87 (s, 2H, CH_2); cmr (deuteriochloroform): δ, ppm 29.6 (CCH_3), 36.0 (NCH_3), 40.2 (CH_2), 155.8 (C-2), 177.1 (C-5).

Anal. Calcd. for $C_6H_8N_2SO_2$ (MW 172.20): C, 41.85; H, 4.68; N, 16.27; S, 18.62. Found: C, 41.69; H, 4.75; N, 16.33; S, 18.50.

2-Acetonyl-4-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**), 7-Methyl-2-methylthio[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10q**) and 5-Methyl-2-methylthio[1,2,4]triazolo[1,5-*a*]pyrimidin-7(8*H*)-one (**11q**).

The mixture of 1.10 g (0.005 mole) of 1-(5-amino-3-methylthio-1*H*-1,2,4-triazol-1-yl)-*N*-methylcarbothiohydrazide (**1**, Q = methylthio) [6] and 12 ml of methyl acetoacetate (**2d**) was refluxed with stirring for 2 hours. After cooling the crystals which precipitated were filtered off and subjected to column chromatography (silica-

gel, eluent a mixture of chloroform and ethanol) to yield 0.48 g (49%) of 7-methyl-2-methylthio[1,2,4]triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**10q**), mp 289-290° (ethanol), lit [5] mp 290-291.5° and 0.11 g (11%) of 5-methyl-2-methylthio[1,2,4]triazolo[1,5-*a*]pyrimidin-7(8*H*)-one (**11q**), mp 286-287° (dimethylformamide), lit [5] mp 286-288°.

The methyl acetoacetate containing mother liquor was evaporated *in vacuo* to dryness and the residue was crystallised from ethanol to yield 0.32 g (42%) of 2-acetonyl-4-methyl-4,5-dihydro-1,3,4-oxadiazole-5-thione (**8**), mp 83-85°. The product is identical (mixed mp, ir) with that of **8** obtained above.

± 1,10a-Dimethyl-2-morpholino-5-thioxo-5,6,8,9,10,10a-hexahydropyrrolo[2,1-*g*][1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-8(11*H*)-one (**12**) and ± 6,7-Dimethyl-2-morpholino-5-thioxo-5,6,7a,8,9,10-hexahydropyrrolo[1,2-*f*][1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-10(7*H*)-one (**13**).

Sodium hydride (80% solution in parafin oil) (0.52 g, 0.018 mole) was washed three times with 15 ml portions of xylene, then 50 ml of xylene was added to it followed by careful addition of 1.1 g (0.003 mole) of ± 6,8-dimethyl-8-(2-ethoxycarbonylethyl)-2-morpholino-5,6,8,9-tetrahydro[1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepine-5(7*H*)-thione (**3e**, Q = morpholino) with stirring the reaction mixture. The reaction mixture was refluxed for 4 hours and the still hot mixture was filtered. After cooling the crystals which precipitated were filtered off and chromatographed on a silica gel column (eluent a mixture of chloroform and methanol) to yield 0.22 g (22%) of ± 6,7-dimethyl-2-morpholino-5-thioxo-5,6,7a,8,9,10-hexahydropyrrolo[1,2-*f*][1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-10(7*H*)-one (**13**), mp 298-300° (2-propanol); ir: ν C=O = 1711 cm^{-1}; ν C=S = 1275 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.37 (s, 3H, CCH_3), 2.08 (m, 1H, CCH_2), 2.45 (m, 2H, $COCH_2$), 2.75 (m, 1H, CCH_2), 3.30 [t (J = 5 Hz), 4H, NCH_2], 3.56 (s, 3H, NCH_3), 3.70 [t (J = 5 Hz), 4H, OCH_2], 7.6 (s, 1H, NH); irradiated at 7.6 ppm DNOE at 1.37 ppm (5.4%) and 3.56 ppm (3.6%); cmr (DMSO-d_6): δ, ppm 22.1 (CCH_3), 30.2* (CCH_2), 30.3* ($COCH_2$), 45.4 (NCH_2), 46.6 (NCH_3), 65.4 (OCH_2), 87.1 (C-10a), 142.3 (C-11a), 163.4 (C-2), 171.1 (C=O), 177.9 (C=S).

Anal. Calcd. for $C_{13}H_{19}N_7SO_2$ (MW 337.40): C, 46.28; H, 5.68; N, 29.06; S, 9.50. Found: C, 46.33; H, 5.69; N, 28.92; S, 9.48.

Continuing the chromatography 0.18 g (18%) of ± 1,10a-dimethyl-2-morpholino-5-thioxo-5,6,8,9,10,10a-hexahydropyrrolo-[2,1-*g*][1,2,4]triazolo[1,5-*d*][1,2,4,6]tetrazepin-8(11*H*)-one (**12**) was obtained, mp 267-269° (2-propanol); ir: ν C=O = 1710 cm^{-1}, ν C=S = 1277 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.60 (s, 3H, CCH_3), 2.22 (m, 2H, CCH_2), 2.42 (m, 2H, $COCH_2$), 3.25 [t (J = 5 Hz), 4H, NCH_2], 3.60 (s, 3H, NCH_3), 3.65 [t (J = 5 Hz), 4H, OCH_2], 8.5 (s, 1H, NH); irradiated at 8.5 ppm DNOE at 1.60 ppm (2.6%) and 2.22 ppm (5.8%); cmr (DMSO-d_6): δ, ppm 25.8 (CCH_3), 26.4 (CCH_2), 32.3 ($COCH_2$), 43.3 (NCH_3), 45.3 (NCH_2), 65.4 (OCH_2), 79.4 (C-10a), 151.8 (C-11a), 163.0 (C-2), 170.0 (C=O), 177.8 (C=S).

Anal. Calcd. for $C_{13}H_{19}N_7SO_2$ (MW 337.40): C, 46.28; H, 5.68; N, 29.06; S, 9.50. Found: C, 46.22; H, 5.70; N, 29.11; S, 9.43.

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