Triazolines, XXXI[1]

Reaction of 5-Amino-4,5-dihydro-4-methylene-1*H*-1,2,3-triazoles with Substituted Thiazolium-4-olates

Paolo Cavalleri, Francesca Clerici, Emanuela Erba, and Pasqualina Trimarco*

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano,
Via Venezian 21, I-20133 Milano, Italy

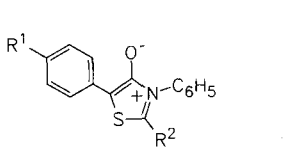
Received August 22, 1991

Key Words: *v*-Triazolines / Thiazolium-4-olates / 2-Pyridinones

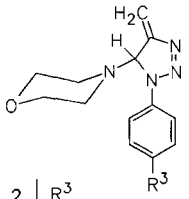
The cycloaddition reaction of 5-amino-*v*-triazolines **2** with thiazolium-4-olates **1** affords two isomeric cycloadducts **3** and **4**. A synthetic utilization has been achieved by their desulfuration: The cycloadducts **3** and **4** are catalytically transformed with Raney nickel to pyridinones **5**. The acid-catalized rearrangement of **3** and **4** affords the 8-thia-6-azabicyclo[3.2.1]-octane derivatives **6**.

Previous papers from our research group have dealt with the reactions of 5-amino-4-methylene-*v*-triazolines with sydnones[2] and münchnones[3]. In both cases the mesoionic compounds undergo a cycloaddition reaction with the methylene-*v*-triazolines to afford labile cycloadducts which eliminate nitrogen and rearrange to furnish heteroaromatic al-

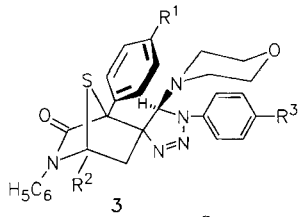
Scheme 1



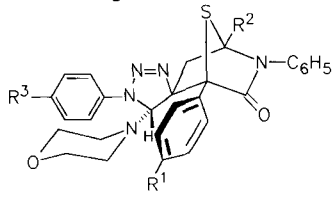
1	R^1	R^2
a	H	C_6H_5
b	H	SC_6H_5
c	CH_3O	C_6H_5
d	NO_2	C_6H_5



2	R^3
a	CH_3
b	OCH_3
c	NO_2

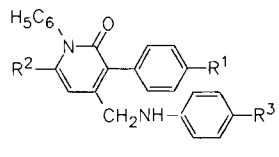


3

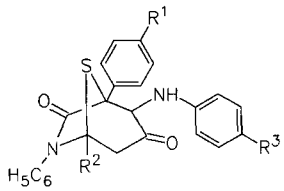


4

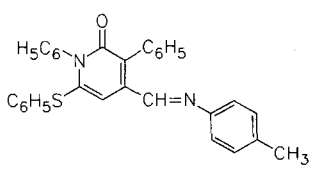
3, 4	R^1	R^2	R^3
a	H	C_6H_5	CH_3
b	H	SC_6H_5	CH_3
c	H	C_6H_5	NO_2
d	NO_2	C_6H_5	NO_2
e	OCH_3	C_6H_5	CH_3
f	H	C_6H_5	OCH_3



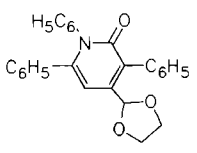
5	R^1	R^2	R^3
a	H	C_6H_5	CH_3
b	OCH_3	C_6H_5	CH_3
c	H	C_6H_5	OCH_3
d	H	H	CH_3



6	R^1	R^2	R^3
a	H	C_6H_5	CH_3
b	H	SC_6H_5	CH_3
c	H	C_6H_5	NO_2
d	OCH_3	C_6H_5	CH_3
e	H	C_6H_5	OCH_3



7



8

  0009–2940/92/0404–0883 $ 3.50+.25/0

dehydes. With sydnones 3-pyrazolecarboxaldehydes are obtained, whereas the use of münchnones represents a route to 3-pyrrolecarboxaldehydes.

As a further development of these studies involving mesoionic 1,3-dipoles we have now examined the cycloaddition reaction of 5-amino-4-methylene-*v*-triazolines with substituted thiazolium-4-olates.

The starting mesoionic compounds **1a–d** and methylene-*v*-triazolines **2a–c** are known compounds and are prepared according to literature procedures. They are brought to reaction in boiling toluene solution and in an inert atmosphere. At lower temperature the reaction is too slow for practical purposes. However, in boiling toluene with reaction times of about 2 h satisfactory yields of the reaction products are obtained in most cases. Two racemic diastereoisomeric cycloadducts **3a–f** and **4a–f** are obtained in each instance (only one enantiomer is represented by the formulas) and are separated by column chromatography and/or fractional crystallization. In most cases a complete separation has been achieved. Only products **3f** and **4d** are obtained in impure form, i.e. they contain a small amount of the corresponding isomer (**4f** and **3d**, resp.). The separation of **3b** and **4b** has not been attempted. The structural assignments for compounds **3** and **4** are based on analytical and spectral data (see Experimental). Configurational assignments can be safely made on the basis of NMR techniques[4].

Concerning the above reactions the following comments are appropriate. Compounds **1** are known to react as 1,3-dipoles of the thiocarbonyl ylide type. Several examples have been reported in the literature[6,7]. Electron-poor alkenes with conjugated electron-withdrawing substituents have been used consistently because simple alkenes have been found to be nonreactive[7] except in intramolecular cycloaddition[8]. Remarkably, in the present case a satisfactory reactivity is observed though substrates **2** are best described as alkenes bearing moderately electron-withdrawing substituents devoid of a conjugative effect[9]. The cycloaddition reaction is characterized in all cases by a very high regioselectivity since only products are formed in which the formally positive carbon of the dipole (C-2 of the thiazole ring) is linked to the CH_2 group of **2**. It should be stressed that this regiochemistry is in fair agreement with the behavior of other 1,3-dipoles with respect to the reaction with compounds **2**, for example nitrile oxides[10], nitrile imines[11], and münchnones[3]. Considering this regiochemical situation, four isomeric reaction products are to be expected taking into consideration the possibility of the occurence of *endo*- or *exo*-transition states in the cycloaddition reactions. However, in this case only two reaction products are formed due to a different orientation of the dipole with respect to the triazoline partner as shown in Scheme 1, leading to compounds **3** and **4**. Since the cycloaddition products are formed in similar amounts (Table 1) the stability of the transition states is scarcely influenced by the mutual orientation of the reactants. Instead, steric effects appear to be very relevant since the approach of the dipole occurs only from the less hindered side of the dipolarophile (i.e. opposite to the large morpholino substituent).

Scheme 2

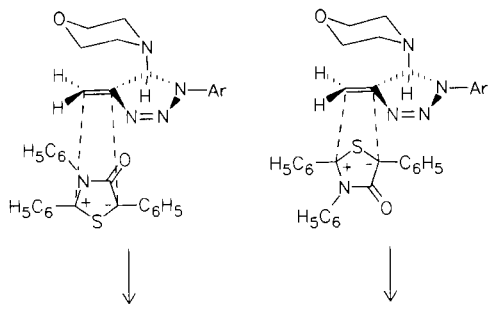


Table 1. Isomer ratios of products **3** and **4**[a]

Thiazolium-4-olates	5-Amino-4-methylene-*v*-triazolines	Products **3**:**4** (ratio)
1a	**2a**	**3a**:**4a** (39:61)
1b	**2a**	**3b**:**4b** (37:63)
1a	**2c**	**3c**:**4c** (44:56)
1d	**2c**	**3d**:**4d** (38:62)
1c	**2a**	**3e**:**4e** (43:57)
1a	**2b**	**3f**:**4f** (60:40)

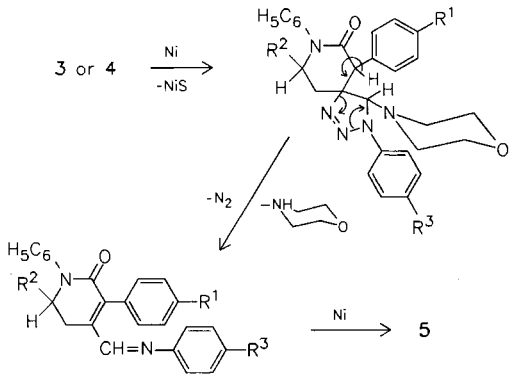
[a] Measured by ^{1}H NMR on crude reaction mixtures.

Both compounds **3** and **4** show a remarkable thermal stability which is rather unusual for strained 5-amino-*v*-triazolines. Synthetically useful transformations of the cycloadducts **3** and **4** occur by desulfurization or acid-catalyzed rearrangement. Thus, **3a,e,f** and **4a,e,f,** both as pure compounds or a mixture of diastereoisomers, readily react with an excess of Raney nickel in ethanol at room temperature to afford the corresponding 1,3,6-triaryl-4-arylaminomethyl-2(1*H*)-pyridinones **5a–c**. Compound **5d** is formed under similar conditions by starting from a mixture of **3b** and **4b**. Expectedly, in this case the phenylthio residue is also eliminated. The structure of products **5** is confirmed by IR absorptions in the 1635–1645 (C=O)[12] and 3120 to 3140 cm^{-1} (N–H) ranges. The ^{1}H-NMR spectra show a signal at about δ = 4.1 (CH_2) and a singlet at about δ = 6.5 to 6.7 (5′-H) in the case of **5a–c**. For compound **5d** a doublet is found at δ = 6.51 (J = 7.1, 5-H).

In scheme 3 a rationalized picture of the formation of compounds **5** is presented. By desulfurization a spiranic intermediate is produced which undergoes cleavage of the triazoline ring with elimination of nitrogen and morpholine. This process is started by the deprotonation at the carbon α to the carbonyl group. The anil thus formed is converted into the final product by dehydrogenation-hydrogenation.

Though stable to strong bases (e.g. potassium *tert*-butoxide in THF), compounds **3** and **4** are susceptible to acid-catalyzed rearrangements, as expected for 5-aminotriazolines[13]. On reaction with HCl/dioxane a slow transformation to the 8-thia-6-azabicyclo[3.2.1]octane derivatives

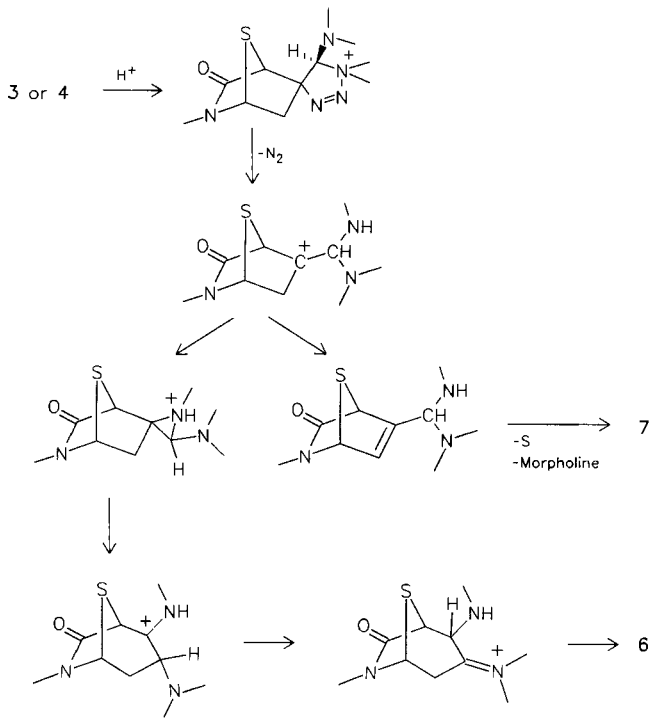
Scheme 3



6a–e occurs. This ring enlargement is accompanied by nitrogen and morpholine elimination. The structure of compounds **6a–e** is confirmed by IR (3340, 1710, 1690 cm^{-1} corresponding to the imino, carbonyl ketone, carbonyl amide group) and ^{1}H-NMR spectrometry (AB system in the range of δ = 2.9–3.5, CH_2, and singlet at about δ = 4.7, CH). Compounds **6** are generally obtained in good yields, and only in two cases minor amounts of byproducts are isolated, i.e. the 2-pyridinone derivative **7** from **3b**/**4b** and **8** from **3a**/**4a**.

In Scheme 4 a rationalization of these results is presented, which shows that both compounds **6** and **7** arise from a common cationic intermediate produced by protonation of the triazoline ring followed by nitrogen elimination. Cationic intermediates of this kind have been often postulated to rationalize the rearrangement reaction of 5-aminotriazolines[16]. Ring enlargement occurs via an intermediate aziridinium ion. Alternatively, compound **7** is produced. The acetal **8** is clearly formed from an anil by analogy with **7** during the prolonged reaction with dioxane/H_2O/HCl.

Scheme 4



This reaction offers an interesting and easy route to highly functionalized derivatives of the hitherto scarcely studied 8-thia-6-azabicyclo[3.2.1]octane ring.

The authors are grateful to Dr. *E. Arlandini* for recording the mass spectra. Financial support of the *Ministero della Pubblica Istruzione*, Roma, is gratefully acknowledged.

Experimental

IR: Perkin-Elmer 197 and Pye-Unicam SP3-200S Philips. – ^{1}H NMR (tetramethylsilane as internal standard): Bruker AC 200. – MS: Varian MAT 311-A, combined FI/FD/EI ion source (EMC range: 13–20 mA), 70 eV, direct inlet system. – Melting points: Büchi mod. 510 (capillary) apparatus.

Thiazolium-4-olates **1a–d** have been already described: **1a** and **1b**[14], **1c** and **1d**[15].

4,5-Dihydro-4-methylene-1H-v-triazoles **2a–c** have been described previously: **2a**[2], **2b**[9], **2c**[16].

(1S,4S*,5S*,5'S*)-1',5'-Dihydro-1'-(4-methylphenyl)-5'-morpholino-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**3a**) *and (1S*,4S*,5R*,5'R*)-1',5'-Dihydro-1'-(4-methylphenyl)-5'-morpholino-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**4a**): 4-Methylene-4,5-dihydrotriazole **2a** (1.6 g, 6.1 mmol) was suspended under nitrogen in anhydrous toluene (20 ml) and the mixture heated to reflux. Then solid thiazolium-4-olate **1a** (2.0 g, 6.1 mmol) was added. The reaction mixture was refluxed for about 2 h until the starting material had disappeared (TLC, benzene/ethyl acetate, 4:1). The solvent was removed in vacuo. The obtained solid residue, dissolved in dichloromethane, yielded compound **4a** as a crystalline product. After filtration and evaporation of dichloromethane the crude **3a** was recovered and recrystallized.

3a: 0.97 g (24%), m.p. 204°C (C_6H_6). – IR (nujol): $\tilde{\nu}$ = 1710 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 1.85–2.44 (m, 2H, CH_2N), 2.60–2.88 (m, 2H, CH_2N), 2.26 (s, 3H, CH_3), 3.32–3.71 (m, 4H, CH_2O), 3.46 and 3.90 (dd, 2H, AB system, J = 12.3 Hz), 4.68 (s, 1H, CH), 6.55–7.70 (m, 19H, aryl-H).

$C_{35}H_{33}N_5O_2S \cdot C_6H_6$ (665.8)
Calcd. C 74.01 H 5.86 N 10.52
Found C 73.78 H 5.77 N 10.65

4a: 1.43 g (40%), m.p. 220°C (Et_2O). – IR (nujol): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). – ^{1}H NMR ($CDCl_3$): δ = 1.96–2.47 (m, 2H, CH_2N), 2.30 (s, 3H, CH_3), 2.73–2.87 (m, 2H, CH_2N), 3.27–3.78 (m, 4H, CH_2O), 3.68 and 3.98 (dd, 2H, CH_2, AB system, J = 12.2 Hz), 5.33 (s, 1H, CH), 6.95–7.91 (m, 19H, aryl-H).

$C_{35}H_{33}N_5O_2S$ (587.7)
Calcd. C 71.52 H 5.66 N 11.92
Found C 71.31 H 5.71 N 11.81

(1R,4S*,5S*,5'S*)-1',5'-Dihydro-1'-(4-methylphenyl)-5'-morpholino-3-oxo-2,4-diphenyl-1-(phenylthio)spiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**3b**) *and (1R*,4S*,5R*,5'R*)-1',5'-dihydro-1'-(4-methylphenyl)-5'-morpholino-3-oxo-2,4-diphenyl-1-(phenylthio)spiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**4b**): 4-Methylene-4,5-dihydrotriazole **2a** (2.3 g, 8.9 mmol) was suspended under nitrogen in anhydrous toluene (40 ml) and the mixture brought to reflux. Then solid thiazolium-4-olate **1b** (3.2 g, 8.9 mmol) was added. The reaction mixture was refluxed for 2 h and allowed to cool. The collected precipitate

was washed twice with diisopropyl ether to yield a mixture of **3b** and **4b**, 4.3 g (79%). – IR (nujol): $\tilde{\nu}$ = 1710, 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.60–2.85 (m, 4H, CH_2N, **3b** and **4b**), 2.23 (s, 3H, CH_3, **3b**), 2.28 (s, 3H, CH_3, **4b**), 3.10–3.60 (m, 4H, CH_2O, **3b** and **4b**), 3.40 and 3.64 (dd, 2H, CH_2, AB system, J = 12.3 Hz, **3b**), 3.40 and 3.61 (dd, 2H, CH_2, AB system, J = 12.2 Hz, **4b**), 4.54 (s, 1H, CH, **3b**), 5.18 (s, 1H, CH, **4b**), 6.50–7.74 (m, 19H, aryl-H, **3b** and **4b**).

$C_{35}H_{33}N_5O_2S_2$ (619.8)
Calcd. C 67.82 H 5.36 N 11.30
Found C 67.46 H 5.40 N 11.12

(1S,4S*,5S*,5'S*)-1',5'-Dihydro-5'-morpholino-1'-(4-nitrophenyl)-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**3c**) *and (1S*,4S*,5R*,5'R*)-1',5'-Dihydro-5'-morpholino-1'-(4-nitrophenyl)-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**4c**): 4-Methylene-4,5-dihydrotriazole **2c** (1.80 g, 6.1 mmol) was suspended in anhydrous toluene (40 ml) and the mixture refluxed under nitrogen. Then solid thiazolium-4-olate **1a** (2.0 g, 6.1 mmol) was added. The reaction mixture was refluxed for 2 h and the solvent evaporated at reduced pressure. The obtained solid residue was chromatographed on a silica gel column (eluent: acetone/cyclohexane, 3:7).

3c: 0.90 g (27%), m.p. 189°C (C_6H_6). – IR (nujol): $\tilde{\nu}$ = 1710 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.98–2.35 (m, 2H, CH_2N), 2.75–3.05 (m, 2H, CH_2N), 3.34–3.70 (m, 4H, CH_2O), 3.52 and 3.89 (dd, 2H, CH_2, AB system, J = 12.2 Hz), 4.68 (s, 1H, CH), 6.85–8.24 (m, 19H, aryl-H).

$C_{34}H_{30}N_6O_4S$ (618.7)
Calcd. C 66.00 H 4.88 N 13.58
Found C 65.88 H 4.97 N 13.46

4c: 1.21 g (32%), m.p. 209°C (iPr_2O). – IR (nujol): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.91–2.25 (m, 2H, CH_2N), 2.75–3.02 (m, 2H, CH_2N), 3.40–3.72 (m, 4H, CH_2O), 3.79 and 3.98 (dd, 2H, CH_2, AB system, J = 12.2 Hz), 5.31 (s, 1H, CH), 6.95–8.22 (m, 19H, aryl-H).

$C_{34}H_{30}N_6O_4S$ (618.7)
Calcd. C 66.00 H 4.88 N 13.58
Found C 65.92 H 4.79 N 13.35

(1S,4S*,5S*,5'S*)-1',5'-Dihydro-5'-morpholino-1',4-bis(4-nitrophenyl)-3-oxo-1,2-diphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**3d**) *and (1S*,4S*,5R*,5'R*)-1',5'-Dihydro-5'-morpholino-1',4-bis(4-nitrophenyl)-3-oxo-1,2-diphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**4d**): 4-Methylene-4,5-dihydrotriazole **2c** (3.0 g, 10.4 mmol) was suspended in anhydrous toluene (60 ml) and the mixture refluxed under nitrogen. Then solid thiazolium-4-olate **1d** (3.9 g, 10.4 mmol) was added and the mixture refluxed for 2 h. The solvent was evaporated in vacuo and the solid residue taken up in dichloromethane. Ethyl ether was added to yield a crystalline mixture of **3d** and **4d**, which was separated on a silica gel column (eluent: acetone/cyclohexane, 3:7); **3d** was obtained in pure form, **4d** as a mixture with **3d** (70:30, ^1H NMR).

3d: 1.38 g (20%), m.p. 188°C (EtOH). – IR (nujol): $\tilde{\nu}$ = 1710 cm^{-1} (C=O). – ^1H NMR ([D_6]DMSO): δ = 1.83–2.18 (m, 2H, CH_2N), 3.10–3.80 (m, 6H, CH_2N and CH_2O), 3.88 and 3.98 (dd, 2H, CH_2, AB system, J = 13.4 Hz), 4.89 (s, 1H, CH), 7.05–8.05 (m, 18H, aryl-H).

$C_{34}H_{29}N_7O_6S$ (663.7)
Calcd. C 61.52 H 4.40 N 14.77
Found C 61.20 H 4.51 N 14.64

3d + **4d** (30:70): 3.10 g (45%). – IR (nujol): $\tilde{\nu}$ = 1710, 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.85–2.30 (m, 2H, CH_2N), 2.75–3.10 (m, 2H, CH_2N), 3.35–4.00 (m, 4H, CH_2O), 3.82 and 4.01 (dd, 2H, CH_2, AB system, J = 12.4 Hz, **4d**), 3.83 and 3.92 (dd, 2H, CH_2, AB system, J = 12.7 Hz, **3d**), 4.59 (s, 1H, CH, **3d**), 5.32 (s, 1H, CH, **4d**), 6.90–8.50 (m, 18H, aryl-H).

(1S,4S*,5S*,5'S*)-1',5'-Dihydro-1'-(4-methylphenyl)-4-(4-methoxyphenyl)-5'-morpholino-3-oxo-1,2-diphenylspiro[7-thia-2-azabicyclo[2.2.1]heptan-5,4'-[4H][1,2,3]triazole]* (**3e**) *and (1S*,4S*,5R*,5'R*)-1',5'-Dihydro-1'-(4-methylphenyl)-4-(4-methoxyphenyl)-5'-morpholino-3-oxo-1,2-diphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'[4H][1,2,3]triazole]* (**4e**): 4-Methylene-4,5-dihydrotriazole **2a** (3.0 g, 11.6 mmol) was suspended in anhydrous toluene (40 ml) and the mixture refluxed under nitrogen. Then solid thiazolium-4-olate **1c** (4.2 g, 11.6 mmol) was added and the reaction mixture refluxed for 2 h. After evaporation of the solvent at reduced pressure the solid residue was dissolved in dichloromethane. Addition of ether afforded **3e** as a crystalline precipitate. The concentrated mother liquor yielded a second crystalline product which was identified as **4e**.

3e: 2.0 g (28%), m.p. 206°C (Et_2O). – IR (nujol): $\tilde{\nu}$ = 1700 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.94–2.04 and 2.22–2.45 (2 m, 1 + 1H, CH_2N), 2.27 (s, 3H, CH_3), 2.63–2.91 (m, 2H, CH_2N), 3.38–3.79 (m, 4H, CH_2O), 3.48–3.90 (dd, 2H, CH_2, AB system, J = 12.2 Hz), 3.65 (s, 3H, OCH_3), 4.66 (s, 1H, CH), 6.65–7.55 (m, 18H, aryl-H).

$C_{36}H_{35}N_5O_3S$ (617.7)
Calcd. C 70.70 H 5.71 N 11.33
Found C 70.41 H 5.65 N 10.98

4e: 3.09 g (34%), m.p. 200°C (C_6H_6). – IR (nujol): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.92–2.09 and 2.19 to 2.45 (2 m, 1 + 1H, CH_2N), 2.35 (s, 3H, CH_3), 2.70–2.92 (m, 2H, CH_2N), 3.20–3.75 (m, 4H, CH_2O), 3.70 and 3.96 (dd, 2H, AB system, J = 12.2 Hz), 3.67 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 6.67–7.79 (m, 18H, aryl-H).

$C_{36}H_{35}N_5O_3S$ (617.7)
Calcd. C 70.70 H 5.71 N 11.33
Found C 70.52 H 5.73 N 11.55

(1S,4S*,5S*,5'S*)-1',5'-Dihydro-1'-(4-methoxyphenyl)-5'-morpholino-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'[4H][1,2,3]triazole]* (**3f**) *and (1S*,4S*,5R*,5'R*)-1',5'-Dihydro-1'-(4-methoxyphenyl)-5'-morpholino-3-oxo-1,2,4-triphenylspiro[7-thia-2-azabicyclo[2.2.1]heptane-5,4'-[4H][1,2,3]triazole]* (**4f**): 4-Methylene-4,5-dihydrotriazole **2b** (3.0 g, 11.0 mmol) was suspended in anhydrous toluene (40 ml) and the mixture refluxed under nitrogen. Then solid thiazolium-4-olate **1a** (3.6 g, 11.0 mmol) was added. The reaction mixture was refluxed for 1 h and the solvent evaporated in vacuo. The solid residue was chromatographed on a silica gel column (eluent: cyclohexane/ethyl acetate, 1:4). The first fraction was identified as a mixture of **3f** and **4f** (70:30, ^1H NMR). The second fraction contained pure **4f**. **3f** + **4f** (70:30) 2.52 g (38%). – IR (nujol): $\tilde{\nu}$ = 1710, 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.92–2.50 (m, 2H, CH_2N), 2.50–2.85 (m, 2H, CH_2N), 3.35–4.10 (m, 6H, CH_2O and CH_2, AB system, **3f** and **4f**), 3.75 (s, 3H, OCH_3, **3f**), 3.78 (s, 3H, OCH_3, **4f**), 4.65 (s, 1H, CH, **3f**), 5.31 (s, 1H, CH, **4f**), 6.5–8.05 (m, 19H, aryl-H).

4f: 1.66 g (25%), m.p. 217°C (iPr_2O). – IR (nujol): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 1.98–2.50 (m, 2H, CH_2N), 2.60–2.85 (m, 2H, CH_2N), 3.35–4.10 (m, 4H, CH_2O), 3.78 (s, 3H,

Table 2. Physical and analytical data of **5**, **6**, **7**, **8**

Compd.	M.p.	Yield %	IR (nujol) $\tilde{\nu}$ [cm^{-1}]	^1H NMR ($CDCl_3$) δ values	Analysis Formula (mol. weight)	Calcd. / Found C	H	N
5a	191[c]	55	3330 (NH), 1635 (C=O)	2.25 (s, 3H, CH_3), 4.13 (s, 3H, CH_2 and NH, H/D exchange with D_2O), 6.71 (s, 1H, 5-H), 6.61–7.43 (m, 19H, aryl-H)	$C_{31}H_{26}N_2O$ (442.5)	84.13 / 84.04	5.92 / 5.88	6.33 / 6.44
5b	200[d]	65	3400 (NH), 1645 (C=O)	2.25 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2), 6.50 (s, 1H, 5-H), 6.30–7.48 (m, 19H, aryl-H and NH, H/D exchange with D_2O)	$C_{32}H_{28}N_2O_2$ (472.5)	81.32 / 80.97	5.97 / 5.97	5.93 / 5.68
5c	207–208[d]	55	3310 (NH), 1630 (C=O)	3.72 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.73 (s, 1H, 5-H), 6.45–7.40 (m, 20H), aryl-H and NH, H/D exchange with D_2O)	$C_{31}H_{26}N_2O_2$ (458.5)	81.19 / 80.91	5.71 / 5.67	6.11 / 5.89
5d	179[d]	55	3340 (NH), 1635 (C=O)	2.22 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 6.51 (d, J = 7.12 Hz, 1H, 5-H), 6.40–7.50 (m, 16H, aryl-H, 6-H and NH, H/D exchange with D_2O)	$C_{25}H_{22}N_2O$ (366.4)	81.93 / 81.65	6.05 / 5.91	7.64 / 7.57
6a[a]	153[c] (dec)	60	3340 (NH), 1710 and 1690 (C=O)	2.25 (s, 3H, CH_3), 3.69 and 3.87 (dd, 2H, CH_2, AB system, J = 15.8 Hz), 4.85 (s, 1H, CH), 6.72–7.67 (m, 20H, aryl-H and NH, H/D exchange with D_2O)	$C_{31}H_{26}N_2O_2S$ (490.6)	75.88 / 75.75	5.34 / 5.26	5.71 / 5.58
6b[a]	185–186[c]	70	3320 (NH), 1710 and 1690 (C=O)	2.21 (s, 3H, CH_3), 2.95 and 3.44 (dd, 2H, CH_2, AB system, J = 16.0 Hz), 4.30 (broad s, 1H, NH, H/D exchange with D_2O), 4.70 (s, 1H, CH), 6.66–6.69 (dd, 4H, aromatic AB system, J = 8.12 Hz), 7.00–7.60 (m, 15H, aryl-H)	$C_{31}H_{26}N_2O_2S_2$ (522.6)	71.23 / 71.48	5.01 / 4.98	5.36 / 5.35
6c[b]	194[d]	70	3375 (NH), 1715 and 1690 (C=O)	3.78 and 3.84 (dd, 2H, CH_2, AB system, J = 16.1 Hz), 4.92 and 4.96 (d, 1H, NH, H/D exchange with D_2O, J = 8.9 Hz), 5.18 and 5.23 (d, 1H, CH, J = 8.9 Hz), 6.80–8.12 (m, 19H, aryl-H)	$C_{30}H_{23}N_3O_4S$ (521.5)	69.08 / 68.77	4.44 / 4.68	8.05 / 7.88
6d[b]	205[d]	65	3350 (NH), 1705 and 1685 (C=O)	2.25 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.65 and 3.85 (dd, 2H, CH_2, AB system, J = 15.7 Hz), 4.80 (s, 1H, CH), 6.70–7.60 (m, 19H, aryl-H and NH, H/D exchange with D_2O)	$C_{32}H_{28}N_2O_3S$ (520.6)	73.82 / 73.64	5.42 / 5.31	5.38 / 5.06
6e[b]	172[d]	50	3330 (NH), 1710 and 1690 (C=O)	3.70 and 3.87 (dd, 2H, CH_2, AB system, J = 15.8 Hz), 3.75 (s, 3H, OCH_3), 4.35 and 4.39 (d, 1H, NH, H/D exchange with D_2O, J = 8.6 Hz), 4.75 and 4.79 (d, 1H, CH, J = 8.6 Hz), 6.39–7.70 (m, 19H, aryl-H)	$C_{31}H_{26}N_2O_3S$ (506.6)	73.48 / 73.27	5.17 / 5.01	5.53 / 5.12
7[a]	187–189[e]	20	1640 (C=O)	2.32 (s, 3H, CH_3), 6.78 (s, 1H, 5-H), 6.92 and 7.15 (dd, 4H, aromatic AB system, J = 8.4 Hz), 7.30–7.50 (m, 15H, aryl-H), 8.24 (s, 1H, CH=N)	$C_{31}H_{24}N_2OS$ (472.6)	78.78 / 78.35	5.12 / 5.07	5.92 / 5.54
8[a]	230[d]	20	1640 (C=O)	3.95–4.15 (m, 4H, OCH_2CH_2O), 5.5 (s, 1H, acetalic H), 6.54 (s, 1H, 5-H), 7.15–7.46 (m, 15H, aryl-H)	$C_{26}H_{21}NO_3$ (395.4)	78.96 / 78.86	5.35 / 5.14	3.54 / 3.30

[a] Compounds **6a**, **6b**, **7** and **8** purified according to method b. – [b] Compounds **6c**, **6d** and **6e** purified according to method a. – [c] From H_2O. – [d] From EtOH. – [e] From iPr_2O. – Appendix: MS data (m/z, %): **7**: EI-MS: 472 (78), 471 (100) [M^+], 395 (21), 363 (20), 115 (43), 91 (31), 77 (37), 65 (35). – **8**: EI-MS: 396 (22), 395 (100) [M^+], 366 (18), 350 (17), 321 (26), 322 (25), 310 (19), 295 (22).

OCH_3), 3.67 and 3.97 (dd, 2H, CH_2, AB system, J = 12.2 Hz), 5.30 (s, 1H, CH), 6.75–8.05 (m, 19H, aryl-H).

$C_{35}H_{33}N_5O_3S$ (603.7)

Calcd. C 69.63 H 5.51 N 11.60

Found C 69.48 H 5.25 N 11.98

2(1H)-Pyridinones **5a–d**, *General Procedure:* 9–10 g of Raney nickel catalyst was suspended in ethanol (under nitrogen) at room temp. **3a** or **4a** or mixtures **3b** + **4b**, **3e** + **4e**, **3f** + **4f** (15 mmol) were added in one portion. The reaction mixture was stirred for 1 h until the starting material had been consumed (monitored by TLC: ethyl acetate/benzene, 1:4). The nickel catalyst was filtered off and washed twice with ethanol. The combined filtrate and washings were concentrated under reduced pressure. The crude product was crystallized from the solvent listed in Table 2 to afford pure products **5a–d** (physical and analytical data in Table 2).

8-Thia-6-azabicyclo[3.2.1]octan-3-ones **6** *and 2(1H)-Pyridinones* **7** *and* **8**. *General Procedure:* A solution of a mixture of **3a–f**, **4a–f** (16 mmol) in dioxane (25 ml) was added dropwise to a mixture of 37% HCl (5 ml) and dioxane (40 ml). The reaction mixture was stirred at room temp. until the starting material had disappeared (monitored by TLC: benzene/ethyl acetate, 4:1). The dioxane was evaporated at reduced pressure. The aqueous phase was neutralized with a 50% sodium hydrogencarbonate solution and extracted several times with dichloromethane (60 ml). The united extracts were dried with Na_2SO_4, the solvent was evaporated, and the product purified by chromatography on a silica gel column (eluent in method a: ethyl acetate/benzene (1:9) for **6c, d, e** and for method b: ethyl acetate/cyclohexane (3:7) for **6a, b, 7, 8**). For analytical data see Table 2.

CAS Registry Numbers

1a: 18100-80-6 / **1b**: 61522-18-7 / **1c**: 66702-52-1 / **1d**: 59208-01-0 / (±)-**2a**: 138813-45-3 / (±)-**2b**: 138813-46-4 / (±)-**2c**: 80857-11-0 / (±)-**3a**: 138813-47-5 / (±)-**3b**: 138813-48-6 / (±)-**3c**: 138813-49-7 / (±)-**3d**: 138813-50-0 / (±)-**3e**: 138813-51-1 / (±)-**3f**: 138813-52-2 / (±)-**4a**: 138875-99-7 / (±)-**4b**: 138876-00-3 / (±)-**4c**: 138876-01-4 / (±)-**4d**: 138876-02-5 / (±)-**4e**: 138876-03-6 / (±)-**4f**: 138876-04-7 / **5a**: 138813-53-3 / **5b**: 138813-54-4 / **5c**: 138813-55-5 / **5d**: 138813-56-6 / **6a**: 138813-57-7 / **6b**: 138813-58-8 / **6c**: 138813-59-9 / **6d**: 138813-60-2 / **6e**: 138813-61-3 / **7**: 138813-62-4 / **8**: 138813-63-5

[1] E. Arlandini, F. Clerici, E. Erba, L. M. Rossi, *Chem. Ber.* **1990**, *123*, 217–220.
[2] R. Destro, E. Erba, L. Forti, D. Pocar, D. Scarcella, *Liebigs Ann. Chem.* **1985**, 1377–1388.
[3] E. Erba, M. L. Gelmi, D. Pocar, P. Trimarco, *Chem. Ber.* **1986**, *119*, 1083–1089.
[4] A separate publication gives a detailed description of these spectroscopic studies[5].
[5] F. Clerici, E. Erba, *Gazz. Chim. Ital.*, in press.
[6] K. T. Potts, J. Baum, E. Houghton, *J. Org. Chem.* **1974**, *39*, 3631–3641.
[7] K. T. Potts, E. Houghton, U. P. Singh, *J. Org. Chem.* **1974**, *39*, 3627–3631.
[8] K. T. Potts, M. O. Dery, W. A. Juzukonis, *J. Org. Chem.* **1989**, *54*, 1077–1088.
[9] N. Almirante, M. Ballabio, G. Bianchetti, A. Cambiaghi, D. Pocar, *J. Chem. Res. (S)* **1986**, 132–133.
[10] D. D'Oria, D. Pocar, L. M. Rossi, P. Trimarco, *J. Chem. Res. (S)* **1980**, 242–243.
[11] P. Dalla Croce, C. La Rosa, D. Pocar, *J. Chem. Res. (S)* **1983**, 296–297.
[12] A. Katritzky, A. V. Chapman, M. J. Cook, J. H. Millet, *J. Chem. Soc., Perkin Trans 1*, **1980**, 2743–2754; L. E. Overman, S. Tsuboi, J. P. Roos, G. F. Taylor, *J. Am. Chem. Soc.* **1980**, *102*, 747–754.
[13] D. Pocar, R. Stradi, L. M. Rossi, *J. Chem. Soc., Perkin Trans 1*, **1972**, 769–771.
[14] K. T. Potts, S. J. Chen, J. Kane, J. L. Marshall, *J. Org. Chem.* **1977**, *42*, 1633–1638.
[15] M. Baudy, A. Robert, A. Foucaud, *J. Org. Chem.* **1978**, *43*, 3732–3736.
[16] P. Dalla Croce, D. Pocar, R. Stradi, P. Trimarco, *J. Chem. Soc., Perkin Trans 1*, **1980**, 141–145.

[325/91]