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BENZOXADIAZOCINES, BENZOTHIADIAZOCINES AND BENZOTRIAZOCINES—III

THE SYNTHESIS OF 2-(subst.)AMINO- AND 2-(2-subst.HYDRAZINO)-6-(ALKYLSULFONYL AND ARYLSULFONYL)-5,6-DIHYDRO-4H-3,1,6-BENZOTHIADIAZOCINES

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Abstract—A series of derivatives of the novel 5,6-dihydro-4*H*-3,1,6-benzothiadiazocine ring system has been synthesised for pharmacological screening by application of a method devised earlier by two of the authors. The proof of structure of the benzothiadiazocine derivatives is based on chemical and spectroscopic evidence.

IN Part I[1] of the present series a general method was described for the synthesis of derivatives of the novel 3,1,6-benzoxadiazocine, 3,1,6-benzothiadiazocine and 1,3,6-benzotriazocine ring systems, the key-step of the synthesis consisting in the ring closure of type **1** intermediates with suitable C=Y or C-Y and  components, respectively, to furnish the desired products **2a** or **2b** (Chart 1). We now report on the synthesis of a series of 2-(subst.) amino- and 2-(2-subst. hydrazino) - 5,6 - dihydro - 4*H* - 3,1,6 - benzothiadiazocines carrying, for the reasons explained in Part I, arylsulfonyl or methylsulfonyl groups attached to position 6 (**2a**, X=S; Y=NH_2, NHR', NR'R"; R=$MeSO_2$, $ArSO_2$; = **10**). The method of synthesis is outlined in Chart 2.

The 2'-nitro-N-sulfonylanilides **5** were obtained by known methods either by nitration of the sulfonylanilides **3** (step Ⓐ or by sulfonylation of the 2-nitranilines **4** (step Ⓑ). Subsequently they were allowed to react with 1,2-dibromoethane at elevated temperatures either in form of the Na-salts prepared in a separate step (method Ⓒ1) or in form of the *in situ* prepared K-salts (method Ⓒ2). Selective catalytic reduction of the nitro groups of the resulting compounds **6** furnished their amino analogues **7** (step Ⓓ) most of which were non-crystalline substances. Therefore and because of their

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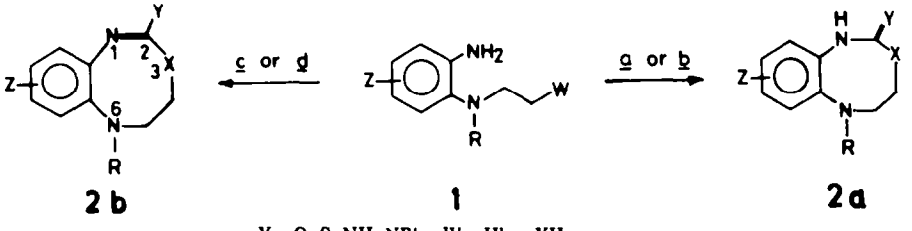
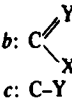


X = O, S, NH, NR'; W = Hlg, -XH

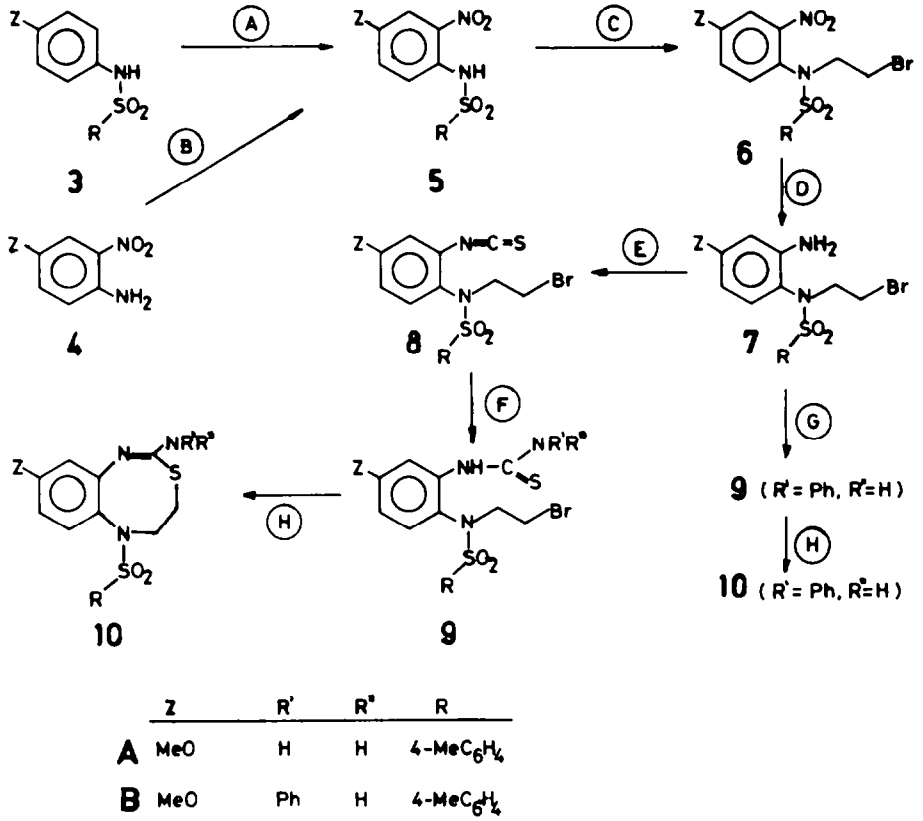
a: C=Y component (when W = XH)

b:  component (when W = leaving group)

c: C-Y component (when W = XH)

d:  component (when W = leaving group)

Chart 1.



	Z	R'	R"	R
A	MeO	H	H	4-MeC$_6$H$_4$
B	MeO	Ph	H	4-MeC$_6$H$_4$

Ⓐ: dil. HNO_3; Ⓑ: R-SO_2Cl + pyridine; (C1): NaOMe + MeOH, then Na-salt + Br~Br, DMF, 120°; (C2): K_2CO_3 + Br~Br, DMF or MeCOEt, steam bath; Ⓓ: H_2/Pd–C; Ⓔ: $CSCl_2/CH_2Cl_2 + H_2O$; Ⓕ: R'R"NH (≈ 1 molar equivalent), Et_2O, reflux; Ⓖ: PhNCS, dioxane, reflux; Ⓗ: Et_3N, EtOH, reflux.

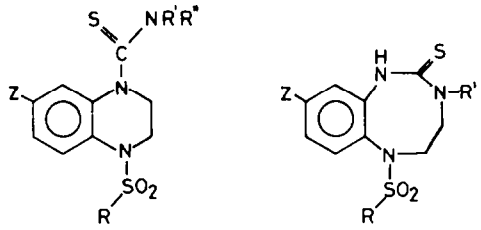
Chart 2.

sensitivity to air they were, without further purification, immediately allowed to react with thiocarbonyl dichloride (step Ⓔ) or phenyl isothiocyanate (step Ⓖ) to obtain the corresponding compounds **8** and **9** (R'=Ph, R"=H), respectively.

Most of the isothiocyanates **8** were non-crystalline substances. They were therefore, after their purity had been checked by TLC, converted without characterization by microanalyses either into the thioureas **9** (step Ⓕ) or, if the compounds **9** were non-crystalline, into the dihydrobenzothiadiazocines **10** (step Ⓕ + Ⓗ). Using an excess of the amines (or addition of a tertiary amine to the reaction mixture) as well as elevation of the temperature and prolongation of the reaction-time favoured the formation of the cyclized products **10**.

In principle, method Ⓖ should be applicable to the synthesis of other type **9** (R"=H) thioureas as well but would require the preparation of the appropriate R'NCS isothiocyanates. Therefore the two-step (Ⓔ + Ⓕ) rather than the one-step method (Ⓖ) of preparation of the thioureas **9** (R"=H) was preferred; moreover, thioureas **9** (R'=H, R"=H) may be synthesised solely by the two-step process.

The method used for the synthesis of the compounds **10** is not structure-proving in itself. The ring closure of the precursors **9** could have furnished in principle the



	11, 12 Z	R'	R"	R
A	MeO	H	H	4-MeC$_6$H$_4$
B	MeO	Ph	H	4-MeC$_6$H$_4$

isomers **11** and, for R"=H, the isomers **12** as well. It was therefore necessary to prove the correctness of structures **10** unambiguously.

The type **12** structures were ruled out for the cyclization products of the thioureas **9** on the basis of the following observations:

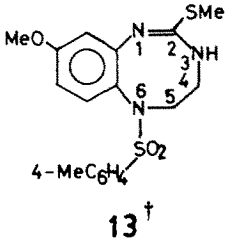
(1) The cyclization product of **9A** was found to be different from **12A** obtained by structure proving synthesis.[8]

(2) The IR and ^{1}H NMR spectra of the cyclization

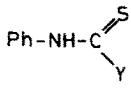
products of **9** were found to be all very similar irrespective of whether R″=H or both R′ and R″≠H, that is whether the formation of type **12** cyclization products is in principle possible or not.

This chemical evidence is in complete agreement with spectroscopic studies which, in addition, ruled out the isomeric structures **11** for the cyclization products as well.

Compounds **9B**, **12A**,[8] **13**[8] thiocarbanilide (**14a**) and N-phenylthiocarbamoylpyrrolidine (**14b**)[9] were used as reference substances for the spectroscopic studies.



13†



14 a: Y=—NHPh

14 b: Y=—N

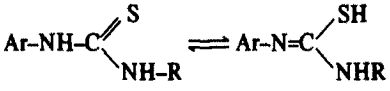
Structures **10A** and **10B** for the cyclization products of **9A** and **9B**, respectively, are proved by the following spectroscopic evidence:

(1) The ^{1}H NMR spectra‡ of the cyclization products of **9A** and **9B** exhibit a triplet§ at δ2.85 ppm and a structured multiplet§ at δ2.8–3.2 ppm, respectively, both of 2H intensity. These values may be compared with the chemical shifts 4.23 (t, 2H), 3.19 (q, 2H) and 7.78 (t, 1H),§ and 4.14 (t) and 3.08 (t) corresponding to the N–CH_2–CH_2–NH and N–CH_2–CH_2–N moieties of **12A** and **13**, respectively, and suggest that the former signals originate from S–CH_2 rather than N–CH_2 groups although the signals of one N–CH_2 group, each, of **12A** and **13** appears at not much lower fields.

(2) The signals of the methylene C atoms of **12A** and **13** appear at 40.5 and 43.2, and 42.0 and 43.7 ppm,¶ respectively, while the cyclization products of **9A** and **9B** exhibited methylene C signals at 31.1 and 33.5 ppm, respectively. By application of the known additivity rules[10] it was shown that these high-field methylene signals result from S–CH_2 groups.

(3) The signals at lowest fields in the ^{13}C NMR spectra of **9b**, **14a** and **14b** are found at 180.1, 179.8 and 177.6 ppm, respectively, and are in agreement with the values reported in literature[10,11] for the chemical shifts of the central C atoms of thiourea groupings. In the spectra of **13** and of the cyclization products of **9A** and **9B** the lowest field signals are found at 151.9, 150.7 and 151.5 ppm, respectively, as expected[10,11] for the chemical shifts of the central C atoms of isothiourea groupings.

The lowest-field signal in the spectrum of **12A** was found at δ 167.7 ppm which possibly indicates the existence of a tautomeric equilibrium of the type



The ^{1}H NMR spectrum of **10A** exhibits an NH_2 signal at δ 6.86 ppm (2H) which proves that this compound exists in solution predominantly if not exclusively in the amino form shown. The same is true in $CHCl_3$ solution since the IR spectrum ($CHCl_3$) exhibits a pair of νNH_2 bands at 3520 and 3400 cm^{-1}, and no other νNH bands.

The benzothiadiazocine derivatives described were screened for pharmacological activities by Dr. L. Petőcz and staff. The toxicities of all compounds are very low and many of them showed CNS activities. The compounds with Z=MeO and –NR′R″ = morpholino were potent Hexobarbital antagonists in mice with their activities decreasing in the order R=Me > Ph > 4-MeC_6H_4. The detailed results will be published elsewhere.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained with a JEOL FX-100 spectrometer at 100 and 25 MHz, respectively, using TMS as the internal reference. The IR spectra were obtained in KBr pellets using a Perkin–Elmer Model 421 spectrometer.

The *2′-nitro-N-sulfonylanilides* **5** (R=4-MeC_6H_4, Z=H;[2] R=4-MeC_6H_4, Z=Cl;[3] R=4-MeC_6H_4, Z=Br;[4] R=4-MeC_6H_4, Z=MeO;[5] R=4-MeC_6H_4, Z=Me;[6] R=Ph, Z=MeO;[7] and R=Me, Z=MeO[7]) were known compounds and have been obtained as described in literature.

For the preparation of N - (2 - *bromoethyl*) - 4′ - *methoxy* - 2′ - *nitrosylanilide* (**6**; R=4-MeC_6H_4, Z=MeO) and N - (2 - *bromoethyl*) - 2′ - *nitrosylanilide* (**6**; R=4-MeC_6H_4, Z=H) by method (C1), see Part II.[8] For additional compounds obtained by this method, see Table 1. For the preparation of N - (2 - *bromoethyl*) - 4′ - *methyl* - 2′ - *nitrosylanilide* (**6**; R=4-MeC_6H_4, Z=Me) by method (C2), see Part II.[8] For additional compounds obtained by this method, see Table 1.

2′ - *Amino* - N - (2 - *bromoethyl*) - 4′ - *methoxytosylanilide* (**7**; R=4-MeC_6H_4, Z=MeO). Compound **6** (R=4-MeC_6H_4, Z=MeO) (42.9 g; 0.1 mol) was reduced in a mixture of dioxane (300 ml) and EtOH (50 ml) at normal pressure and room temp. in the presence of a 5% Pd–C catalyst (2 g). After uptake of the calculated amount of H_2 the catalyst was filtered off and the filtrate was evaporated to dryness at room temp *in vacuo*. The residue was dissolved in EtOH (200 ml); saturated aqueous (10 ml) $Na_2S_2O_4$ soln was added and the mixture was concentrated *in vacuo* until crystallization of the product just started. The mixture was allowed to cool, and the colourless crystals (30.4 g; 76%) of the title compound, m.p. 125–127° from EtOH, were filtered off and washed with water. (Found: Br, 19.59; N, 7.40; S, 8.41. $C_{16}H_{19}BrN_2O_3S$ (399.3) requires: Br, 20.01; N, 7.01; S, 8.03%.)

N - (2 - *Bromoethyl*) - 2′ - *isothiocyanato* - 4′ - *methoxytosylanilide* (**8**; R=4-MeC_6H_4, Z=MeO). To the soln of **7** (R=4-MeC_6H_4, Z=MeO) (32 g; 80 mmol) in CH_2Cl_2 (160 ml) was added a mixture of ice (200 g) and water (100 ml) and subsequently dropwise with vigorous stirring thiocarbonyl dichloride (8 ml; 110 mmol). The mixture was stirred for 2 hr at 0°C and kept overnight in a refrigerator. The organic layer was separated and extracted successively with two portions of water (40 ml, each), 10% $NaHCO_3$ aq (40 ml) and water (40 ml), dried ($MgSO_4$) and evaporated to dryness to obtain 31.5 g (89%) of an oil which gradually turned crystalline, m.p. 98–100° from EtOH. (Found: C, 46.69; H, 3.70; Br, 18.00. $C_{17}H_{17}BrN_2O_3S_2$ (441.4) requires: C, 46.25; H, 3.88; Br, 18.10%.)

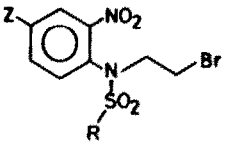
†Or tautomeric 1,4,5,6-tetrahydro form.

‡The NMR spectra of **9B** and its cyclization product (**10B**) were obtained in $CDCl_3$, all other NMR spectra in DMSO-d_6.

§The multiplicities indicate rapid inversion of the 8-membered rings of **12A** and of the cyclization product of **9A** which results in the equatorial and axial methylene protons becoming equivalent on the average; and that, in contrast, in the cyclization product of **9B** the 8-membered ring exists predominantly in form of the most stable of its conformers.

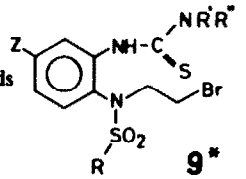
¶By selective ^{13}C{^{1}H} decoupling it was shown that the signals at higher field originate from the methylene C atoms directly attached to the thiourea and isothiourea grouping, respectively.

Table 1. Preparation, m.p's and analytical data of compounds

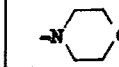
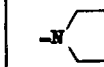
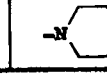


6

Z	R	Method	Yield,%	M.p., °C (recryst. from.)	Molecular formula (Molecular weight)	Calculated Found, %
MeO	4-MeC_6H_4	C_1 C_2	70 89	114-115 (EtOH)	Ref.8.	
H	4-MeC_6H_4	C_1	41	90 (EtOH)	Ref.8.	
Cl	4-MeC_6H_4	C_1	78	123-125 (EtOH)	$C_{15}H_{14}BrClN_2O_4S$ (433.7)	C,41.53; H,3.25; N,6.46 C,41.45; H,3.42; N,6.18
Br	4-MeC_6H_4	C_2	82	126 (EtOH)	$C_{15}H_{14}Br_2N_2O_4S$ (478.2)	Br,33.42; N,5.86; S,6.70 Br,33.83; N,5.74; S,6.94
Me	4-MeC_6H_4	C_2	82	110-111 (EtOH)	Ref.8.	
MeO	Ph	C_1	67	105-106 (MeOH)	$C_{15}H_{15}BrN_2O_5S$ (415.3)	Br,19.24; N,6.75; S,7.72 Br,19.51; N,6.96; S,7.47
MeO	Me	C_1	88	136-137 (MeOH)	$C_{10}H_{13}BrN_2O_5S$ (353.3)	Br,22.63; N,7.93; S,9.08 Br,22.51; N,8.11; S,8.85

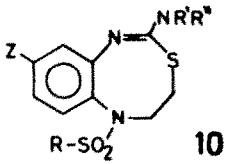
Table 2. Preparation, m.p's and analytical data of compounds 

9*

Z	-NR'R''	Method	Yield,%	M.p., °C (recryst. from)	Molecular formula (Molecular weight)	Calculated / Found, %
MeO	-NHPh	F G	82 60	162 (nitromethane)	$C_{19}H_{24}BrN_3O_3S_2$ (534.5)	Br,14.95; N,7.86; S,11.99 Br,14,87; N,8.06; S,11.93
MeO	$-NHC_6H_4Cl-(4)$	G	81	156 (EtOH)	$C_{23}H_{23}BrClN_3O_3S_2$ (568.9)	N,7.38; S,11.27 N,7.49; S,10.97
MeO	$-NHC_6H_4NO_2-(4)$	G	76	150-151 (EtOH)	$C_{23}H_{23}BrN_4O_5S_2$ (579.5)	Br,13.79; N,9.67; S,13.79 Br,13.60; N,9.69; S,13.60
MeO	$-NHC_6H_4-COOMe-(2)$	G	75	180 (nitromethane)	$C_{25}H_{26}BrN_3O_5S_2$ (592.6)	C,50.67; H,4.44; N,7.08; S,10.82 C,50.97; H,4.11; N,7.00; S,10.55
MeO	$-NHC_6H_4-COOEt-(4)$	G	70	205 (nitromethane)	$C_{26}H_{28}BrN_3O_5S_2$ (606.6)	Br,13.17; N,6.93; S,10.57 Br,13.15; N,6.87; S,10.36
MeO		G	93	161 (MeOH)	$C_{21}H_{26}BrN_3O_4S_2$ (528.5)	Br,15.12; N,7.95; S,12.13 Br,15.10; N,7.79; S,12.36
MeO	-NH-NHMe	G	29	124-125 (EtOH)	$C_{18}H_{23}BrN_4O_3S_2$ (487.4)	Br,16.38; N,11.49; S,13.16 Br,16.03; N,11.24; S,13.70
Cl		G	83	155-156 (MeOH)	$C_{20}H_{23}N_3BrClO_3S_2$ (552.9)	C,45.07; H,4.35; N,7.88; S,12.03 C,45.35; H,4.53; N,8.05; S,11.83
Br		G	63	145 (dec.) (MeOH)	$C_{20}H_{23}N_3Br_2O_3S_2$ (519.4)	Br,27.68; N,7.28; S,11.10 Br,27.25; N,7.50; S,10.83
Me		G	83	175 (EtOH)	$C_{21}H_{26}BrN_3O_3S_2$ (512.5)	Br,15.59; N,8.19; S,12.51 Br,15.86; N,8.10; S,12.83

* R = $4-CH_3C_6H_4$ throughout

Table 3. Preparation of 6-alkylsulfonyl- and 6-arylsulfonyl-5,6-dihydro-4*H*-3,1,6-benzothiadiazocines



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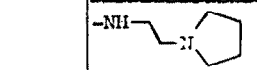
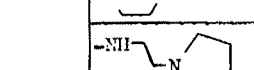
Z	R	-NR'R''	Method	Yield, %[a]	M.p., °C (recryst. from)	Formula Mol. wt.	Calculated/Found, % C	H	N	S	Br
MeO	4-MeC$_6$H$_4$-	-NH$_2$	H	20	196 (EtOH)	$C_{17}H_{19}N_3O_3S_2$ 377.4	54.11 54.41	5.08 5.26		16.96 16.83	
		-NHPh	H	81	182-183 (EtOH)	$C_{23}H_{23}N_3O_3S_2$ 453.5	60.90 60.93	5.11 5.41	9.26 9.37	14.13 13.65	
		-NHC$_6$H$_4$Cl-(4)	H	60	156 ($MeNO_2$)	$C_{23}H_{22}ClN_3O_3S_2$ 488.0	56.61 56.75	4.54 4.84	8.61 8.37	13.14 12.84	
		-NHC$_6$H$_4$NO$_2$-(4)	H	50	220 (EtOH)	$C_{23}H_{22}N_4O_5S_2$ 498.5	55.42 55.26	4.45 4.53	11.24 11.08		
		-NHC$_6$H$_4$COOMe-(2)	H	70	273 ($MeNO_2$)	$C_{25}H_{25}N_3O_5S_2$ 511.6	58.71 58.50	4.93 4.71	8.22 8.66	12.51 12.89	
		-NHC$_6$H$_4$COOEt-(4)	H	55	160 ($MeNO_2$)	$C_{26}H_{27}N_3O_5S_2$ 525.6	59.42 59.37	5.18 4.82	8.00 7.69	12.20 12.11	
			H	94	182 (MeOH)	$C_{21}H_{25}N_3O_4S_2$ 447.6	56.35 56.29	5.63 5.52	9.38 9.68	14.32 14.68	
		-NH-CH$_2$-COOEt	F+H[b]	47	100 (EtOH)	$C_{20}H_{25}N_3O_5S_2$ 451.6	54.40 54.25	5.43 5.51	9.06 8.88	13.83 13.61	
			F+H[c]	69	239-240(d) (EtOH-ether)	$C_{21}H_{29}BrN_4O_3S_2$ 529.5			10.58 10.78	12.11 11.60	15.10 14.77

MeO	4-MeC$_6$H$_4$-	-NH- 	F+H[c]	68	218-220 (EtOH-ether)	$C_{23}H_{31}BrN_4O_3S_2$ 555.6			10.08 9.88	11.54 11.22	14.38 14.82
		-NH- 	F+H[c]	65	207-208 (EtOH-ether)	$C_{24}H_{33}BrN_4O_3S_2$ 569.6			9.83 9.72	11.25 10.94	14.03 14.18
		-NH- 	F+H[c]	77	219 (EtOH)	$C_{23}H_{31}BrN_4O_3S_2$ 571.6	48.33 48.66	5.47 5.60	9.80 9.54	11.22 10.86	
		-NH- 	F+H[c]	81	219 (EtOH)	$C_{22}H_{31}BrN_4O_3S_2$ 543.6	48.61 48.90	5.75 6.02	10.31 10.43		14.71 14.50
		-NH- 	F+H[c]	61	113-115 (EtOH-ether)	$C_{26}H_{39}BrN_4O_3S_2$ 599.7			9.34 9.04	10.69 11.09	13.32 13.74
		-NH-CH$_2$- 	F+H[c]	40	136 (EtOH)	$C_{23}H_{25}BrN_4O_3S_2$ 549.5			10.19 9.85	11.67 11.51	14.54 14.61
		-NH-NH-Me	H	64	125-126 (acetone)	$C_{18}H_{22}N_4O_3S_2$ 406.5	53.17 53.07	5.45 5.37	13.78 13.45		
		-NH-NH-Ph	F+H[b]	66	165 (EtOH)	$C_{23}H_{24}N_4O_3S_2$ 468.6	58.95 58.70	5.16 5.24	11.96 11.98		
	Ph	-N 	F+H[b]	66[d]	170-172 (EtOH)	$C_{20}H_{23}N_3O_4S_2$ 435.5	55.41 56.03	5.35 5.61	9.69 9.94	14.79 14.98	
	Me	-N 	F+H[b]	38	194-195 (EtOH)	$C_{15}H_{21}N_3O_4S_2$ 371.5	48.49 48.49	5.69 5.84	11.31 11.20	17.26 17.86	

Table 3. (*Contd*)

Z	R	-NR'R''	Method	Yield, %[a]	M.p., °C (recryst. from)	Formula Mol. wt.	Calculated/Found, % C	H	N	S	Br
H	4-MeC$_6$H$_4$-		F+H[b]	64[d]	197 (MeNO$_2$)	$C_{20}H_{23}N_3O_3S_2$ 417.6	57.53 57.76	5.55 5.89	10.06 9.89		
			F+H[c]	26[d]	242 (EtOH-ether)	$C_{22}H_{29}BrN_4O_2S_2$ 525.6			10.66 10.31	12.27 12.77	15.20 15.34
Cl			H	66	208-209 (EtOH)	$C_{20}H_{22}ClN_3O_3S_2$ 452.0	53.14 53.03	4.97 4.88	9.29 9.10	14.16 14.20	
		-NH-NH-Ph	F+H[b]	37[d]	218 (EtOH)	$C_{22}H_{21}ClN_4O_2S_2$ 473.1			11.84 11.96	13.56 13.23	7.50[e] 7.50
Br			H	73	230 (EtOH)	$C_{20}H_{32}BrN_3O_3S_2$ 496.4			8.46 8.15	12.91 13.14	16.09 16.04
Me			H	98	175 (EtOH)	$C_{21}H_{25}N_3O_3S_2$ 431.6	58.43 58.17	5.84 5.55	9.73 9.96	14.85 15.26	
			F+H[c]	32[d]	254-256 (EtOH-ether)	$C_{23}H_{31}BrN_4O_2S_2$ 539.6			10.38 10.17	11.88 12.17	14.81 15.20

[a] If not otherwise stated, based on the starting compound 9 (Method H) and 8 (Method F+H), respectively

[b] In the presence of triethylamine

[c] Using one molar equivalent of the diamine. Product is the monohydrobromide

[d] Overall yield for the reaction sequence starting with the corresponding nitro compound 6

[e] Cl

N - {2 - [N - (2 - *Bromoethyl*) - N - *tosylamino*] - 4 - *methoxyphenyl*} - N' - *phenylthiourea* (**9B**; = **9**, R=4-MeC_6H_4, Z=MeO, R'=Ph, R"=H)

(a) *By method* Ⓕ. A mixture of **8** (R=4-MeC_6H_4, Z=MeO) (17.6 g; 40 mmol), aniline (4 ml; 42 mmol) and ether (150 ml) was refluxed with continuous stirring for 3 hr. After about 1 hr a crystalline ppt appeared. The mixture was allowed to cool, and the colourless crystals of the title compound (17.6 g; 82%), m.p. 162° from $MeNO_2$ were filtered off and washed with a small amount of ether. For the microanalytical data, see Table 2.

(b) *By method* Ⓖ. A mixture of **7** (R=4-MeC_6H_4, Z=MeO) (2.0 g; 5 mmol), phenyl isothiocyanate (0.7 ml; 7 mmol) and dioxane (150 ml) was refluxed for 0.5 hr and evaporated to dryness *in vacuo*. The resulting oil was triturated with a small amount of ether to obtain 1.6 g (60%) of a product which proved identical (m.p., m.m.p., IR) with the sample obtained according to (a).

^{13}C NMR ($CDCl_3$): δ 21.6, 140.2, 129.7, 128.0, 144.4 (tosyl), 28.7, 53.8 (*N*-2-bromoethyl), 55.7 (MeO), 159.4 (C_{ar} attached to MeO), 18.1 ppm (thiourea carbon).

4' - *Bromo* - N - (2 - *bromoethyl*) - 2' - (*morpholinothiocarbonylamino*) - *tosylanilide* (**9**, Z=Br, R=4-MeC_6H_4, -NR'R" = morpholino). Compound **6** (Z=Br, R=4-MeC_6H_4) (4.8 g; 10 mmol) was reduced in dioxane (50 ml) at room temp and normal pressure in the presence of an 8% Pd–C catalyst (1 g). After uptake of the calculated amount of H_2 the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to obtain a yellowish oil (4.4 g; 98%) which, according to TLC, proved to contain **7** (Z=Br, R=4-MeC_6H_4) as a single substance.

To the mixture of the amine, CH_2Cl_2 (30 ml) and ice-water (20 g) thiocarbonyl dichloride (1 ml; 13 mmol) was added dropwise with external ice-cooling and vigorous stirring. The mixture was stirred for a further 3 hr at 0° and kept overnight in a refrigerator. The organic layer was washed with 5% $NaHCO_3$ aq until neutral, and water, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* furnished 4.1 g (84%) of **8** (Z=Br, R=4-MeC_6H_4) in form of a viscous yellow oil; IR (film): 2050 cm^{-1}, s.

The warm ethereal (30 ml) soln of **8** was treated with Norite and, after addition of morpholine (0.87 ml; 10 mmol), refluxed for 10 min to obtain, after allowing the mixture to cool, the yellowish crystals (3.0 g; 63%) of the title compound, m.p. 145° (dec).

For the microanalytical results, see Table 2.

2 - *Anilino* - 9 - *methoxy* - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine* (**10B**; = **10**, Z=MeO, R'=Ph, R"=H, R=4-MeC_6H_4) (*Method* Ⓗ). A mixture of **9B** (17.6 g; 33 mmol), EtOH (80 ml) and Et_3N (10 ml; 72 mmol) was refluxed for 3 hr and evaporated to dryness *in vacuo*. The crystalline residue was thoroughly triturated with water to obtain 12 g (81%) of the title compound, light yellow crystals, m.p. 182–183° dec; from EtOH. For the microanalytical data, see Table 3.

^1H NMR ($CDCl_3$): δ 2.8–3.3 m (3H) + 4.52 dm (1H), 4- and 5-H's; 3.73s, MeO; 6.50dd, 8-H; 6.55d, 10-H; 6.75s, 7-H; 6.95–7.4 m (5H) + 7.57 dm (4H), other ArH's.

^{13}C NMR ($CDCl_3$): δ 33.5 (C-4); 53.5 (C-5); 55.4 (MeO); 21.5, 137.3, 129.5, 127.7, 143.3 (tosyl); 151.5 (C-2); 155.9 ppm (C-9).

2 - *Amino* - 9 - *methoxy* - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine* (**10A**; = **10**, Z=MeO, R'=R"=H, R=4-MeC_6H_4). For the preparation, see Table 3.

^1H NMR (DMSO-d_6): δ 2.41 Me of tosyl, 3.71, MeO; 2.85t, 4-H's; 4.0–4.4m, 5-H's; 6.39d, 10-H; 6.43dd, 8-H; 6.60d, 7-H; 6.87, NH_2; 7.65 and 7.42, ArH's of tosyl.

^{13}C NMR (DMSO-d_6); δ 31.1 (C-4); 52.9 (C-5); 55.1 (MeO); 21.0, 137.0, 129.7, 127.3, 143.1 (tosyl); 150.7 (C-2); 159.2 ppm (C-9).

9 - *Bromo* - 2 - *morpholino* - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine* (**10**; Z=Br, -NR'R" = morpholino, R=4-MeC_6H_4) (Method Ⓗ). Compound **9** (Z=Br, -NR'R" = morpholino, R=4-MeC_6H_4; see above) (3.0 g; 5.2 mmol) was refluxed with the mixture of Et_3N (0.9 ml; 6.5 mmol) and EtOH (100 ml) for 3 hr. After about 2 hr the crystals of the product started to precipitate, and were filtered off after cooling to obtain 1.9 g (73%) of the title compound, m.p. 230° from EtOH. For the microanalytical results, see Table 3.

2 - (2 - *Dimethylaminoethylamino*) - 9 - *methoxy* - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine*, HBr *salt* (**10**; HBr; Z=MeO, R'=$Me_2NCH_2CH_2$–, R"=H, R=4-MeC_6H_4). A mixture of **8** (Z=MeO, R=4-MeC_6H_4) (6.0 g; 13.6 mmol), 2-dimethylaminoethylamine (1.2 g; 13.6 mmol) and ether (30 ml) was refluxed for 3 hr with continuous stirring, and evaporated to dryness *in vacuo*. The residue was crystallized from EtOH-ether to obtain 5.5 g (68%) of the title compound, m.p. 240° dec; from ethanol–ether. For the microanalytical results, see Table 3.

9 - *Methoxy* - 2 - (2 - *phenylhydrazino*) - 6 - *tosyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine* (**10**; Z=MeO, R'=PhNH, R"=H, R=4-MeC_6H_4). A mixture of **8** (Z=MeO, R=4-MeC_6H_4) (4.1 g; 10 mmol), phenylhydrazine (1.2 g; 11 mmol) and ether (40 ml) was refluxed for 3 hr and evaporated to dryness *in vacuo*. The residue was refluxed for 4 hr with a mixture of EtOH (20 ml) and Et_3N (5 ml) and again evaporated to dryness *in vacuo*. The oily residue was triturated with water (about 30 ml) to obtain an amorphous solid which was filtered off and dried by azeotropic distillation with benzene, using a water separator. The benzene soln was evaporated to dryness *in vacuo* and the residue was crystallized from EtOH to obtain 3.1 g (66%) of the title compound, m.p. 165° from EtOH. For the microanalytical data, see Table 3.

9 - *Methoxy* - 2 - *morpholino* - 6 - *phenylsulfonyl* - 5,6 - *dihydro* - 4H - 3,1,6 - *benzothiadiazocine* (**10**; Z=MeO, -NR'R" = morpholino, R=Ph). Compound **6** (Z=MeO, R=Ph) (30 g; 72 mmol) was reduced in the mixture of dioxane and EtOH (100 ml, each) in the presence of an 8% Pd–C catalyst at room temp and normal pressure. After uptake of the calculated amount of H_2 the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to obtain **7** (Z and R as above) (27.5 g; 98%) in form of a yellowish oil.

To the mixture of **7** (27.5 g), CH_2Cl_2 (270 ml) and ice-water (230 g) was added dropwise with external ice-cooling and vigorous stirring at 0° thiocarbonyl dichloride (6.8 ml; 88 mmol). The mixture was stirred for a further 3 hr at 0° and kept overnight in a refrigerator. The organic phase was washed with 5% $NaHCO_3$ aq until neutral, and with water, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The oily residue was dissolved in ether (200 ml), the mixture was treated with Norite, and the filtrate was again evaporated to dryness to obtain **8** (R, Z as above) (25 g; 82%) in form of a yellowish oil. IR (film): 2050 cm^{-1}, s.

A mixture of the isothiocyanate (25 g), morpholine (5.1 g; 58.5 mmol) and 2-propanol (500 ml) was refluxed for 1 hr. Et_3N (13 ml; 92 mmol) was added and refluxing was continued for a further 2 hr. The solvent was distilled off *in vacuo* and the oily residue was triturated with ether to obtain the crystals (16.8 g; 66%) of the title compound, m.p. 170–172° from EtOH. For the microanalytical data, see Table 3.

9 - *Methoxy* - 6 - *tosyl* - 3,4,5,6 - *tetrahydro* - 1,3,6 - *benzotriazine* - 2(1H) - *thione* (**12A**). For the preparation, see Ref. 8. ^1H NMR (DMSO-d_6): δ 2.46s, 7.29 + 7.62 (AA'BB'), tosyl; 3.19q (J = 6 Hz), 4-H's; 3.79, MeO; 4.23t (J = 6 Hz), 5-H's; 6.70d, 6.82dd, 7.25d ($J_o \approx 8.5$, $J_m \approx 2$ Hz), 10-H, 8-H and 7-H; 7.78t (J = 6 Hz), 3-H; 12.66 ppm, 1-H.

^{13}C NMR (DMSO-d_6): δ 20.9, 137.2, 129.5, 126.2, 142.5, tosyl; 40.5, C-4; 4.2, C-5; 55.6, MeO; 159.2, C-9, 167.7 ppm.

9 - *Methoxy* - 2 - *methylthio* - 3,4,5,6 - *tetrahydro* - 1,3,6 - *benzotriazine* (**13**). For the preparation, see Ref. 8. ^1H NMR (DMSO-d_6): δ 2.36s, 7.31 + 7.65 (AA'BB'), tosyl; 3.08t, 4-H's; 3.78s, MeO; 4.14, 5-H's; 6.80dd, 7.10d, 8.29d, 8-H, 7-H and 10-H; 7.75 ppm s, 3-H.

^{13}C-NMR (DMSO-d_6): δ 14.4, MeS; 20.9, 137.1, 129.5. 126.3, 142.5, tosyl; 42.0, C-4; 43.7, C-5; 55.5, MeO; 151.9, C-2; 155.3 ppm, C-9.

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