SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF SOME 4-AMINO SUBSTITUTED 2-PHENYL-6*H*-5,1,3-BENZOTHIADIAZOCINES

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Some 4-amino substituted 2-phenyl-6*H*-5,1,3-benzothiadiazocines (**4a–4j**) were prepared by cyclization of the corresponding N^1-[*N*-(2-chloromethylphenyl)benzimidoyl]-N^2-substituted thioureas (**3a–3j**). The IR, ^{1}H NMR and mass spectra of the title compounds are reported together with the results of antibacterial screening.

Key words: *N*-(2-Chloromethylphenyl)benzimidoyl isothiocyanate; 6*H*-5,1,3-benzothiadiazocines.

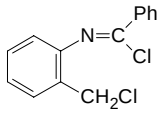
Literature data describing the preparation of benzothiadiazocines are scarce. So far, five structural types of these compounds with the sulfur atom in position 1 and 2 have been described[1–3].

We have found that the as yet undescribed 5,1,3-benzothiadiazocines can be easily prepared starting from substituted benzimidoyl chlorides. The starting *N*-(2-chloromethylphenyl)benzimidoyl chloride on treatment with potassium thiocyanate afforded *N*-(2-chloromethylphenyl)benzimidoyl isothiocyanate (**2**) which reacted with amines to give the corresponding thioureas **3a–3j**. Thermal cyclization of the thioureas in boiling benzene gave rise to 4-amino substituted 2-phenyl-6*H*-5,1,3-benzothiadiazocines **4a–4j**.

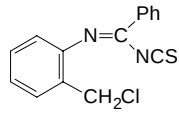
The structure of the cyclization products has been confirmed by ^{1}H NMR spectra that exhibited, among other signals, two conspicuous doublets at 4.5 and 3.5 ppm, with coupling constant J(A,B) = 12 Hz, belonging to two protons of the methylene group[4] incorporated in the rigid skeleton of the non-planar eight-membered thiadiazocine ring. A similar signal pattern was observed in other non-planar rings, e.g. in benzothiazepines[5,6].

The ^{13}C NMR spectrum of the model 2-phenyl-4-anilino-6*H*-5,1,3-benzothiadiazocine **4c** displayed the following signals: 32.59 (C-6 of the thiadiazocine), aromatic carbon signals grouped in quasi doublets at 119.12 and 120.64 (2 C), 122.92 and 123.62 (2 C), 127.78 and 127.89 (2 C), 128.54 (2 C), 128.77 (2 C), 129.53 and 130.99

(2 C), 135,73 and 140.12 (2 C), in addition to the single-bonded carbon signals at 146.46, 150.04, 156.94 and 157.14.



1



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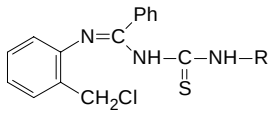

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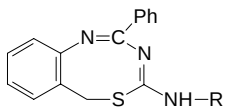
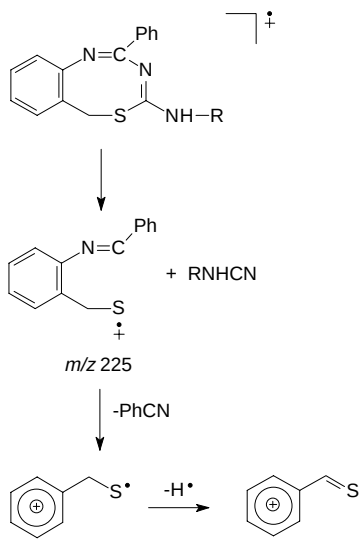


4

3,4	R
a	cyclohexyl
b	benzyl
c	phenyl
d	2-tolyl
e	3-tolyl
f	4-tolyl
g	4-nitrophenyl
h	2-methoxyphenyl
i	4-bromophenyl
j	2-fluorophenyl

The principal paths of molecular fragmentation in the mass spectra are shown in Scheme 1. The basic pattern is the loss of an aryl- or alkylcyanamide ion and formation of fragments testifying the presence of sulfur in the ring. A similar fragmentation pat-



SCHEME 1

tern has been described for benzothiazepines[7]. On the basis of the above spectral data and the known cyclization behaviour of thioureas we assigned to the final product the structure of 6*H*-5,1,3-benzothiadiazocines **4a–4j**.

Antibacterial activity of all the prepared thioureas **3** and benzothiadiazocines **4** was assessed on selected types of bacteria. As can be seen from the data in Table I, none of the tested compounds showed any significant activity. An interesting, although hardly unexpected, activity has been found for the starting *N*-(2-chloromethylphenyl)benzimidoyl isothiocyanate **2** which nevertheless remained well below that of the standard tetracycline.

TABLE I
Antimicrobial activity (IC_{50}, μg/ml) of compounds **2–4**[a]

Compound	*B. subtilis*	*S. aureus*	*E. coli*
2	62[b]	160[d]	180[d]
3a	218[c]	385	252
3b	219[c]	>500	>500
3c	215[d]	228[d]	220[d]
3d	205[d]	280	200[d]
3e	290	190[d]	220[d]
3f	289	192[d]	238[d]
3g	340	202[d]	315
3h	260	170[d]	225
3i	500	228[d]	350
3j	370	340	>500
4a	240	228[d]	190[d]
4b	450	370	>500
4c	190[d]	225[b]	198[d]
4d	285	278	228[d]
4e	228[d]	226[c]	227[d]
4f	460	>500	>500
4g	220[d]	226[d]	250
4h	258	270	191[d]
4i	205[c]	227[d]	222[d]
4j	195[c]	490	195
Tetracycline	0.3	0.35	–

[a] MIC or MBC of other compounds were higher than 500 μg/ml. [b] MIC is 100 μg/ml; MBC is 500 μg/ml. [c] MIC and MBC is 500 μg/ml. [d] The highest concentration tested (500 μg/ml) caused bacteriostatic effect.

EXPERIMENTAL

The ^{1}H NMR spectra (δ, ppm; *J*, Hz; $CDCl_3$, tetramethylsilane as an internal standard) were recorded on a Tesla BS 587 (80 MHz) spectrometer, ^{13}C NMR spectra on a Jeol FX-100 apparatus, mass spectra with an MS 902 S spectrometer (AEI Manchester). The IR spectra (cm^{-1}) of compounds in KBr pellets were measured with a Philips PU 9800 FTIR apparatus.

The antimicrobial activity of the prepared compounds was evaluated using G^- *Escherichia coli* CCM 5172, G^+ *Bacillus subtilis* CCM 1718 and *Staphylococcus aureus* CCM 3824. Concentrations 500, 100, 10, and 1 μg cm^{-3} of the tested compounds were used. Chromatographically pure deriva-

TABLE II
Physico-chemical data on thioureas **3**

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
3a	$C_{21}H_{24}ClN_3S$	130–133	65.35	6.27	10.87	8.31
	(386.0)	52	65.22	6.20	10.77	8.25
3b	$C_{22}H_{20}ClN_3S$	180–185	67.08	5.12	10.67	8.14
	(393.9)	20	66.89	5.10	10.58	8.05
3c	$C_{21}H_{18}ClN_3S$	125–128	66.39	4.78	11.06	8.44
	(379.9)	52	66.25	4.69	10.98	8.37
3d	$C_{22}H_{20}ClN_3S$	145–148	67.08	5.12	10.67	8.14
	(393.9)	27	66.92	5.08	10.51	8.02
3e	$C_{22}H_{20}ClN_3S$	208–210	67.08	5.12	10.67	8.14
	(393.9)	20	66.87	5.05	10.49	8.00
3f	$C_{22}H_{20}ClN_3S$	113–115	67.08	5.12	10.67	8.14
	(393.9)	40	66.89	5.03	10.52	8.03
3g	$C_{21}H_{17}ClN_4O_2S$	220–222	59.36	4.03	13.19	7.55
	(424.9)	35	59.22	3.89	13.01	7.40
3h	$C_{22}H_{20}ClN_3OS$	125–126	64.46	4.92	10.25	7.82
	(409.9)	45	64.33	4.86	10.11	7.77
3i	$C_{21}H_{17}BrClN_3S$	137–138	54.98	3.73	9.16	6.99
	(458.8)	35	54.87	3.65	9.08	6.87
3j	$C_{21}H_{17}ClFN_3S$	187–189	63.39	4.31	10.56	8.06
	(397.9)	32	63.25	4.29	10.44	7.96

tives were dissolved in dimethyl sulfoxide; its final concentration never exceeded 1.0 vol.% in either control or treated samples.

Inhibitory concentration IC_{50} (i.e. such concentration of the derivative at which the growth of the microorganisms is reduced by 50% compared with a control) and minimum inhibitory concentration (MIC) were determined by the dilution method in a Difco-made nutrient broth (bacteria). The IC_{50} and MIC values were estimated from the toxicity curves. MIC experiments on subculture dishes were used to assess the minimum bactericidal concentration (MBC) values. Subcultures were prepared separately in Petri dishes containing nutrient broth agar and incubated at 37 °C for 48 h. The MBC value was taken as the lowest concentration which showed no visible growth of bacterial colonies in the subculture dishes. The antimicrobial activity data are given in Table I.

N-(2-Chloromethylphenyl)benzimidoyl Chloride (**1**)

To a solution of *N*-(2-tolyl)benzimidoyl chloride[8] (20 g, 0.087 mol) in dry benzene (200 ml) bis(azoisobutyronitrile) (0.2 g) and thionyl chloride (8.0 ml, 0.1 mol) were added. The mixture was refluxed for 4 h. The benzene and excess thionyl chloride were evaporated under diminished pressure and the oily product was purified by distillation in vacuo, b.p. 210–215 °C/1.99 kPa. Yield 80%. For $C_{13}H_{10}Cl_2N$ (251.1) calculated: 62.18% C, 4.01% H, 5.58% N; found: 62.01% C, 3.95% H, 5.44% N. ^{1}H NMR spectrum: 6.89–8.23 m, 9 H (H-arom); 4.52 s, 2 H (CH_2).

N-(2-Chloromethylphenyl)benzimidoyl Isothiocyanate (**2**)

N-(2-Chloromethylphenyl)benzimidoyl chloride (**1**; 5.0 g, 0.019 mol) in dry acetone (30 ml) was stirred and cooled at –10 to –5 °C, whereafter a solution of potassium thiocyanate (1.94 g, 0.02 mol) in dry acetone (20 ml) was added dropwise. The stirring was continued at –5 °C for 1 h. The precipitated KCl was filtered off; the solvent was evaporated in vacuo and the product was recrystallized from acetonitrile. Yield 70%, m.p. 80–82 °C. For $C_{15}H_{11}ClN_2S$ (286.8) calculated: 62.82% C, 3.87% H,

TABLE III
IR spectral data ($\tilde{\nu}$, cm^{-1}) on thioureas **3**

Compound	C=N	CH(alif)	NH
3a	1 626	2 928, 2 851	3 208
3b	1 610	2 915, 2 811	3 060
3c	1 636	2 907, 2 849	3 189
3d	1 605	2 951, 2 897	3 040
3e	1 600	2 732	3 020
3f	1 634	2 915, 2 853	3 195
3g	1 622	2 980, 2 897	3 195
3h	1 636	2 942, 2 911	3 193
3i	1 642	2 942	3 193, 3 144
3j	1 672, 1 650	2 946, 2 888	3 080

9.77% N, 11.18% S; found: 62.55% C, 4.05% H, 9.85% N, 11.32% S. IR spectrum: 2 044 (NCS), 1 612 (C=N).

N′-Substituted *N*-(2-Chloromethylphenyl)benzimidoyl Thioureas **3a–3j**

To a solution of crude **2** (0.02 mol) in dry acetone (30 ml) the corresponding amine (0.02 mol) was added and the mixture was stirred at room temperature for 24 h. The precipitated crystalline thiourea **3** was filtered off and recrystallized from ethanol.

TABLE IV
Physico-chemical data on benzothiadiazocines **4**

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
4a	$C_{21}H_{23}N_3S$	165–167	72.17	6.63	12.02	9.17
	(349.5)	83	71.98	6.60	11.89	9.03
4b	$C_{22}H_{19}N_3S$	155–156	73.92	5.36	11.75	8.97
	(357.1)	56	73.79	5.26	11.65	8.86
4c	$C_{21}H_{17}N_3S$	217–218	73.44	4.99	10.23	9.34
	(343.1)	73	73.32	4.87	10.13	9.28
4d	$C_{22}H_{19}N_3S$	110–111	73.92	5.36	11.75	8.97
	(357.1)	74	73.88	5.27	11.63	8.81
4e	$C_{22}H_{19}N_3S$	205–206	73.92	5.36	11.75	8.97
	(357.1)	56	73.85	5.24	11.60	8.79
4f	$C_{22}H_{19}N_3S$	213–215	73.92	5.36	11.75	8.97
	(357.1)	22	73.86	5.25	11.65	8.84
4g	$C_{21}H_{16}N_4O_2S$	215–217	64.93	4.15	14.42	8.25
	(388.1)	37	64.81	4.10	14.35	8.20
4h	$C_{22}H_{19}N_3OS$	125–126	70.75	5.13	11.25	8.59
	(373.1)	40	70.63	5.09	11.18	8.44
4i	$C_{21}H_{16}BrN_3S$	218–220	59.72	3.82	9.95	7.49
	(422.0)	55	59.67	3.80	9.89	7.35
4j	$C_{21}H_{16}FN_3S$	222–223	69.78	4.46	11.63	8.87
	(361.1)	66	69.66	4.41	11.58	8.72

TABLE V
Infrared (ν, cm^{-1}), ^1H NMR (δ, ppm) and mass spectral data (*m/z*) of benzothiadiazocines **4**

Compound	IR (ν, cm^{-1})			*m/z*	^1H NMR (δ, ppm)			
	C=N	CH(aliph)	NH	M^+	H-arom	CH_2	NH	H-aliph
4a	1 620	2 934 2 849	3 216	349	7.03–8.10 m (10 H)	4.53 d (1 H) 3.36 d (1 H)	[a]	1.60 m (11 H)
4b	1 632	2 998 2 928	3 224	357	6.88–7.99 m (14 H)	4.53 d (1 H) 3.39 d (1 H)	4.88 bs (1 H)	4.37 d (2 H)
4c	1 644	2 842 2 797	3 160	343	6.99–8.14 m (14 H)	4.55 d (1 H) 3.45 d (1 H)	6.40 bs (1 H)	
4d	1 644	2 932	3 136	357	7.03–8.05 m (13 H)	4.54 d (1 H) 3.45 d (1 H)	6.15 bs (1 H)	1.99 s (3 H)
4e	1 653	2 984 2 936	3 179	357	6.88–8.15 m (13 H)	4.55 d (1 H) 3.46 d (1 H)	6.37 bs (1 H)	2.27 s (3 H)
4f	1 644	2 986 2 917 2 845	3 162 3 104	357	7.09–8.13 m (13 H)	4.54 d (1 H) 3.45 d (1 H)	6.96 bs (1 H)	2.26 s (3 H)
4g	1 653	2 996 2 934	3 195	–	7.15–8.36 m (13 H)	4.58 d (1 H) 3.56 d (1 H)	6.86 bs (1 H)	
4h	1 640	2 940 2 838	3 193	–	6.41–8.89 m (13 H)	4.55 d (1 H) 3.45 d (1 H)	6.48 bs (1 H)	3.66 s (3 H)
4i	1 642	2 984 2 944	3 195	422	6.97–8.09 m (13 H)	4.55 d (1 H) 3.47 d (1 H)	6.37 bs (1 H)	
4j	1 642	2 986 2 946	3 162	–	6.94–8.20 (13 H)	4.57 d (1 H) 3.48 d (1 H)	6.60 bs (1 H)	

[a] Burried in multiplet of H-arom.

2-Phenyl-4-substituted 6*H*-5,1,3-Benzothiadiazocines **4a–4j**

A mixture of the substituted thioureas **3a–3j** (0.01 mol), triethylamine (0.02 mol) and dry benzene (50 ml) was stirred at reflux for 4 h. The precipitated triethylammonium chloride was filtered off, the filtrate was evaporated in vacuo until dry and the residue was recrystallized from methanol or hexane.

The characteristic data for compounds **3** and **4** are given in Tables II–V.

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