Benzothiazole compounds. VII. *N*-Substituted *N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas

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N-Substituted *N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas were synthesized and their infrared spectra were interpreted. Antibacterial activity *in vitro* was studied. *N*-(3,4-Dichlorophenyl) and *N*-(4-chlorophenyl-3-trifluoromethyl) derivatives were found to be the most active of the synthesized compounds.

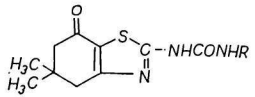
Инфракрасной спектроскопией была подтверждена структура полученных *N*-замещенных *N'*-(5,5-диметил-4,5,6,7-тетрагидро-7-оксо-2-бензтиазолил)мочевин. *Ин витро* изучалось их антибактериальное воздействие. Наиболее эффективной оказалась *N*-(3,4-дихлорфенил)-*N'*-(5,5-диметил-4,5,6,7-тетрагидро-7-оксо-2-бензтиазолил)мочевина и *N*-(3-трифторметил-4-хлорфенил)-*N'*-(5,5-диметил-4,5,6,7-тетрагидро-7-оксо-2-бензтиазолил)-мочевина.

In the recent literature, a series of derivatives of *N*-(2-benzoxazolyl)- and *N*-(2-benzothiazolyl)ureas and -thioureas have been described. These compounds are interesting as bacteriostatics, and herbicides and can be applied also in human medicine. A review of these compounds and of the proceedings of their synthesis was presented in [1].

In this work the attention was focused to the preparation of *N*-substituted *N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas and these compounds were tested for antibacterial and herbicidal activities. The starting 2-amino-4,5,6,7-tetrahydro-5,5-dimethyl-7-oxobenzothiazole has been used so far for the preparation of various 4,5,6,7-tetrahydro-5,5-dimethyl-7-oxobenzothiazole-2-azobenzenes which are applied in analytical chemistry as acid-base indicators, chelate-forming agents, redox indicators, or metallochromic indicators [2—4].

Table 1

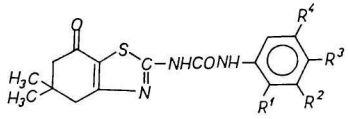
The synthesized *N*-R-*N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas



No.	R	Formula	*M*	Calculated/found					Yield	M.p.
				% C	% H	% N	% S	% Cl	%	°C
I	Methyl	$C_{11}H_{15}N_3O_2S$	253.3	52.11	5.97	16.60	12.67		94.2	287—289
				52.09	5.79	16.44	12.90			
II	Phenyl	$C_{17}H_{17}N_3O_2S$	315.4	61.00	5.43	13.33	10.17		97.1	296—298
				60.87	5.32	13.51	10.04			
III	3-Methylphenyl	$C_{17}H_{19}N_3O_2S$	329.4	62.05	5.82	12.76	9.74		90.8	306—307
				61.89	5.90	12.48	9.74			
IV	4-Methylphenyl	$C_{17}H_{19}N_3O_2S$	329.4	62.05	5.82	12.76	9.74		96.6	293—295
				62.20	5.76	12.91	9.73			
V	2-Methylphenyl	$C_{17}H_{19}N_3O_3S$	345.4	59.17	5.55	12.17	9.20		94.2	303—305
				59.22	5.26	12.29	9.41			
VI	3-Methoxyphenyl	$C_{17}H_{19}N_3O_3S$	345.4	59.17	5.55	12.17	9.29		97.7	232—234
				59.08	5.34	11.93	9.28			
VII	4-Methoxyphenyl	$C_{17}H_{19}N_3O_3S$	345.4	59.17	5.55	12.17	9.20		98.0	290—293
				59.26	5.37	12.05	9.38			
VIII	3-Chlorophenyl	$C_{16}H_{16}ClN_3O_2S$	348.8	54.88	4.60	12.00	9.16	10.13	97.1	304—306
				54.76	4.52	12.19	9.42	10.07		
IX	4-Chlorophenyl	$C_{16}H_{16}ClN_3O_2S$	348.8	54.88	4.60	12.00	9.16	10.13	97.4	303—304
				54.71	4.39	12.23	9.07	10.18		
X	3,4-Dichlorophenyl	$C_{16}H_{15}ClN_3O_2S$	384.2	50.04	3.93	10.93	8.34	18.46	94.2	292—294
				50.22	3.87	11.15	8.53	18.28		
XI	2,4,5-Trichlorophenyl	$C_{16}H_{14}ClN_3O_2S$	418.7	45.86	3.36	10.02	7.65	23.38	93.1	306—308
				45.71	3.40	9.87	7.74	25.17		
XII	3-Chloro-4-methylphenyl	$C_{17}H_{18}ClN_3O_2S$	363.8	56.09	4.95	11.57	8.82	8.76	94.6	296—297
				55.88	4.90	11.35	9.00	9.72		
XIII	4-Fluorophenyl	$C_{16}H_{16}FN_3O_2S$	333.4	57.70	4.84	12.61	9.62		90.7	304—307
				57.58	4.70	12.80	9.72			
XIV	3-Trifluoromethyl-phenyl	$C_{17}H_{16}F_3N_3O_2S$	383.4	53.30	4.20	10.96	8.37		96.2	303—305
				53.14	4.32	10.79	8.54			
XV	3-Trifluoromethyl--4-chlorophenyl	$C_{17}H_{15}ClF_3N_3O_2S$	417.8	48.84	3.61	10.07	7.68	8.50	90.2	306—308
				48.75	3.48	10.26	7.90	8.71		
XVI	3-Nitrophenyl	$C_{16}H_{16}N_4O_4S$	360.4	53.37	4.40	15.55	8.90		89.1	270—272
				53.19	4.37	15.60	8.71			
XVII	4-Nitrophenyl	$C_{16}H_{16}N_4O_4S$	360.4	53.37	4.44	15.55	8.90		87.2	290—292
				53.48	4.31	15.42	8.74			
XVIII	3-Nitro-4-chlorophenyl	$C_{16}H_{15}ClN_4O_4$	394.8	48.64	3.82	14.17	8.11	8.97	90.9	264—265
				48.55	3.97	14.39	8.02	8.81		

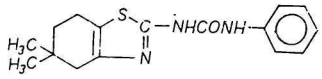
The above-mentioned ureas (Table 1) were synthesized by a reaction of 2-amino-4,5,6,7-tetrahydro-5,5-dimethyl-7-oxobenzothiazole [3] with the corresponding isocyanates. Their structures were confirmed by evaluation of the infrared spectra.

In the i.r. spectra (taken in solid phase) of the compounds of general formula *A*



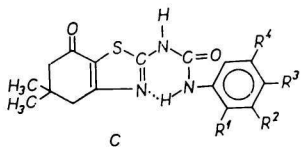
A

a strong band belonging to the C=O stretching vibration of the —NH—CO—NH— group was observed in the region of 1729—1707 cm^{-1}. With the unsubstituted derivative *II* ($R^1 = R^2 = R^3 = R^4 = H$) this band appeared at 1711 cm^{-1}, which was in a good agreement with the value of ν(C=O) 1713 cm^{-1} observed in the spectrum of the model compound *B*.



B

As known from the literature [5, 6], the derivatives of urea in solid phase absorb in the 1650—1630 cm^{-1} region, this being caused by the intermolecular hydrogen bonds of the C=O · · · H—N— type in the cyclic dimers. The high value (1729—1707 cm^{-1}) of the C=O stretching frequency with the compounds of the general formula *A* in solid phase can be explained only by the fact that these compounds appear mostly in a tautomeric form and conformation illustrated in the Scheme *C*



C

where the formation of cyclic dimers was sterically hindered. Nevertheless, in the spectra of both the compounds *A* and the model compound *B* a shoulder was observed at 1650 cm^{-1} beside that at 1729—1707 cm^{-1}. This proved that in equilibrium a minor part of molecules was bound by intermolecular hydrogen bonds of the C=O · · · H—N— type or appeared in tautomeric form where the C=O group was conjugated with the double bond C=N. The absorption band belonging to the C=O stretching vibration in the unsaturated ring was observed as a shoulder in the region of 1715—1696 cm^{-1} with all compounds of the general formula *A*. This

shoulder was not observed in the spectrum of the model compound *B*. Several absorption bands belonging to N—H stretching vibration of the free N—H group were observed at 3360—3300 cm^{-1}. The N—H group bound by a hydrogen bond showed a broad maximum at 3200—3100 cm^{-1}. The strong absorption band in the 1626—1618 cm^{-1} region was attributed to the stretching vibration of the thiazole and benzene rings.

The antimicrobial activity of the synthesized compounds was presented in Table 2. *N*-(3,4-Dichlorophenyl)- and *N*-(4-chlorophenyl-3-trifluoromethyl)-*N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas (*X* and *XV*) were found to be the most active of all the compounds tested. With these compounds, favourable effects were found mainly against the test-strains of both the gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and gram-negative (*Escherichia coli*) nonspecific bacterial flora. These three test-organisms were inhibited by the concentration 10 μg/ml while *Pseudomonas aeruginosa* was not sensitive to these compounds even at the highest concentration 200 μg/ml. Good antibacterial activity was found also with *N*-(methyl)-*N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)urea (*I*). The above-mentioned three compounds showed the best effects on *Candida pseudotropicalis*.

3-(Nitrophenyl)- and 4-(nitrophenyl)-*N'*-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)ureas (*XVI* and *XVII*) had good antimycobacterial activity. These compounds acted against *Mycobacterium bovis* BCG as bactericides at the concentration of 100 μg/ml and caused bacteriostasis even at 10 μg/ml. With respect to *Mycobacterium fortuitum*, which is more resistant to antituberculotics, 400 μg/ml acted bactericidally and 200 μg/ml still caused a bacteriostasis.

No particular herbicidal and fungicidal activities were observed and all compounds were eliminated after the first screening.

Experimental

Physical constants and data of elemental analysis of the synthesized compounds are given in Table 1.

Infrared spectra were measured on a UR-20 (Zeiss, Jena) spectrophotometer in the region of 3800—700 cm^{-1}. The samples were prepared in the form of nujol suspensions. Polystyrene foil was used for calibration of wavenumbers.

The microbiological activity on the test-organisms presented in Table 2 was determined according to [7]. The starting 2-amino-4,5,6,7-tetrahydro-5,5-dimethyl-7-oxobenzothiazole was prepared according to [8].

N-R-N'-(4,5,6,7-tetrahydro-5,5-dimethyl-7-oxo-2-benzothiazolyl)urea (I—XVIII)

To 2-amino-4,5,6,7-tetrahydro-5,5-dimethyl-7-oxobenzothiazole (9.8 g; 0.05 mole) and the appropriate isocyanate (0.055 mole), toluene (benzene at *I*) (100 ml) and triethylamine (0.1 ml) were added. The reaction mixture was stirred for 2 hrs at 40—50°C and for another 3 hrs at boiling under reflux. After cooling the precipitated solid products were filtered off and washed with benzene or toluene.

Table 2

Antimicrobial activity of the synthesized compounds

No.	MIC					Bactericidal/bacteriostatical concentration			Lethal concentration	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida pseudotropicalis*	BGC	*Mycobacterium fortuitum*	*Trypanosoma cruzi*	*Trichomonas foetus*	*Euglena gracilis*
I	50	50	100	>200	200	>100/100	>500/500	>200	>500	>500
II	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
III	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
IV	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
V	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
VI	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
VII	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
VIII	>200	>200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
IX	200	200	>200	>200	>200	>100/100	>500/500	>200	>500	>500
X	10	10	10	>200	10	>100/100	>500/500	>200	>500	>500
XI	200	200	200	>200	200	100/50	500/500	>200	>500	>500
XII	100	100	100	>200	>200	100/50	>500/500	>200	>500	>500
XIII	200	200	>200	>200	>200	>100/50	>500/500	>200	500	>500
XIV	>200	200	>200	>200	>200	>100/100	>500/600	>200	>500	>500
XV	10	10	10	>200	200	100/50	500/300	>200	>500	>500
XVI	>200	200	>200	>200	>200	100/10	400/200	>200	>500	>500
XVII	>200	200	>200	>200	>200	100/10	400/200	>200	>500	>500
XVIII	200	200	200	>200	>200	>100/100	>500/500	>200	>500	>500

MIC = minimal inhibitory concentration, μg/ml.

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