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Synthesis and Antibacterial Evaluation of 2-(Substituted Phenylureido)-4-thiocyanatobenzothiazoles

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Abstract □ The synthesis and antibacterial evaluation of a number of 2-(substituted phenylureido)-4-thiocyanatobenzothiazoles are described. The more active compounds against the test organisms *in vitro* generally were those substituted with halogens on the phenyl and benzothiazole rings.

Keyphrases □ Benzothiazoles, various substituted—synthesized, evaluated for antibacterial activity □ Antibacterial activity—evaluated for various substituted benzothiazoles □ Structure–activity relationships—various substituted benzothiazoles evaluated for antibacterial activity

Previously, the synthesis and antiparasitic screening of a series of thiocyanatobenzothiazoles were reported (1). These compounds exhibited significant anthelmintic and antifungal activities. As an extension of this work, the synthesis of some 2-(substituted phenylureido)-4-thiocyanatobenzothiazoles is reported here. These compounds possess a high degree of *in vitro* activity against the Gram-positive bacteria *Staphylococcus aureus* and *Corynebacterium liquefaciens*.

DISCUSSION

The method of preparation of the 2-(substituted phenylureido)-4-thiocyanatobenzothiazoles (V–XII) (Table I) involved the reaction of the appropriate 2-amino-4-thiocyanatobenzothiazole (I–IV) with a phenyl isocyanate. The synthesis of I, II, and IV was reported previously (1, 2); the synthesis of III is reported here. The general procedure for the preparation of V–XII is shown in Scheme I. The assignment of structures for other compounds of the V–XII type was discussed previously (1).

The compounds were tested for antibacterial activity against *S. aureus* and *C. liquefaciens* using *in vitro* serial dilution techniques (3). Compounds V–XII exhibited activity against the test organisms at levels of from 0.048 to 6.25 μg/ml of test media. The test results for V–XII and the reference standard, nifuradene[1] (XIII) (4), are shown in Table I.

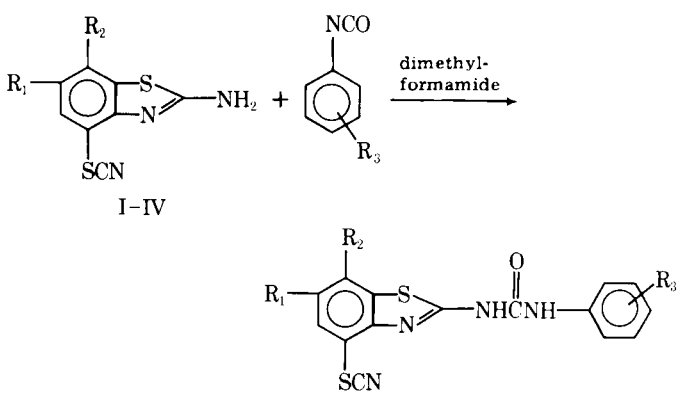
[1] U.S. Adopted Name for 1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone.

Table I—Antibacterial Evaluation of Phenylureidothiocyanatobenzothiazoles

Compound	R_1	R_2	R_3	Minimal Inhibitory Concentration, μg/ml	
				S. aureus[a]	*C. liquefaciens*[b]
V	CH_3	H	4-NO_2	0.75	0.75
VI	Cl	H	H	0.38	3.1
VII	Cl	H	4-Cl	0.19	0.75
VIII	*n*-Bu	H	4-Br	6.25	6.25
IX	Cl	Cl	4-Cl	0.19	1.5
X	Cl	Cl	4-Br	0.38	0.048
XI	Cl	Cl	3,4-$(Cl)_2$	3.1	6.25
XII	Cl	Cl	4-F	0.38	1.5
XIII	Nifuradene			3.10	12.5

[a] Strain No. Mi-12, Norwich Pharmacal Co. [b] Strain No. Co-11, ATCC 11828.

In general, the compounds possessing the highest degree of antibacterial activity against the test organisms were substituted with halogen atoms on both the phenyl and benzothiazole rings (VII and IX–XII). However, no other structure–activity trends were apparent among the eight compounds tested.



Scheme I

Table II—Analytical and Physical Data for New Compounds

Compound	Melting Point	Yield, %	Recrystallization Solvent	Formula		Analysis, % Calc.	Found
V	283–284°	65	Ethanol–dimethylformamide	$C_{16}H_{11}N_5O_3S_2$	C	49.86	49.73
					H	2.88	2.90
					N	18.17	18.12
VI	329–330°	79	Methanol–dimethylformamide	$C_{15}H_9ClN_4OS_2$	C	49.93	49.60
					H	2.51	2.51
					N	15.53	15.75
VII	239–240°	67	Nitromethane–dimethylformamide	$C_{15}H_8Cl_2N_4OS_2$	C	45.57	45.25
					H	2.04	2.07
					N	14.18	14.41
VIII	259–260°	99	Methanol–dimethylformamide	$C_{19}H_{17}BrN_4OS_2$	C	49.46	49.17
					H	3.71	3.77
					N	12.14	11.91
IX	238–239°	51	Ethanol	$C_{15}H_7Cl_3N_4OS_2$	C	41.92	41.70
					H	1.64	1.66
					N	13.04	12.96
X	243–245°	50	Ethanol	$C_{15}H_7BrCl_2N_4OS_2$	C	37.99	37.60
					H	1.49	1.45
					N	11.82	11.77
XI	313–320°	50	Ethanol	$C_{15}H_6Cl_4N_4OS_2$	C	38.81	38.66
					H	1.30	1.35
					N	12.07	12.13
XII	308–310°	63	Nitromethane	$C_{15}H_7Cl_2FN_4OS_2$	C	43.59	43.23
					H	1.70	1.77
					N	13.56	13.55

EXPERIMENTAL[2]

2-Amino-6-(*n*-butyl)-4-thiocyanatobenzothiazole (III) was prepared as follows. A solution of sodium thiocyanate (81 g, 1.0 mole) in methanol (300 ml) was chilled to −7° in an ice–salt bath. The stirred solution was treated dropwise with bromine (90 g, 0.57 mole) in sodium bromide-saturated methanol (150 ml).

After all of the bromine had been added, *p*-butylaniline (30 g, 0.2 mole) was poured into the reaction mixture. The mixture was stirred for 4.5 hr and was then filtered and poured into 400 ml of water. After neutralization with ammonium hydroxide, the product was removed by filtration and recrystallized from methanol to give cream-colored needles (37 g, 71% yield), mp 167–169°.

Anal.—Calc. for $C_{12}H_{13}N_3S_2$: C, 54.72; H, 4.97; N, 15.96. Found: C, 54.43; H, 4.97; N, 15.89.

6-Methyl-2-{1-[3-(*p*-nitrophenyl)ureido]}-4-thiocyanatobenzothiazole (V) was prepared in the following manner. A solution of 2-amino-6-methyl-4-thiocyanatobenzothiazole (I) (35 g, 0.16 mole) in dimethylformamide (250 ml) was treated portionwise with *p*-nitrophenyl isocyanate (27 g, 0.16 mole). The stirred reaction mixture was heated on a steam bath for 5 hr and then diluted with water to precipitate 40 g (65% yield) of off-white solid.

Recrystallization from ethanol–dimethylformamide provided an analytical sample, mp 283–284°.

Anal.—Calc. for $C_{16}H_{11}N_5O_3S_2$: C, 49.86; H, 2.88; N, 18.17. Found: C, 49.73; H, 2.90; N, 18.12.

Compounds VI–XII were prepared in a similar fashion. Spectral data for V–XII are consistent with the structure assignments. Two characteristic features of the IR spectra of V–XII are absorptions at 2150 (SCN) and 1700 (C=O) cm^{-1}. NMR spectra for V–XII in dimethyl sulfoxide-d_6 were as expected and readily interpretable. The analytical and physical data for V–XII are shown in Table II.

[2] Melting points were determined in open capillary tubes using a Mel-Temp melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 137 Infracord (Nujol). NMR spectra were obtained on a Varian A-60A instrument in dimethyl sulfoxide-d_6, using tetramethylsilane as an internal standard.

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