Benzothiazole compounds. III. Synthesis and biological activity of substituted *N*-(2-benzothiazolyl)ureas and benzothiazolyldihydrouracils

V. SUTORIS and J. HALGAŠ

Department of Organic Chemistry and Biochemistry, Faculty of Natural Sciences, Komenský University, 801 00 Bratislava

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N-(4-X-6-X^1-2-Benzothiazolyl)-*N'*-(β-bromopropionyl)ureas were prepared by treatment of 4,6-substituted 2-aminobenzothiazoles with β-bromopropionyl isocyanate and converted to cyclic 1-(4-X-6-X^1-2-benzothiazolyl)dihydrouracils. Antibacterial, antifungal, and antiprotozoal effects *in vitro* were observed with the described compounds.

It is known from the literature [1—4] that some benzothiazolylureas or thiazolylureas [5—8] are biologically active. In this work, attention was paid to the synthesis of *N*-(4-X-6-X^1-2-benzothiazolyl)-*N'*-(β-bromopropionyl)ureas (X = H, SCN; X^1 = CH_3, *i*-C_3H_7, Cl, Br, NO_2, SCN) and their cyclization to 1-(4-X-6-X^1-2-benzothiazolyl)-dihydrouracils. The starting 4,6-substituted 2-aminobenzothiazoles were prepared according to [3, 9—12]. 2-Amino-4-thiocyanato-6-isopropylbenzothiazole, not described as yet, was synthesized by a modified method. Its structure was proved by i.r. spectrum.

The reactions of 4,6-substituted 2-aminobenzothiazoles with β-bromopropionyl isocyanate proceeded in the mixture of ether—tetrahydrofuran (2 1; compounds *I—III*) or tetrahydrofuran (compounds *IV—VII*) according to their solubility. Yields of the prepared derivatives of *N*-(2-benzothiazolyl)-*N'*-(β-bromopropionyl)urea varied from 44 to 63% (Table 1).

2-Aminobenzothiazole occurs in two tautomeric forms [13] and probably both amino and imino forms could react. The i.r. spectra of the prepared ureas did not show absorption bands of imino group (C=N— stretching vibrations at 1645—1620 cm^{-1} and =N—H stretching vibrations at 3400—3300 cm^{-1}). Therefore we assume that only the amino group reacted with β-bromopropionyl isocyanate. This is in agreement with the literature data about the structure of the reaction products of 2-aminobenzothiazole with other isocyanates [3, 4, 16]. This renders possible to explain also the lower yields when compared with those obtained in reactions of other arylamines with β-bromopropionyl isocyanate [14, 15].

The heating of *N*-(6-X-2-benzothiazolyl)-*N'*-(β-bromopropionyl)ureas (X = Cl, Br) with diethylamine in acetone led to the formation of 1-(6-X-2-benzothiazolyl)dihydrouracils (X = Cl, Br; Scheme 1) instead of *N*-(6-X-2-benzothiazolyl)-*N'*-(β-diethylaminopropionyl)ureas.

Their structures were determined by interpretation of the n.m.r. spectra where a resonance signal (6.76 τ) corresponding to $-CH_2-N<$ group was observed. This signal was split into a triplet due to the interaction with protons of the neighbouring methylene group. Another triplet (8.28 τ) corresponding to protons of $-CH_2-CO-$ group was also observed. It was impossible to prove reliably the structure by i.r. spectroscopy because

Table 1

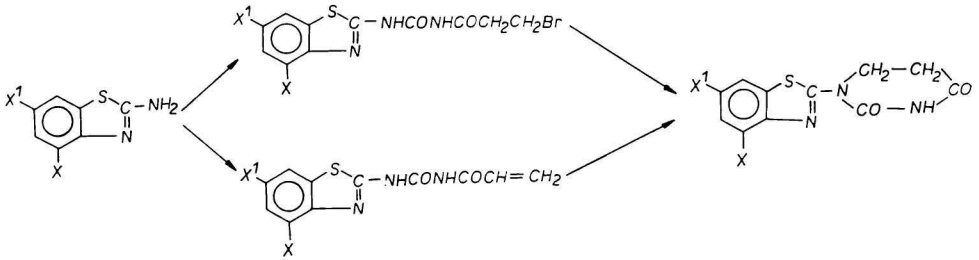
Synthesized *N*-(4-X-6-X¹-2-benzothiazolyl)-*N'*-(β-bromopropionyl)ureas

No.	X	X¹	Formula	*M*	Calculated/found % N	% S	% Br	Yield [%]	M.p. [°C]
I	H	CH_3	$C_{12}H_{12}BrN_3O_2N$	342.2	12.27 12.07	9.37 9.33	23.35 23.12	57	263 decomposition
II	SCN	CH_3	$C_{13}H_{11}BrN_4O_2S_2$	399.2	14.03 14.17	16.06 16.26	20.01 20.19	57	260 decomposition
III	SCN	$CH(CH_3)_2$	$C_{15}H_{15}BrN_4O_2S_2$	427.3	13.11 13.29	15.01 15.08	18.73 18.61	60	203—205
IV	H	Cl	$C_{11}H_9BrClN_3O_2S$	362.6	11.59 11.73	8.84 9.01	22.04 21.80	62	285 decomposition
V	H	Br	$C_{11}H_9Br_2N_3O_2S$	407.1	10.32 10.15	7.87 7.96	39.26 39.08	63	288 decomposition
VI	H	NO_2	$C_{11}H_9BrN_4O_4S$	373.1	15.01 14.88	8.60 8.74	21.41 21.23	44	285 decomposition
VII	H	SCN	$C_{12}H_9BrN_4O_2S$	385.2	14.54 14.29	16.65 16.71	20.74 21.00	52	278 decomposition

the spectra could have been measured only in nujol (low solubility in chloroform) which excluded the assignment of absorption bands to vibrations of the methylene groups.

The structure of the synthesized dihydrouracils was confirmed also by a synthetic way, *i.e.* by cyclization of *N*-(6-X-2-benzothiazolyl)-*N'*-acryloylurea (Scheme 1). The cyclization proceeded in dimethylformamide in the presence of triethylamine at 95—100°C. The mixed melting point of the cyclization product of *N*-(6-chloro-2-benzothiazolyl)-*N'*-acryloylurea and *N*-(6-chloro-2-benzothiazolyl)-*N'*-(β-bromopropionyl)urea was without depression.

Antibacterial, antifungal, and antiprotozoal effects of all the compounds were investigated *in vitro*. 2-Amino-6-thiocyanatobenzothiazole was the most effective among the substituted benzothiazoles. The minimal inhibition concentrations of this compound (5—10 μg/ml) were higher for all tested organisms than those of many other benzothiazole derivatives. The substituted ureas were less effective than the starting 2-aminobenzothiazoles. The minimal inhibition concentration of *N*-(6-thiocyanato-2-benzothiazolyl)-*N'*-(β-bromopropionyl)urea was 50 μg/ml for all tested organisms which still represented a high efficiency.



X = H, SCN; X¹ = CH_3, *i*-C_3H_7, Cl, Br, NO_2, SCN.

Scheme 1

Experimental

Melting points (Kofler) and analytical data of the synthesized *N*-(4-X-6-X^1-2-benzothiazolyl)-*N'*-(β-bromopropionyl)ureas are given in Table 1. Infrared spectra were measured with a UR-20 (Zeiss, Jena) spectrophotometer in paraffin oil. Nuclear magnetic resonance spectra were measured on a Tesla BS 487A spectrometer at 80 MHz in deuteriodimethyl sulfoxide. Tetramethylsilane was used as internal standard. β-Bromopropionyl isocyanate was prepared by rearrangement of *N*-bromosuccinimide [13], acryloyl isocyanate was prepared as described in [17], and biological activities on objects tested were measured according to [18—20].

2-Amino-4-thiocyanato-6-isopropylbenzothiazole

p-Isopropylaniline (27 g; 0.2 mole) and sodium thiocyanate (32.4 g; 0.4 mole) were dissolved in glacial acetic acid (300 ml). After cooling to 5—8°C, a solution of bromine (32 g; 0.2 mole) in acetic acid (60 ml) was added dropwise under stirring during 30 minutes so that the temperature did not exceed 10°C. Then the reaction mixture was stirred for another 2 hours at room temperature. Then the solution was diluted with the same volume of water and neutralized with sodium carbonate. The formed orange oil was dissolved in hot 70% etnanol and from the cooled solution, 2-amino-4-thiocyanato-6-isopropylbenzothiazole (m.p. 212—214°C) crystallized. Yield 28.5 g, *i.e.* 57%.

For $C_{11}H_{11}N_3S_2$ (249.3) calculated: 25.75% S, 16.86% N; found: 25.67% S, 16.73% N.

The obtained i.r. data: 2157 cm^{-1} [$\tilde{\nu}$(C≡N)], 3395 cm^{-1} [$\tilde{\nu}$(=N—H)], 3315 cm^{-1} [$\tilde{\nu}$(N—H)], 1655 cm^{-1} [$\tilde{\nu}$(C=N)], and 1538 cm^{-1} [$\delta\tilde{\nu}$(CNH)].

N-(4-X-6-X^1-2-Benzothiazolyl)-N'-(β-bromopropionyl)ureas (I—VII)
(X = H, SCN; X^1 = CH_3, *i*-C_3H_7, Cl, Br, NO_2, SCN)

4,6-Substituted 2-aminobenzothiazole (0.05 mole) was dissolved in the mixture of ether (100 ml) and tetrahydrofuran (50 ml; for *I—III*) or in tetrahydrofuran (150 ml; for *IV—VII*) under stirring and the solution of β-bromopropionyl isocyanate (8.9 g; 0.05 mole) in ether (50 ml) was added dropwise. The reaction mixture was heated for 2 hours to the boiling temperature and after cooling, the solid was filtered off and the filtrate evaporated to dryness. The solid and the evaporation residue were crystallized from the mixture of acetone and ethanol (1 1; *I—III*) or from acetone (*IV—VII*).

1-(6-X^1-2-Benzothiazolyl)dihydrouracils
(X^1 = Cl, Br)

Method A

N-(6-X^1-2-Benzothiazolyl)-*N'*-(β-bromopropionyl)urea (0.005 mole) and diethylamine (1.1 g; 0.015 mole) were dissolved in anhydrous acetone (150 ml) and heated for 6 hours to boiling temperature. In the course of reaction, the appropriate dihydrouracil, crystallized; after cooling it was filtered and washed with acetone. The yield of 1-(6-chloro-2-benzothiazolyl)dihydrouracil (m.p. 312—315°C) was 0.75 g, *i.e.* 53.5%.

For $C_{11}H_8ClN_3O_2S$ (281.7) calculated: 11.38% S, 14.91% N; found: 11.16% S, 14.68% N.

The yield of 1-(6-bromo-2-benzothiazolyl)dihydrouracil (m.p. 310—313°C) was 0.9 g, *i.e.* 54.5%.

Method B

N-(6-X^1-2-Benzothiazolyl)-*N'*-acryloylurea (3 g) was dissolved the mixture of dimethylformamide (20 ml) and triethylamine (10 ml). The mixture was heated on a water bath for 4 hours. A small amount of solid was formed, filtered off, evaporated under reduced pressure to 1/3 volume, and allowed to crystallize. The solid was filtered again and crystallized from dimethylformamide together with the solid obtained previously.

The yield of 1-(6-chloro-2-benzothiazolyl)dihydrouracil (m.p. 314—315°C) was 1.5 g, *i.e.* 50%. Found: 11.19% S, 14.82% N. The yield of 1-(6-bromo-2-benzothiazolyl)dihydrouracil (m.p. 310—312°C) was 2.25 g, *i.e.* 75%. Found: 9.72% S, 12.69% N.

N-(6-X^1-2-Benzothiazolyl)-N'-acryloylureas (X^1 = Cl, Br)

To 6-X^1-2-aminobenzothiazole (0.02 mole) in the mixture of dry ether (60 ml) and tetrahydrofuran (30 ml), a solution of acryloyl isocyanate (1.94 g; 0.02 mole) in ether (10 ml) was added dropwise. The reaction mixture was stirred for 3 hours and the precipitate was crystallized from dimethylformamide.

The yield of *N*-(6-chloro-2-benzothiazolyl)-*N'*-acryloylurea (m.p. 221—223°C) 3.5 g, *i.e.* 62%.

For $C_{11}H_8ClN_3O_2S$ (281.7) calculated: 11.38% S, 14.91% N; found: 11.23% S, 14.78% N.

The yield of *N*-(6-bromo-2-benzothiazolyl)-*N'*-acryloylurea (m.p. 219—221°C) was 4.0 g, *i.e.* 60%.

For $C_{11}H_8BrN_3O_2S$ (326.1) calculated: 9.83% S, 12.88% N; found: 9.92% S, 12.71% N.

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