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Bis-arylsulfonamide Derivatives of 2-Amino-5(6)-(4-aminophenylthio)benzimidazole

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Abstract—Three different procedures have been developed for the preparation of bis-arylsulfonamide derivatives of 2-amino-5(6)-(4-aminophenylthio)benzimidazole, and biological activity of the products have been studied.

A large number of methyl 5(6)-(4-aminophenoxy)- and 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate derivatives exhibit high antihelminthic activity [1–16]. Unfortunately, most of them possess embryotoxic and teratogenic properties which restrict their application in medical practice.

We have developed a procedure for preparation of new bis-arylsulfamide derivatives of 2-amino-5(6)-(4-aminophenylthio)benzimidazole with the goal of studying their antihelminthic activity, as well as embryotoxicity and teratogenic action. Analysis of published data has shown that the simplest possible routes to bis-arylsulfamide derivatives (phenylsulfonyl or *p*-tolylsulfonyl) of 2-amino-5(6)-(4-aminophenylthio)benzimidazole are the following:

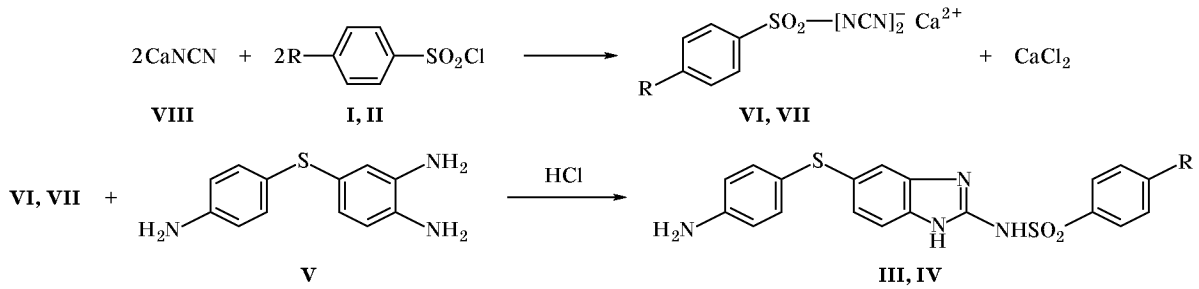
(1) Reaction of benzenesulfonyl chloride (**I**) or *p*-toluenesulfonyl chloride (**II**) with 5(6)-(4-aminophenylthio)-2-phenylsulfonylaminobenzimidazole (**III**) or 5(6)-(4-aminophenylthio)-2-(*p*-tolylsulfonylamino)-benzimidazole (**IV**) in aprotic organic solvents in the presence of triethylamine or sodium carbonate. In turn, benzimidazoles **III** and **IV** can be prepared from 3,4,4′-triaminodiphenyl sulfide (**V**) or compounds **VI** and **VII** which are products of the reaction of sulfonyl chlorides **I** and **II** with calcium or sodium cyanamide (**VIII**) (Scheme 1);

(2) Reaction of sulfonyl chlorides **I** and **II** with methyl 5(6)-[4-(phenylsulfonylamino)phenylthio]-2-benzimidazolylcarbamate (**IX**) or methyl 5(6)-[4-(*p*-tolylsulfonylamino)phenylthio]-2-benzimidazolylcarbamate (**X**);

(3) Reaction of sulfonyl chlorides **I** and **II** with 2-amino-5(6)-(4-aminophenylthio)benzimidazole which is prepared by alkaline hydrolysis of 5(6)-(4-aminophenylthio)-2-benzoylaminobenzimidazole (**XI**). The latter is available through the reaction of benzoyl chloride (**XII**) with calcium or sodium cyanamide (**VIII**), followed by condensation with triamine **V**.

First of all, we have developed a procedure for the synthesis of benzimidazole derivatives **III** and **IV**

Scheme 1.



I, **III**, **VI**, R = H; **II**, **IV**, **VII**, R = Me.

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Table 1. Synthesis of 5(6)-(4-aminophenylthio)-2-phenylsulfonylbenzimidazole (**III**)

Run no.	Phenylsulfonylcyanamide calcium salt (**VI**)[a]				5(6)-(4-Aminophenylthio)-2-phenylsulfonyl-benzimidazole (**III**)[b]					Concentration, wt %		Yield of crude product, wt %
	amounts of reactants, mol				amounts of reactants, mol					**III**	hydro-chloride	
	VIII	**I**	water	HCl	**V**	HCl	*i*-PrOH[c]	AcOH	water[c]			
1	0.22	0.20	256	0.20	0.1	–	256	0.45	–	85.1	10.6	88.9
2	0.22	0.20	256	0.20	0.1	–	256	0.45	–	85.9	9.8	88.7
3	0.22	0.20	256	0.25	0.1	–	256	0.45	–	80.7	17.3	89.4
4	0.22	0.20	256	0.25	0.1	–	256	0.45	–	80.3	18.1	90.2
5	0.22	0.20	256	–	0.1	0.3	256	0.1	–	86.8	13.2	71.1
6	0.22	0.20	250	0.20	0.1	0.1	250	–	–	90.6	6.24	69.3
7	0.22	0.20	256	0.20	0.1	0.3	256	–	–	86.6	8.3	80.6
8	0.22	0.20	256	0.20	0.1	0.3	256	–	–	86.1	7.5	79.4
9	0.22	0.20	250	0.20	0.11	0.33	250	–	–	88.0	10.3	71.0
10	0.22	0.20	250	0.10	0.1	0.3	250	–	–	92.1	7.2	98.0
11	0.22	0.20	250	–	0.124	0.372	250	–	–	69.1	19.5	67.0
12	0.22	0.20	250	–	0.124	0.372	250	–	–	71.2	19.1	68.0
13	0.22	0.20	250	–	0.1	0.3	–	0.2	50	87.6	2.5	76.3
14	0.22	0.20	250	0.2	0.1	0.3	–	–	50	89.8	1.8	61.1
15	0.44	0.40	256	0.4	0.1	0.3	–	–	50	90.3	1.9	98.5
16	0.22	0.20	256	0.2	0.1	0.3	–	–	50	86.7	2.9	71.2
17	0.516	0.468	500	0.6	0.234	0.702	600	–	–	82.0	3.3	93.2
18	0.516	0.468	500	0.6	0.234	0.702	600	–	–	81.8	3.7	92.8
19	0.516	0.468	500	0.6	0.234	0.702	600	–	–	78.7	6.5	89.3
20	0.516	0.468	500	0.6	0.165	0.495	–	–	300	71.5	19.1	77.2
21	0.516	0.468	500	0.25	0.234	0.702	600	–	–	93.2	4.2	76.9
22	0.516	0.468	500	0.25	0.234	0.702	600	–	–	93.7	6.2	84.1
23	0.516	0.468	500	0.30	0.234	0.702	600	–	–	95.9	3.3	75.0
24	0.516	0.468	500	0.30	0.234	0.702	600	–	–	94.3	5.4	74.4

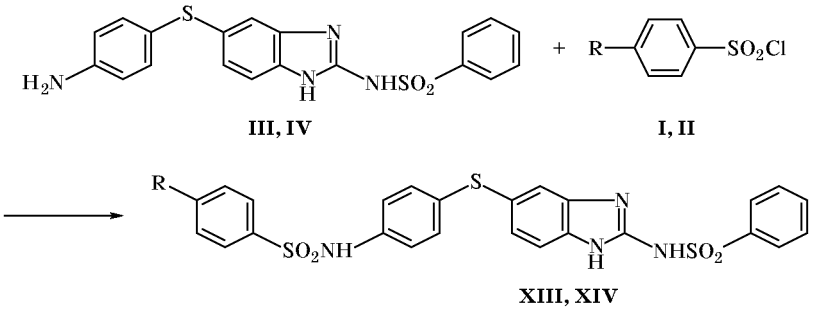
[a] Reaction temperature 40–45°C.
[b] Reaction temperature 80–85°C.
[c] In ml.

from phenylsulfonyl- and *p*-tolylsulfonylcyanamide calcium (or sodium) salts **VI** and **VII** and triamine **V**. The reaction is carried out in water in the presence of hydrochloric acid which converts cyanamide salt **VI** or **VII** into more reactive neutral form. Condensation of the latter with 3,4,4′-triaminodiphenyl sulfide (**V**) yields benzimidazoles **III** and **IV** (Scheme 1). Table 1 lists the results of optimization of the reaction conditions. According to the data of IR and NMR spectroscopy and elemental analysis, the major impurity in the crude product is hydrochloride **XII** formed by protonation of the amino group in the aniline fragment of benzimidazole **III**.

As follows from Table 1 (cf. run nos. 3–5 and nos. 1, 2, 6, 10, 15, 16, 21–24), the concentration of hydrochloride **XII** in crude product **III** increases with rise in the amount of hydrochloric acid used for acidification of the filtrate in the first stage or added in the second stage. The best results (93.0% concentration of benzimidazole **III** in the crude product) were obtained at a calcium cyanamide–benzenesulfonyl chloride–HCl–triamine **V** molar ratio of 2.20 : 2.0 : 4.28 : 1.0. The optimal volume ratio of water and isopropyl alcohol in the second stage was 1.00 : 1.20. Under these conditions, the yield of crude product **III** is no less than 74%.

Condensation of benzimidazole **III** with sulfonyl chlorides **I** and **II** in aprotic organic solvents (chloroform or dichloroethane) in the presence of triethylamine at 60–80°C (reaction time 1.5–2.0 h) gave,

Scheme 2.



III, IV **I, II**

XIII, XIV

XIII, R = H; **XIV**, R = Me.

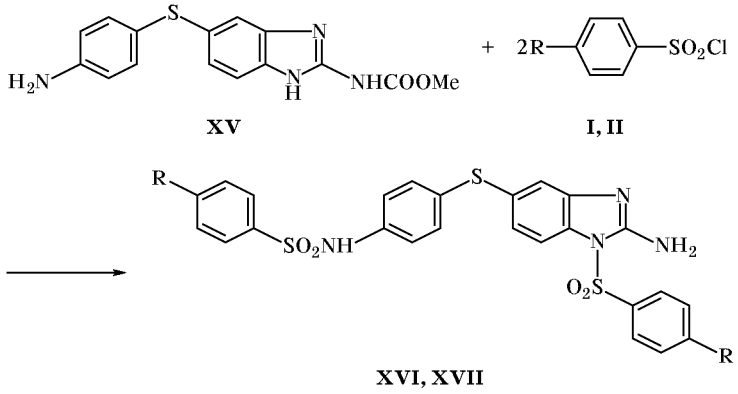
respectively, 5(6)-[4-(phenylsulfonylamino)phenylthio]-2-phenylsulfonylaminobenzimidazole (**XIII**) and 5(6)-[4-(*p*-tolylsulfonylamino)phenylthio]-2-phenylsulfonylaminobenzimidazole (**XIV**) (Scheme 2).

The obtained compounds turned out to be nontoxic even at a dose of 500 mg/kg; they showed a high antihelminthic activity at a dose of 30 mg/kg against gastrointestinal helminthiasis in sheeps, while no embryotoxic effect was observed at both therapic doses and at a dose of 100 mg/kg.

By reactions of methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate (**XV**) with arenesulfonyl chlorides **I** and **II** we obtained 2-amino-5(6)-[4-(phenylsulfonylamino)phenylthio]-1-phenylsulfonylbenzimidazole (**XVI**) and 2-amino-5(6)-[4-(*p*-tolylsulfonylamino)phenylthio]-1-(*p*-tolylsulfonyl)benzimidazole (**XVII**) having sulfonyl groups in position *1* and in the aniline moiety (Scheme 3). The reactions were carried out in the presence of triethylamine in an aprotic organic solvent (chloroform or dichloroethane) on heating under reflux. The same products were synthesized in high yields by independent method, namely by reaction of preliminarily prepared methyl 2-benzimidazolylcarbamates **IX** and **X** with arenesulfonyl chlorides **I** and **II** under analogous conditions (Scheme 4).

The biological activity of 2-aminobenzimidazoles **XVI** and **XVII** turned out to be similar to that of their

Scheme 3.

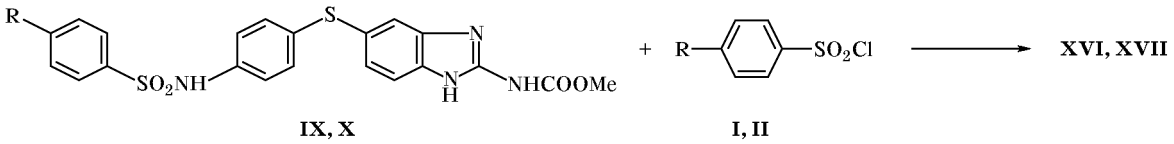


XV **I, II**

XVI, XVII

XVI, R = H; **XVII**, R = Me.

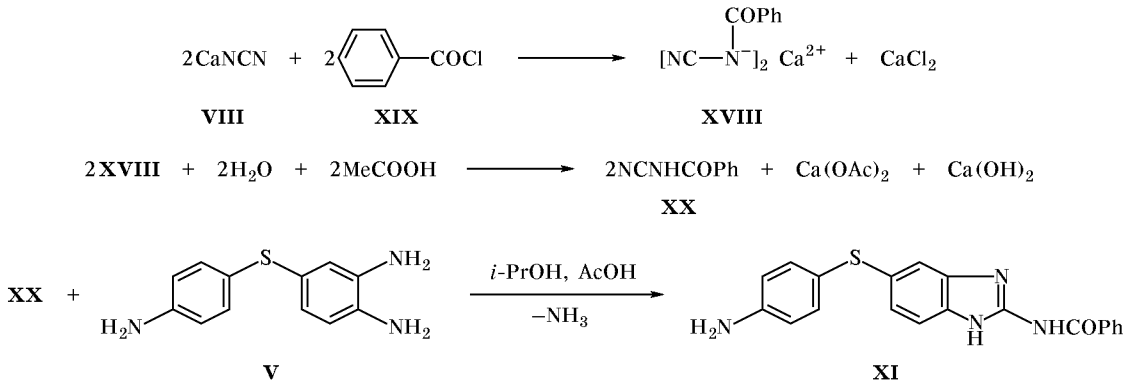
Scheme 4.



IX, X **I, II**

IX, R = H; **X**, R = Me.

Scheme 5.



isomers **XIII** and **XIV**. A number of drug formulations have been developed on the basis of the above compounds. They showed a 100% efficiency in the treatment of sheep helminthiasis at a dose of 10–15 mg/kg (with respect to the acting component) with no embryotoxic or teratogenic effect. The procedures for their preparation and application were covered by inventor's certificate [17].

The reaction of benzoyl chloride **XIX** with calcium or sodium cyanamide gave the corresponding benzoylcyanamide salt **XVIII** which was brought into reaction with triamine **V**. As a result, we obtained 2-benzoylaminobenzimidazole derivative **XI** in 84% yield (Scheme 5). The first stage of the process was carried out in water. The yield of the product depends on the size of calcium cyanamide particles in an aqueous suspension and on the temperature. Better results were obtained with preliminarily powdered calcium cyanamide at 40–45°C. At a lower temperature, the solubility of calcium cyanamide in water decreases, which considerably reduced the rate of the process.

The reaction of benzoylcyanamide calcium salt (**XVIII**) with 3,4,4′-triaminodiphenyl sulfide (**V**) was performed in a mixture of isopropyl alcohol with acetic acid (the latter dissolves triamine **V**) to which an aqueous solution of salt **VIII** was slowly added. Due to the presence of acetic acid the acidity of the medium is sufficient to convert benzoylcyanamide calcium salt into more active neutral form **XX**. Also, acetic acid binds the ammonia released during the condensation. Partial protonation with acetic acid of the amino group in position *4* of triamine **V** hampers formation of guanidine derivative **XXI** as by-product (Scheme 6). On the other hand, the acidity of acetic acid is insufficient for complete protonation of compound **V**, which could inhibit the main process.

The results of our experiments on optimization of the conditions of synthesis of 2-benzoylaminobenzimidazole **XI** (Table 2) showed that the time necessary for complete disappearance of triamine **V** from the reaction mixture increases as the temperature decreases. Increase of the reaction duration, the temperature being the same, reduces the concetration of target compound **XI** in the crude product and simultaneously increases the fraction of guanidine derivative **XXI** (cf. run nos. 2, 5, 7 and 1, 4, 6; Table 2). The large concentration of **XXI** in the crude product obtained in this series of experiments is explained by the low molar ratio triamine **V**–benzoylcyanamide **XX** (1.0 : 1.9). When the ratio **V** : **XX** is 1.0 : 1.3, increase in the reaction time from 5 to 9 h leads to decrease of the fraction of **XI** in the crude product

Scheme 6.

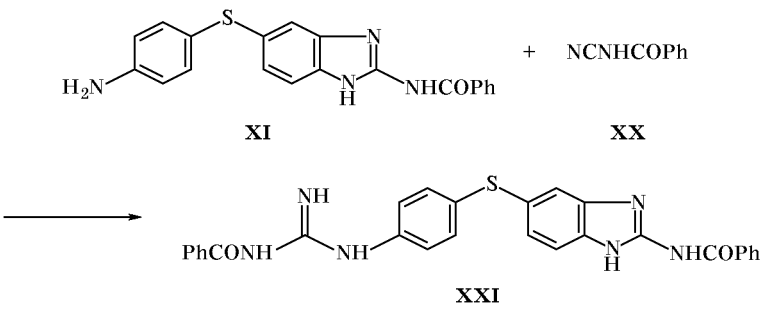


Table 2. Effect of the temperature and reaction time on the results of synthesis of 5(6)-(4-aminophenylthio)-2-benzoylaminobenzimidazole (**XI**); molar ratio triamine **V**–benzoylcyanamide **XX**–acetic acid 1.0 : 1.9 : 5.0, volume ratio isopropyl alcohol–water 0.4 : 1.0

Run no.	Temperature, °C	Time, h	Concentration, wt %	
			XI	**XXI**
1	60	9	44.1	49.5
2	60	11	38.2	53.3
3	71	7	46.3	46.7
4	78	4	50.7	43.5
5	78	7	47.8	45.5
6	86	4	57.5	34.7
7	86	7	49.4	43.5

Table 3. Effect of the molar ratio acetic acid–triamine **V** on the results of synthesis of 5(6)-(4-aminophenylthio)-2-benzoylaminobenzimidazole (**XI**); molar ratio triamine **V**–benzoylcyanamide **XX** 1.0 : 1.9, volume ratio isopropyl alcohol–water 0.4 : 1.0

Temperature, °C	Time, h	Molar ratio AcOH : **V**	Concentration, wt %	
			XI	**XXI**
80	7.0	4 : 1	42.8	51.8
86	6.0	5 : 1	55.4	39.7
80	6.0	7 : 1	56.0	35.3
80	6.5	8.4 : 1	57.5	34.5

Table 4. Effect of the molar ratio triamine **V**–benzoylcyanamide **XX** on the results of synthesis of 5(6)-(4-aminophenylthio)-2-benzoylaminobenzimidazole (**XI**); molar ratio triamine **V**–acetic acid 1.0 : 5.0, volume ratio isopropyl alcohol–water 0.4 : 1.0, temperature 86°C

Run no.	Time, h	Molar ratio **V** : **XX**	Concentration, wt %	
			XI	**XXI**
1	5	1.0 : 1.3	91.5	–
2	9	1.0 : 1.3	81.5	8.5
3	5	1.0 : 1.6	76.9	15.1
4	5	1.0 : 1.9	49.4	43.5
5	5	1.0 : 2.5	38.5	56.6
6	5	1.0 : 3.0	38.3	56.8
7	15	1.0 : 3.0	4.7	82.8

from 91.5 to 81.5%, while the concentration of guanidine derivative rises from 0 to 8.5%. At a **V**-to-**XX** molar ratio of 1.0 : 3.0, increase in the reaction time from 5 to 15 h results in decrease of the concentration of **XI** from 39.3 to 4.7% and increase of the concentration of **XXI** from 55.1 to 82.8%.

The data in Table 3 illustrate the effect of the acetic acid–triamine **V** molar ratio on the yield and purity of 2-benzoylaminobenzimidazole **XI**. It is seen that change in the molar ratio AcOH : **V** from 4 : 1 to 8.4 : 1 increases the concentration of target compound **XI** in the crude product from 44 to 57% and reduces the concentration of guanidine derivative **XXI** from 51 to 35%. The effect of the triamine **V**-to-benzoylcyanamide **XX** ratio is illustrated by the data in Table 4. Reduction of this ratio from 1.0 : 1.3 to 1.0 : 2.5 leads to a considerable increase of the fraction of guanidine derivative **XXI** (from 0 to 56 wt %), while the concentration of **XI** falls down from 91.5 to 39%. Further decrease of the **V**-to-**XX** ratio (the reaction time remaining the same) has almost no effect on the composition of the crude product.

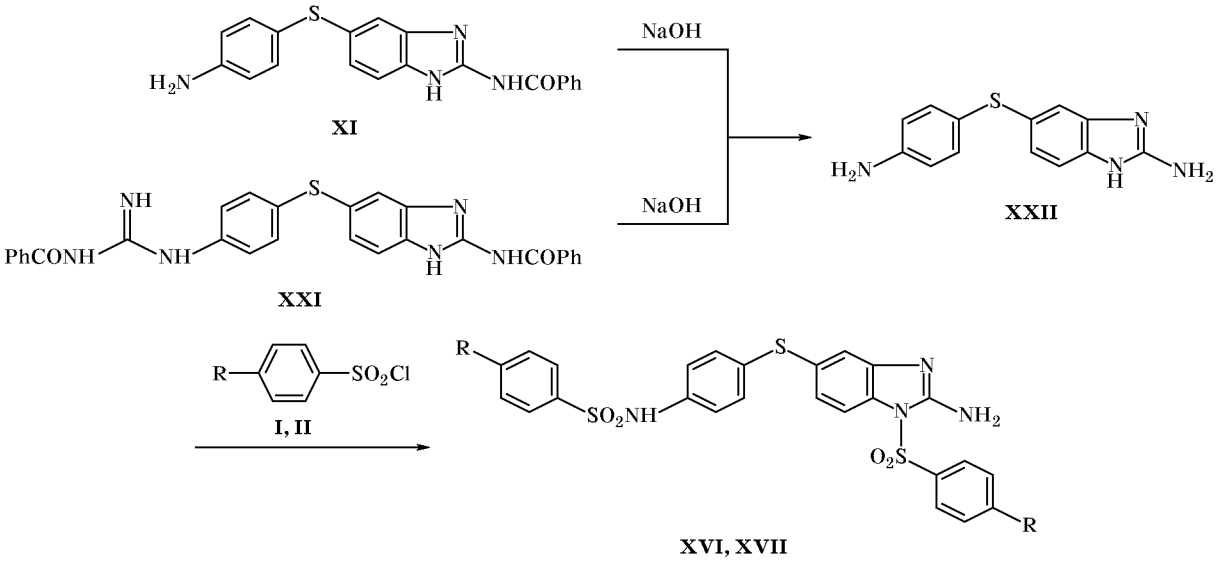
Thus the opimal conditions are the following: the presence of acetic acid as a component of the reaction medium at a ratio of no less than 5 : 1 with respect to 3,4,4′-triaminodiphenyl sulfide (**V**), temperature 80–85°C, and a ratio of triamine **V** to benzoylcyanamide **XX** of no less than 1.0 : 1.3; otherwise, the yield of guanidine derivative **XXI** increases.

It should be noted that the formation of even appreciable amounts of guanidine derivative **XXI** in the synthesis of 2-benzoylaminobenzimidazole **XI** does not impair the quality of bis-arylsulfonamide derivatives formed in the subsequent reaction of **XI** with arenesulfonyl chlorides **I** and **II**. Both 2-benzoylaminobenzimidazole **XI** and its guanidine derivative react with alkali to give the same intermediate product, 2-amino-5(6)-(4-aminophenylthio)benzimidazole (**XXII**), which then react with sulfonyl chlorides **I** and **II** to give compounds **XVI** and **XVII**, respectively (Scheme 7).

When the reaction was carried out in a dioxane–water mixture (volume ratio 1.0 : 3.3), at an alkali–benzoylaminobenzimidazole **XI** molar ratio of 5.0 : 1.0 (temperature 90–95°C), the concentration of guanidine derivative **XXI** in the crude product at the initial moment and 10 and 20 min after addition of alkali was, respectively, 45.3, 19.2, and 6.1 wt %; after 30 min, compound **XXI** disappeared almost completely. 2-Aminobenzimidazole **XXII** thus formed is readily soluble in water.

Using 2-benzoylaminobenzimidazole **XI** as model compound, we examined hydrolysis of the benzoylamino group with the goal of involving the hydrolysis

Scheme 7.



products in the synthesis bis-arylsulfonamide derivatives **XVI** and **XVII**. Samples of the reaction mixture were withdrawn during the process, and the concentrations of benzoylaminobenzimidazole **XI** and 2-aminobenzimidazole **XXII** were determined by HPLC. The reaction was carried out in aqueous dioxane at 85°C, the molar ratio water–dioxane–**XI**–NaOH being 150 : 10 : 1 : 5. The results showed that the hydrolysis takes at least 8 h to be complete. The mixture was then cooled to 2–5°C, and benzenesulfonyl chloride (**I**) or *p*-toluenesulfonyl chloride **II** was added to obtain bis-arylsulfonamide derivatives **XVI** and **XVII**, respectively.

Thus we have demonstrated the possibility, in principle, for obtaining antihelminthic agents on the basis of benzimidazole derivatives having other substituents than those present in the known benzimidazolylcarbamates. Bis-arylsulfonamide derivatives of 2-amino-5(6)-(4-aminophenylthio)benzimidazole are low toxic, and they exhibit neither embryotoxic nor teratogenic effect at therapeutic doses.

EXPERIMENTAL

Analyses were performed with the use of an Altex Model 330 isocratic liquid chromatograph equipped with a Model 110A pump, Model 160 UV detector, and Model 210 sample loop (20 μl); samples were injected with a 50-μl Hamilton SNR microsyringe.

The IR spectra in the range from 4000 to 400 cm^{-1} were recorded on a Jasco 810-IR spectrometer from samples prepared as solutions in carbon tetrachloride or suspensions in mineral oil. The ^{13}C NMR spectra were obtained on a Bruker CXP-100 instrument at 22.63 MHz. The spectra were recorded with and without decoupling from protons using dimethyl sulfoxide as solvent and hexamethyldisiloxane as reference. The signals were assigned on the basis of the chemical shifts, coupling constants, and signal multiplicities and intensities. Known data for model compounds and calculated shielding constants for aromatic carbon nuclei were also used.

Methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate **XV** was determined by HPLC using a 0.25-m × 4.6-mm stainless steel column packed with Ultraspher-ODS reversed phase (grain size 5 μm; tested by Altex); eluent acetonitrile–water (70 : 30, by volume) with addition of 5% (of the overall volume) of dimethylformamide; detection at λ 254 nm. The quantitation was performed by the internal normalization method (from peak areas).

Methyl ester **XV** in the reaction mixture obtained at the stage of synthesis of methyl 5(6)-(4-phenylsulfonylphenylthio)-2-benzimidazolylcarbamate (**IX**) was determined by thin-layer chromatography on silica gel (Silufol plates), followed by diazotization and diazo coupling with α-naphthol; R_f 0.17 (**XV**), 0.05 (**IX**). The other products do not interfere with the determination of **XV**.

Unreacted benzoyl chloride in the synthesis of benzoylcyanamide was determined by alkaline hydrolysis and subsequent mercurimetric titration of chloride ion in acid medium using diphenylcarbazone as indicator. Preliminarily, the concentration of free chloride ions in the sample was determined.

The weight fractions of 2-aminobenzimidazoles **XVI** and **XVII** in the crude products were determined by HPLC using an Ultraspher-ODS column (reversed phase); eluent methyl alcohol–water–dimethylformamide (67.5 : 29.0 : 3.5, by volume) with addition of 4 ml/l of tetrabutylammonium phosphate (0.5 g per 20 ml of water). The compounds were quantitated by the peak area normalization method or by the internal standard technique (diphenylamine).

3,4,4′-Triaminodiphenyl sulfide (**V**) (in the synthesis of 2-phenylsulfonylaminobenzimidazole **III**) was analyzed by TLC, followed by thermal oxidation; R_f 0.11 (**V**), 0.05 (**III**); eluent benzene–ethanol (10 : 1); the chromatograms were developed by heating for 5 min at 220°C. The other products do not interfere with the determination of **V**.

Triamine **V**, 2-benzoylaminobenzimidazole **XI**, and 2-aminobenzimidazole **XVI** in the reaction mixture were detected by TLC on silica gel using benzene–ethanol (10 : 1) as eluent. Dioxane was added to samples of the reaction mixture for dissolution.

Methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate (XV). Methyl chloroformate, 49.4 g (40 ml, 0.52 mol), was added dropwise to a suspension of 54.0 g (0.51 mol) of 77% calcium cyanamide (**VIII**) in 450 ml of distilled water under stirring at 38–41°C. The mixture was stirred for 1 h at that temperature and filtered from undissolved inorganic material, and the precipitate was washed with 60 ml of water on a filter. The filtrate was added to a solution of 62.45 g (0.27 mol) of 3,4,4′-triaminodiphenyl sulfide (**V**) in a mixture of 200 ml of 2-propanol and 110 ml of acetic acid, and the mixture was heated for 6 h under reflux. Yield 69.50 g (82%), mp 247–249°C; published data [5]: mp 249°C; R_f 0.42 (benzene–ethanol, 3 : 1).

5(6)-(4-Aminophenylthio)-2-phenylsulfonylaminobenzimidazole (III). Benzenesulfonyl chloride **I**, 27.56 g (20 ml, 0.156 mol), was added dropwise to a suspension of 17.86 g (0.172 mol) of 77% calcium cyanamide (**VIII**) in 420 ml of distilled water under stirring at 40–45°C. The mixture was stirred for 1 h at that temperature and filtered, and the precipitate was washed on a filter with 40 ml of water. The filtrate was added to a solution of 18.04 g (0.078 mol) of triamine **V** in a mixture of 200 ml of 2-propanol and 20 ml of acetic acid, 20 ml of 36% hydrochloric acid was added, and the mixture was heated for 12 h under reflux. It was then cooled, and the precipitate was filtered off, washed with acetic acid and water, and dried. Yield 14.0 g (45%), mp 260–262°C. Found, %: C 57.46; H 3.92; N 14.32; S 15.85. $C_{19}H_{16}N_4O_2S$. Calculated, %: C 57.55; H 4.07; N 14.13; S 16.17.

Methyl 5(6)-(4-phenylsulfonylaminophenylthio)-2-benzimidazolylcarbamate (IX). Benzenesulfonyl chloride (**I**), 7.0 ml (0.055 mol), was added dropwise to a solution of 15.75 g (0.05 mol) of methyl 2-benzimidazolylcarbamate **XV** in 80 ml of pyridine under stirring at room temperature, and the mixture was left overnight. It was then poured into water, and the precipitate was filtered off, washed with a 25% solution of acetic acid and with water (until neutral), and dried in air. Yield 20 g (88%), mp 160–162°C (from alcohol). Found, %: N 12.48; S 14.65. $C_{21}H_{18}N_4O_4S_2$. Calculated, %: N 12.33; S 14.10.

Methyl 5(6)-[4-(*p*-tolylsulfonylamino)phenylthio]-2-benzimidazolylcarbamate (X). Triethylamine, 19.07 g (26.3 ml, 0.188 mol), or potassium carbonate, 26.2 g (0.188 mol), was added to a suspension of 39.69 g (0.126 mol) of methyl 2-benzimidazolylcarbamate **XV** in 500 ml of dry dioxane. *p*-Toluenesulfonyl chloride (**II**), 30.00 g (0.126 mol, purity 80%), was then added, and the mixture was stirred for 8–10 h at 60°C and poured into water. The precipitate was filtered off, washed with water, and dried. Yield 57.2 g (97%), mp 135–136°C (from alcohol). Found, %: N 11.82; S 13.61. $C_{22}H_{20}N_4O_4S_2$. Calculated, %: N 11.96; S 13.68.

2-Phenylsulfonylamino-5(6)-(4-phenylsulfonylaminophenylthio)benzimidazole (XIII). Triethylamine, 10.5 g (14.7 ml, 0.13 mol), and benzenesulfonyl chloride (**I**), 23 g (16.6 ml, 0.13 mol), were added to a suspension of 39.6 g (0.1 mol) of 2-phenylsulfonylaminobenzimidazole **III** in 200 ml of acetonitrile. The mixture was heated for 1.5–2 h at 60–65°C and poured into 1 l of water. The resulting mixture was vigorously stirred for 3–4 h, and the precipitate was filtered off, washed with water, and dried. Yield 50.9 g (95%), mp 160–162°C. Found, %: N 10.36; S 17.44. $C_{25}H_{20}N_4O_4S_3$. Calculated, %: N 10.44; S 17.92.

Benzimidazole **XIV** was synthesized in a similar way. Yield 92.7%, mp 118–120°C. Found, %: N 10.22; S 17.32. $C_{26}H_{22}N_4O_4S_3$. Calculated, %: N 10.17; S 17.46.

2-Amino-1-phenylsulfonyl-5(6)-(4-phenylsulfonylaminophenylthio)benzimidazole (XVI). A mixture of 62.8 g (0.2 mol) of methyl 2-benzimidazolylcarbamate **XV**, 77.0 g (55.6 ml, 0.44 mol) of benzenesulfonyl chloride (**I**), and 64.7 g (89.8 ml, 0.64 mol) of triethylamine in 200 ml of chloroform was heated for 14 h under reflux. Water, 1.0 l, was added, the mixture was thoroughly stirred, the aqueous–organic

layer was separated, an additional amount of water was added, and the mixture was thoroughly stirred for 3–4 h. The precipitate was filtered off, washed with water, and dried. Yield 91 g (85%), mp 169–171°C. Found, %: C 55.80; H 3.62; S 17.61. $C_{25}H_{20}N_4O_4S_3$. Calculated, %: C 55.95; H 3.76; S 17.92.

2-Amino-1-(*p*-tolylsulfonyl)-5(6)-[4-(*p*-tolylsulfonylamino)phenylthio]benzimidazole (XVII) was synthesized in a similar way. Yield 82%, mp 172–174°C. Found, %: C 57.39; H 4.52; S 16.72. $C_{27}H_{24}N_4O_4S_3$. Calculated, %: C 57.42; H 4.28; S 17.04.

In strongly alkaline media benzenesulfonyl chloride and *p*-toluenesulfonyl chloride undergo appreciable hydrolysis to give, respectively, benzenesulfonic acid and *p*-toluenesulfonic acid. In order to minimize the contribution of this process, the reactions were carried out at a reduced temperature in relatively weakly alkaline media. Excess alkali which remained in the reaction mixture after hydrolysis of 2-benzoylaminobenzimidazole **XI** and its guanidine derivative **XXI** (Scheme 7) was bound with sodium hydrogen carbonate. When the synthesis of bis-arylsulfonamide derivatives **XVI** and **XVII** was complete, the mixture was poured in a 3–4-fold amount of cold water and was vigorously stirred for 3–4 h. The product was filtered off, thoroughly washed from inorganic and organic impurities on a filter, and dried.

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