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Reaction of Methyl 5(6)-(4-Aminophenylthio)-2-benzimidazolylcarbamate with Isocyanates

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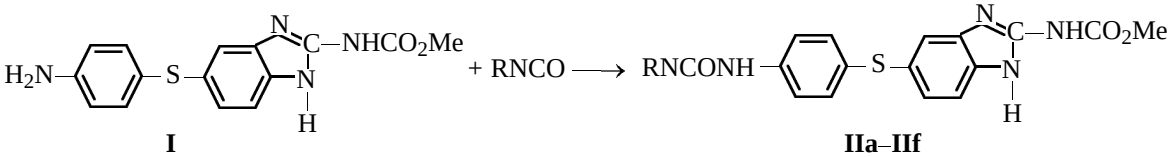
Abstract — Methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate reacts with aliphatic and aromatic isocyanates to give mono- and disubstitution products. The former are formed by the reaction involving the aniline nitrogen and the latter, by the reaction involving both the aniline and benzimidazole nitrogens. Biological activity of the products was assessed.

A great number of methyl 5(6)-(4-aminophenoxy)- and 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate derivatives are known, that act as potent helminthocides [1–10]. Unfortunately, many of them possess embriotoxic and teratogen properties and thus are of limited use. For this reason, as well as in view of the urgency of animal helminthiasis control, search for new nontoxic helminthocides is a topical problem.

The presence in methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate (**I**) of two nucleophilic centers (aniline and benzimidazole nitrogens) makes possible its mono- and dicondensation with isocyanates. At the same time [11], N-substituted benzimidazoles are mild acylating agents. This property is of great biological importance, since *N*-acetylimidazoles are involved in enzymatic transacylation reactions [12]. Consequently, aminobenzimidazole **I** will react with isocyanates by both its nucleophilic centers only the latter reagents are taken in excess. With equimolar reagent amounts, probably, derivatives by aniline nitrogen will only be formed.

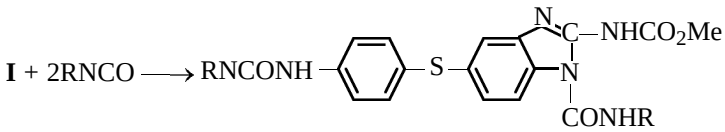
Aminobenzimidazoles substituted by the aniline nitrogen atom (compounds **IIa**–**IIf**) were obtained in thoroughly dried DMSO at 1 : 1 reactant ratios at room temperature within 16–18 h in yields of 80–100% [scheme (1), Table 1].



I **IIa**–**IIf** (1)

R = Me (**a**), Ph (**b**), 2-ClC_6H_4 (**c**), 3-ClC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 3,4-$Cl_2C_6H_3$ (**f**).

Disubstituted aminobenzimidazoles **IIIa**–**IIIf** were obtained in a similar way with double molar excesses of isocyanates at 60–70°C within 3 h [scheme (2), Table 1].



IIIa–**IIIf** (2)

for R, see scheme (1).

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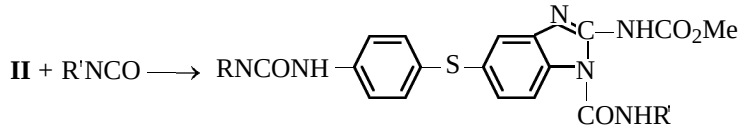
Table 1. Aminobenzimidazole derivatives **II**–**IV**

Comp. no.	mp, °C	Yield, %	Found, %					Formula	Calculated, %				
			C	H	N	S	Hlg		C	H	N	S	Hlg
IIa	256–258	97.2	54.79	4.48	18.66	8.39	–	$C_{17}H_{17}N_5O_3S$	54.97	4.61	18.82	8.63	–
IIb	179–181	99.5	60.75	4.21	15.96	7.00	–	$C_{22}H_{19}N_5O_3S$	60.95	4.42	16.15	7.39	–
IIc	156–158	98.7	56.34	3.52	14.82	6.48	7.32	$C_{22}H_{18}ClN_5O_3S$	56.46	3.87	14.97	6.85	7.58
IId	183–185	98.7	56.24	3.62	14.86	6.52	7.24	$C_{22}H_{18}ClN_5O_3S$	56.46	3.87	14.97	6.85	7.58
IIe	237–239	98.0	56.30	3.55	14.79	6.45	7.38	$C_{22}H_{18}ClN_5O_3S$	56.46	3.87	14.97	6.85	7.58
IIf	178–180	98.0	52.21	3.21	13.70	5.98	14.01	$C_{22}H_{17}Cl_2N_5O_3S$	52.59	3.41	13.94	6.38	14.11
IIIa	196–198	78.1	53.05	4.52	19.38	7.01	–	$C_{19}H_{20}N_6O_4S$	53.26	4.70	19.62	7.48	–
IIIb	143–145	81.8	62.88	4.09	14.95	5.33	–	$C_{29}H_{24}N_6O_4S$	63.03	4.38	15.21	5.80	–
IIIc	98–100	88.7	55.82	3.37	13.34	4.85	11.30	$C_{29}H_{22}Cl_2N_6O_4S$	56.04	3.57	13.52	5.16	11.41
IIId	138–140	96.7	55.85	3.28	13.29	4.95	11.21	$C_{29}H_{22}Cl_2N_6O_4S$	56.04	3.57	13.52	5.16	11.41
IIIe	245–247	98.0	55.84	3.36	13.40	4.85	11.21	$C_{29}H_{22}Cl_2N_6O_4S$	56.04	3.57	13.52	5.16	11.41
IIIf	118–120	97.1	50.25	2.72	11.95	4.24	20.35	$C_{29}H_{20}Cl_4N_6O_4S$	50.45	2.92	12.17	4.64	20.54
IVa	167–169	91.9	55.86	3.47	13.35	4.77	11.15	$C_{29}H_{22}Cl_2N_6O_4S$	56.04	3.57	13.52	5.16	11.41
IVb	146–148	98.0	52.98	3.12	12.53	4.58	15.93	$C_{29}H_{21}Cl_3N_6O_4S$	53.10	3.23	12.81	4.89	16.21
IVc	130–132	81.9	56.28	3.42	11.21	4.95	12.78	$C_{29}H_{22}BrN_5O_4S$	56.49	3.60	11.36	5.20	12.56
IVd	170–172	80.0	60.61	3.69	12.02	5.38	6.05	$C_{29}H_{22}ClN_5O_4S$	60.89	3.88	12.24	5.60	6.20
IVe	161–163	84.9	57.86	4.24	12.96	5.51	6.38	$C_{26}H_{24}ClN_5O_4S$	58.04	4.50	13.02	5.96	6.59
IVf	173–175	96.6	59.66	3.87	11.42	5.01	5.67	$C_{30}H_{24}ClN_5O_5S$	59.84	4.02	11.63	5.33	5.89
IVg	238–240	96.4	60.71	3.71	12.11	5.20	6.07	$C_{29}H_{22}ClN_5O_4S$	60.89	3.88	12.24	5.60	6.20
IVh	170–172	87.6	53.29	3.04	10.51	4.49	17.53	$C_{29}H_{21}BrClN_5O_4S$	53.50	3.25	10.76	4.93	17.73
IVi	166–168	93.9	57.14	3.29	11.35	5.02	11.45	$C_{28}H_{21}Cl_2N_5O_4S$	57.43	3.49	11.55	5.29	11.69

Moreover, mixed derivatives **IVa**–**IVi** with different isocyanate substituents at aniline and benzimidazole nitrogens were obtained from monosubstituted aminobenzimidazole **II** with isocyanates having different substituents [scheme (3), Table 1].



(3)

IVa–**IVi**

R = 3,4-$Cl_2C_6H_3$ (**a, b**), 2-BrC_6H_4 (**c, h**), 2-ClC_6H_4 (**d, i**), $CH_3(CH_2)_2$ (**e**), $C_6H_5OCH_2$ (**f**), C_6H_5 (**g**); R' = C_6H_5 (**a, c, d–), 4-ClC_6H_5 (**b**), 4-ClC_6H_4 (**e**–**i**).

The latter reactions were performed in conditions similar to those used in the synthesis of disubstituted aminobenzimidazoles **III** with identical radicals.

Compounds **II**–**IV** were tested for antihelminth activity and toxicity at the Skryabin Russian Institute of Helminthology (Moscow). The resulting data are given in Table 2. Toxicity tests were performed with mice and antihelmith activity tests, with rats experimentally infected with nippostrongilus larvae.

From data in Table 2 we can draw the following conclusions. First, monocarbamoyl derivatives **IIb**–**IIf** and dicarbamoyl derivatives **IIIb**–**IIIe** and **IVa**–**IVi**, unlike aminobenzimidazole **I**, exhibit no toxicity even at a dose of 1000 mg/kg, except for methyl isocyanate derivatives **IIa** and **IIIa**. The toxicity of the latter two compounds is probably associated with the fact that they undergo fast cleavage in the organism to give the parent aminobenzimidazole. Second, dicarbamoyl derivatives **IIIb**, **IIIc**, **IIIe**, and **IIIf** showed a higher antihelminth activity compared with monocarbamoyl derivatives **IIb**, **IIc**, **IIe**, and **IIf**, except for 3-chloro-

phenyl isocyanate derivatives **IId** and **IIId**. Mixed derivative **IVa** proved to be as potent helminthocide as aminobenzimidazole **I**. The most active derivatives (compounds **IIe**, **IIIe**, **IIIf**, and **IVa**) were tested for embriotropic activity in pregnant rats in critical days, and they all proved to act as embriotropic agents in therapeutic doses.

The fact that compounds **IIe**, **IIIe**, **IIIf**, and **IVa** exhibit embriotoxicity and lack total toxicity can be explained in terms of faster metabolism in embryos and the resulting faster release of the parent aminobenzimidazole compared with adult animals. Thus, these compounds can be used as helmintocides only in mixtures with special additives we developed for suppression of their embriotropic activity.

EXPERIMENTAL

Methyl 5(6)-(4-aminophenylthio)-2-benzimidazolylcarbamate **I** and its derivatives **II**–**IV** were analyzed by HPLC on Ultrasphere-ODS in the following eluents (vol%): (1) acetonitrile : water, 70 : 30, with 5% of DMF and (2) methanol : water : DMF, 67.5 : 29 : 3.5, plus 4 ml/l tetrabutylammonium phosphate (0.5 g per 20 ml of water), UV detectection at λ_{max} 254 nm.

Monocarbamoyl derivatives IIa–IIf. To a solution of 0.05 mol of aminobenzimidazole **I** in 60 ml of DMSO, 0.05 mol of corresponding isocyanate was added. The mixture was left to stand for 16–18 h at room temperature and then poured into water. The precipitate was filtered off, washed with water, and dried.

Dicarbamoyl derivatives IIIa–IIIf. To a solution of 0.05 mol of aminobenzimidazole **I** in 60 ml of DMSO, 0.11 mol of isocyanate was added. The mixture was heated for 3 h at 70–80°C and then cooled and poured into water. The precipitate was filtered off, washed with water, and dried.

Mixed carbamoyl derivatives IVa–IVi. To a solution of 0.05 mol of compound **II** in 100 ml of DMSO, 0.055 mol of corresponding isocyanate was added. The reaction mixture was stirred for 3 h at 70–80°C and then cooled and poured into water. The precipitate was filtered off, washed with water, and dried.

For analysis the products were dissolved in DMSO, the solution was poured into methanol, the precipitate was filtered off, washed with methanol, and dried.

Most isocyanates used were prepared by reactions of excess phosgene with primary amine hydrochlorides. The reactions were performed at elevated temperatures according to the procedures in [13–17].

Table 2. Biologic properties of compounds **II**–**IV**

Comp. no.	Toxicity		Antihelminth activity		
	dose, mg/kg	deaths of enimals, %	dose, mg/kg	quantity of nematodes per head[a]	effectiveness, %
I	40	100	20	6.1	85.0
IIa	100	50	100	16.0	60.0
IIb	1000	0	100	30.6	23.0
IIc	1000	0	100	31.6	21.0
IIc	1000	0	100	16.0	60.0
IIe	1000	0	100	15.6	61.2
IIf	1000	0	100	11.2	72.2
IIIa	100	25	25	17.2	59.0
IIIb	1000	0	25	37.8	10.0
			100	22.4	44.0
IIIc	1000	0	100	22.4	44.0
IIId	1000	0	100	28.0	30.0
IIIe	1000	0	25	19	54.0
			100	1.0	96.0
IIIf	1000	0	100	1.6	94.0
IVa	1000	0	25	0.84	98.0
IVb	1000	0	25	13.9	67.0

[a] The quantity of nematodes per head in the control group was 40.2.

Biological tests. Toxicity tests were performed with mice 18–20 g in weight. Samples as suspensions were introduced orally in one portion in doses of 100 to 1000 mg/ kg. The animals were observed over the course of 5 days, keeping a record of deaths.

Nematocide activity tests were performed with rats 50–60 g in weight experimentally infected with nippostrongilus larvae (300–350 per head). Samples as suspensions were introduced orally in doses of 10 to 100 mg/kg eight days after infection. For each dose, five infected and five control rats were used. After 5-day exposure the animals were killed. The efficiency of the preparations was judged about by data of helminthological examination of thin intestines for tested and control groups.

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