2-PHENYL- AND 2-BENZAMIDO-BENZIMIDAZOLES

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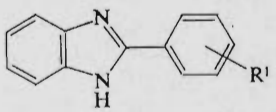
2-Phenylbenzimidazoles *I*—*VI* with chlorine atom or methoxy group on the benzene ring were prepared by a modified method. Acylation of 2-aminobenzimidazole with substituted benzoyl chlorides afforded the 2-benzamidobenzimidazoles *VII*—*XXXVI*. All these compounds were tested for anthelmintic and coccidiostatic activity.

Statistical evaluation of relation between structure and anthelmintic activity of the already used anthelmintics, as well as of compounds prepared by us, led to some conclusions about structural features, characteristic for anthelmintically active organic compounds. The most important of them are benzimidazole nucleus, benzamido group and a chlorine atom or methoxy group on the benzene ring of the benzamido group. We tried to make use of these results in the preparation of compounds, described in this communication. We synthesized two series of compounds, the first being benzimidazoles with a chlorophenyl or methoxyphenyl group in the position 2. In the second series of derivatives, the phenyl group and the 2-benzimidazole moiety are linked by a —CONH— grouping.

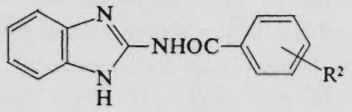
2-(Chlorophenyl)benzimidazoles (*I*) and 2-(methoxyphenyl)benzimidazole are known compounds[1-6] and their anthelmintic activity has also been described[7]; however, their relatively high toxicity prevented practical application. We synthesized these derivatives by heating *o*-phenylenediamine with the corresponding carboxylic acid in polyphosphoric acid[1] or by reaction of *o*-phenylenediamine with the appropriate substituted benzaldehyde in the presence of nitrobenzene as dehydrogenation agent[8].



I, R^1 = 2-Cl
II, R^1 = 3-Cl
III, R^1 = 4-Cl
IV, R^1 = 2-OCH_3
V, R^1 = 3-OCH_3
VI, R^1 = 4-OCH_3

2-Benzamidobenzimidazoles were prepared by acylation of 2-aminobenzimidazole with the corresponding benzoyl chlorides in pyridine[9]. 2-Aminobenzimidazole was synthesized by a modified reaction of *o*-phenylenediamine with cyanogene bromide in an aqueous medium.

The prepared compounds were tested for the anthelmintic and coccidiostatic activity. The anthelmintic activity was assayed on rats, invaded with the parasite *Nippostrongylus brasiliensis* and on mice, invaded with the tapeworm *Hymenolepis nana*[10]. Some compounds were moreover tested on the helmints *Fasciola hepatica*, *Aspiculutis tetraptera* and *Trichinella spiralis*. The most significant anthelmintic activity was exhibited by compound *V* against *Fasciola hepatica*, compound *IV* against the parasite *Aspiculuric tetraptera*, and compound *I* against *Trichinella spiralis*. Statistically significant activity against *Nippostrongylus brasiliensis* was found for compounds *II* and *V*, whereas compounds *XI*, *XV*, *XXVI* and *XXXII* were active against *Hymenolepis nana*. The coccidiostatic activity was evaluated on chickens, invaded by coccidia *Eimeria tenella*, using the so called battery test[10]. Only compound *IV* showed statistically significant activity.



VII, R^2 = 2-Cl
VIII, R^2 = 3-Cl
IX, R^2 = 4-Cl
X, R^2 = 2-OCH_3
XI, R^2 = 3-OCH_3
XII, R^2 = 4-OCH_3
XIII, R^2 = 2-OH-5-Cl
XIV, R^2 = 2-OH-5-Br
XV, R^2 = 2-OCH_3-5-Cl
XVI, R^2 = 2-OCH_3-5-Br

XVII, R^2 = 2-OC_2H_5-5-Cl
XVIII, R^2 = 2-OC_2H_5-5-Br
XIX, R^2 = 2-OC_3H_7-n-5-Cl
XX, R^2 = 2-OC_3H_7-n-5-Br
XXI, R^2 = 2-OC_3H_7-i-5-Cl
XXII, R^2 = 2-OC_3H_7-i-5-Br
XXIII, R^2 = 2-OC_4H_9-n-5-Cl
XXIV, R^2 = 2-OC_4H_9-n-5-Br
XXV, R^2 = 2-OC_4H_9-i-5-Cl
XXVI, R^2 = 2-OC_4H_9-i-5-Br

XXVII, R^2 = 2-OC_5H_{11}-n-5-Cl
XXVIII, R^2 = 2-OC_5H_{11}-n-5-Br
XXIX, R^2 = 2-$OCH_2CH_2OCH_3$-5-Cl
XXX, R^2 = 2-$OCH_2CH_2OCH_3$-5-Br
XXXI, R^2 = 2-OH-3,5-Cl_2
XXXII, R^2 = 2-OH-3,5-Br_2
XXXIII, R_2 = 2-OCH_3-3,5-Cl_2
XXXIV, R^2 = 2-OCH_3-3,5-Br_2
XXXV, R^2 = 2-OC_2H_5-3,5-Cl_2
XXXVI, R^2 = 2-OC_2H_5-3,B-$5r_2$

According to the mentioned anthelmintic screening, no definite relations between structure and biological activity of the synthesized 2-phenyl- and 2-benzamido-benz-

imidazoles can be derived. Interposition of the carbamide function between the benzimidazole and phenyl nuclei did not bring the expected increase in the anthelmintic activity.

EXPERIMENTAL

Melting points were determined on a Mettler FP2 instrument. UV spectra were registered in methanol on a Unicam SP 8000 spectrometer, IR spectra in KBr pellets on a Unicam SP 200G instrument.

2-(4-Chlorophenyl)benzimidazole (*III*)

This compound was prepared by a modified method according to Rope and coworkers[5]. A suspension of 4-chlorobenzoic acid (15·7 g; 0·1 mol) and *o*-phenylendiamine (10·8 g; 0·1 mol) in polyphosphoric acid (100 g) was heated to 210°C for 2 h. The warm melt was mixed with water (500 ml) and neutralized with ammonia. The precipitate was collected on a filter, washed with water and ethanol and crystallized from 80% dimethylformamide (Table I).

2-Phenylbenzimidazoles *I*, *II*, *IV*—*VI*

The compounds were prepared by the modified method of Jerchel[6]. The appropriate benzaldehyde (0·2 mol) was added to a suspension of *o*-phenylenediamine (0·2 mol) in ethanol (100 ml) and after 15 min the mixture was taken down under reduced pressure. The residue was mixed with nitrobenzene (50 ml) and heated. The remaining ethanol distilled at 110°C and then the mixture was kept at 200°C for 2 h. On cooling, it was heated with ether (100 ml), the separated solid filtered, washed with ether and crystallized; see Table I.

TABLE I

2-Phenylbenzimidazoles *I*—*VI*

Compound (yield, %)	M.p., °C (solvent)	Compound (yield, %)	M.p., °C (solvent)
I[a] (41·3)	233·4—233·9 (80% ethanol)	*IV*[e] (30·9)	184·7—185·2 (50% ethanol)
II[b] (29·8)	234·7—235·3 (70% ethanol)	*V*[f] (49·2)	210·0—210·4 (60% ethanol)
III[c] (79·5)	294—295[d] (80% dimethylformamide)	*VI*[g] (67·6)	229·0—229·7 (60% ethanol)

[a] Ref.[4] m.p. 231·4—232·9°C; [b] ref.[5] m.p. 238°C; [c] ref.[6] m.p. 294°C; [d] m.p. determined on a Thiele copper block; [e] ref.[1] m.p. 181·0—181·4°C; [f] ref.[2] m.p. 205°C; [g] ref.[3] m.p. 227°C.

TABLE II

2-Benzamidobenzimidazoles *VII*—*XXXVI*

Compound (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% Hal	% N
VII	273·2—273·8	$C_{14}H_{10}ClN_3O$	61·88	3·71	13·05	15·47
(42·7)	(2-methoxyethanol)	(271·7)	61·93	3·78	13·28	15·71
VIII	255·1—255·6	$C_{14}H_{10}ClN_3O$	61·88	3·71	13·05	15·47
(77·9)	(2-methoxyethanol)	(271·7)	61·76	3·78	12·79	15·79
IX[a]	243·6—244·7	$C_{14}H_{10}ClN_3O$	61·88	3·71	13·05	15·47
(88·3)	(80% dimethylformamide)	(271·7)	61·68	3·97	12·86	15·27
X	219·7—220·5	$C_{15}H_{13}N_3O_2$	67·40	4·90	—	15·72
(39·6)	(ethanol)	(267·3)	67·48	5·01	—	16·52
XI	235·4—235·8	$C_{15}H_{13}N_3O_2$	67·40	4·90	—	15·72
(72·7)	(2-methoxyethanol)	(267·3)	67·25	4·97	—	16·04
XII[b]	250·9—251·4	$C_{15}H_{13}N_3O_2$	67·40	4·90	—	15·72
(22·0)	(ethanol)	(267·3)	67·39	4·98	—	15·82
XIII	329—330[c]	$C_{14}H_{10}ClN_3O_2$	58·44	3·50	12·33	14·61
(33·8)	(2-methoxyethanol)	(287·7)	58·68	3·52	12·12	14·65
XIV	323—324[c]	$C_{14}H_{10}BrN_3O_2$	50·62	3·04	24·06	12·65
(61·5)	(2-methoxyethanol)	(332·2)	50·54	2·97	24·03	12·86
XV	197·8—198·5	$C_{15}H_{12}ClN_3O_2$	59·71	4·01	11·75	13·93
(46·5)	(ethanol)	(301·7)	59·67	3·97	11·87	14·20
XVI	200·0—200·8	$C_{15}H_{12}BrN_3O_2$	52·04	3·50	23·09	12·14
(53·7)	(ethanol)	(346·2)	52·21	3·61	23·25	12·29
XVII	208·5—208·9	$C_{16}H_{14}ClN_3O_2$	60·86	4·47	11·23	13·31
(40·8)	(ethanol)	(315·8)	60·72	4·49	11·52	13·26
XVIII	215·0—215·6	$C_{16}H_{14}BrN_3O_2$	53·35	3·92	22·19	11·67
(28·4)	(90% 2-methoxyethanol)	(360·2)	53·44	4·02	22·26	11·84
XIX	207·8—208·3	$C_{17}H_{16}ClN_3O_2$	61·91	4·89	10·75	12·74
(36·7)	(ethanol)	(329·8)	61·78	4·84	10·83	12·68
XX	236·4—236·9	$C_{17}H_{16}BrN_3O_2$	54·56	4·31	21·36	11·23
(44·4)	(90% 2-methoxyethanol)	(374·2)	54·87	4·49	21·08	11·18
XXI	177·8—178·6	$C_{17}H_{16}ClN_3O_2$	61·91	4·89	10·75	12·74
(22·5)	(ethanol)	(329·8)	61·43	4·81	11·02	12·92
XXII	193·3—193·9	$C_{17}H_{16}BrN_3O_2$	54·56	4·31	21·36	11·23
(35·9)	(ethanol)	(374·2)	54·53	4·37	21·19	11·60
XXIII	232·5—233·3	$C_{18}H_{18}ClN_3O_2$	62·88	5·28	10·31	12·22
(39·0)	(2-methoxyethanol)	(343·8)	63·05	5·32	10·21	12·16

TABLE II
(Continued)

Compound (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% Hal	% N
XXIV	233·2—234·0	$C_{18}H_{18}BrN_3O_2$	55·68	4·67	20·58	10·82
(32·8)	(2-methoxyethanol)	(388·3)	55·88	4·73	20·87	10·81
XXV	188·4—189·1	$C_{18}H_{18}ClN_3O_2$	62·88	5·28	10·31	12·22
(18·4)	(ethanol)	(343·8)	62·92	5·33	10·34	12·31
XXVI	212·7—213·4	$C_{18}H_{18}BrN_3O_2$	55·68	4·67	20·58	10·82
(10·3)	(ethanol)	(388·3)	55·89	4·62	20·86	10·84
XXVII	195·4—196·0	$C_{19}H_{20}ClN_3O_2$	63·77	5·63	9·91	11·74
(58·8)	(2-methoxyethanol)	(357·8)	63·56	5·30	10·08	12·03
XXVIII	197·1—197·6	$C_{19}H_{20}BrN_3O_2$	56·72	5·01	19·87	10·45
(59·7)	(2-methoxyethanol)	(402·3)	56·67	5·00	19·75	10·47
XXIX	168·5—169·2	$C_{17}H_{16}ClN_3O_3$	59·05	4·66	10·26	12·15
(64·4)	(ethanol)	(345·8)	59·27	4·88	10·03	12·32
XXX	184·3—184·9	$C_{17}H_{16}BrN_3O_3$	52·32	4·13	20·48	10.77
(62·8)	(ethanol)	(390·2)	52·29	4·24	20·68	10·73
XXXI	340—341[c]	$C_{14}H_9Cl_2N_3O_2$	52·20	2·82	22·01	13·04
(58·4)	(2-methoxyethanol)	(322·1)	52·20	3·24	21·96	12·83
XXXII	317—318[c]	$C_{14}H_9Br_2N_3O_2$	40·90	2·21	38·88	10·22
(45·7)	(acetic acid)	(411·1)	41·09	2·23	38·44	10·11
XXXIII	203·1—204·5	$C_{15}H_{11}Cl_2N_3O_2$	53·59	3·30	21·09	12·50
(54·5)	(ethanol)	(336·2)	53·64	3·33	21·30	12·71
XXXIV	195·8—197·7	$C_{15}H_{11}Br_2N_3O_2$	42·38	2·61	37·60	9·88
(40·0)	(ethanol)	(425·1)	42·39	2·51	37·25	10·19
XXXV	193·0—193·8	$C_{16}H_{13}Cl_2N_3O_2$	54·87	3·74	20·25	12·00
(28·8)	(ethanol)	(350·2)	54·72	3·94	20·50	12·34
XXXVI	216·8—217·3	$C_{16}H_{13}Br_2N_3O_2$	43·76	2·98	36·40	9·57
(40·3)	(ethanol)	(439·1)	43·78	2·78	36·32	9·60

[a] Ref.[9]; m.p. 242—246°C; [b] ref.[9] m.p. 247—249°C; [c] melting points determined on a Thiele copper block.

2-Aminobenzimidazole

The following simplified procedure is well reproducible. A solution of sodium cyanide (27·0 g; 0·55 mol) in water (170 ml) was added dropwise to a mixture of bromine (79·9 g; 0·5 mol) and water (8 ml), cooled to 5°C with ice. The arising suspension was added portionwise during 1/2 h

to a stirred and cooled (water) suspension of *o*-phenylenediamine (54·1 g; 0·5 mol) in water (300 ml). The mixture was stirred at room temperature for 5 h. Next day, the solution was decolorized with charcoal, filtered and the filtrate basified (pH 11) with a 20% NaOH solution (100 ml). The precipitate was collected on filter, washed with water and dried; m.p. 226·7—228·2°C; yield 49·8 g (74·6%).

2-Benzamidobenzimidazoles *VII—XXXVI*

The appropriate benzoyl chloride (0·1 mol) was added (in small portions or dropwise) at about 18°C to a solution of 2-aminobenzimidazole (0·1 mol) in pyridine (80 ml). The mixture was stirred at room temperature for 5 h and poured into water (500 ml). The precipitate was filtered, washed with water and ethanol and crystallized; see Table II.

UV and IR Spectra

X, UV spectrum: λ_{max} 299 nm (log ε 4·31), 240 nm (log ε 4·12). IR spectrum: 3 330, 1 670, 1 530 cm^{-1} (sec. amide), 3 300 cm^{-1} (sec. amine). *XI*, UV spectrum: λ_{max} 303 nm (log ε 4·28), 243 nm infl. (lo ε 4·00). IR spectrum: 3 340, 1 672, 1 525 cm^{-1} (sec. amide), 3 300 cm^{-1} (sec. amine). *XIV*, UV spectrum: λ_{max} 356 nm (log ε 4·03), 299 nm (log ε 4·32), 248 nm infl. (log ε 4·19), 225 nm (log ε 4·59), 207 nm (log ε 4·43). IR spectrum: 3 180, 1 630, 1 565 cm^{-1} (sec. amide), 3 365 cm^{-1} (sec. amine). *XVI*, UV spectrum: λ_{max} 304 nm (log ε 4·26), 231 nm infl. (lo ε 4·25), 212 nm (log ε 4·68). IR spectrum: 3 260, 1 630, 1 565 cm^{-1} (sec. amide), 3 300 cm^{-1} (sec. amine). *XXXII*, UV spectrum: λ_{max} 366 nm (log ε 4·03), 301 nm (log ε 4·27), 250 nm infl. (log ε 4·19), 232 nm (log ε 4·56), 207 nm (log ε 4·61). IR spectrum: 3 240, 1 630, 1 565 cm^{-1} (sec. amide), 3 400 cm^{-1} (sec. amine).

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