2-PHENYLBENZIMIDAZOLES AS POTENTIAL ANTHELMINTHICS

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Received March 9th, 1976

Reaction of ethers of 5-chloro- and 5-bromosalicylic and thiosalicylic acids *I—XXXIX* with 1,2-diaminobenzene was used to prepare 2-phenylbenzimidazoles *XL—LXXVIII* substituted in position 2 of the benzene ring. The compounds were tested for anthelminthic and coccidiostatic activity.

In a previous communication[1] we published the preparation and results of biological screening of a number of derivatives of 5-chloro- and 5-bromosalicylic and thiosalicylic acids. Since one can prepare 2-substituted benzimidazoles from the carboxylic acids in a reaction of 1,2-diaminobenzene, the acids were used for the synthesis of the corresponding 2-phenylbenzimidazoles. We were interested particularly in the anthelminthic activity of these substances as a number of modern veterinary and human anthelminthics are derived from benzimidazoles substituted in position 2 (ref.[2]).

In contrast with aliphatic carboxylic acids which react with 1,2-diaminobenzene relatively smoothly (on heating with dilute hydrochloric acid or by melting) to the corresponding benzimidazoles, the aromatic carboxylic acids react with 1,2-diaminobenzene only in the presence of dehydration agents. The starting 5-halogenosalicylic acids *I—XXXIX* are partly known from the literature, the preparation of others was dealt with in an earlier paper[1]. The acids were condensed with 1,2-diaminobenzene by heating with phosphorus pentoxide[3] (method *A*) or with polyphosphoric acid[4] (method *B*). When 1,2-diaminobenzene was condensed in this way with 5-chloro-2-methoxybenzoic acid, the first method led to 2-(5-chloro-2-hydroxyphenyl)benzimidazole, *i.e.* the condensation was accompanied by a demethylation. The same result was obtained on melting the two components. When heating with polyphosphoric acid to 200°C a mixture of 2-methoxy and 2-hydroxy derivatives was obtained. Since the demethylation is caused by the highly acid medium and by high temperature, the two components were condensed without the dehydrating agents simply by removing water through azeotropic distillation. The reaction proceeded too slowly in toluene but it was satisfactory in xylene. In this way it was possible to obtain pure 2-(5-chloro-2-methoxyphenyl)benzimidazole (*XLIII*). Azeotropic dehydration

I, *XL*: R = 2-OH-5-Cl
II, *XLI*: R = 2-OH-3,5-Cl_2
III, *XLII*: R = 2-OH-3,5,6-Cl_3
IV, *XLIII*: R = 2-CH_3O-5-Cl
V, *XLIV*: R = 2-CH_3O-3,5-Cl_2
VI, *XLV*: R = 2-C_2H_5O-5-Cl
VII, *XLVI*: R = 2-n-C_3H_7O-5-Cl
VIII, *XLVII*: R = 2-n-C_4H_9O-5-Cl
IX, *XLVIII*: R = 2-i-C_4H_9O-5-Cl
X, *XLIX*: R = 2-n-$C_5H_{11}O$-5-Cl
XI, *L*: R = 2-n-$C_6H_{13}O$-5-Cl
XII, *LI*: R = 2-$CH_3OCH_2CH_2O$-5-Cl
XIII, *LII*: R = 2-$C_6H_5CH_2O$-5-Cl
XIV, *LIII*: R = 2-(2-$ClC_6H_4CH_2O$)-5-Cl
XV, *LIV*: R = 2-(3-$ClC_6H_4CH_2O$)-5-Cl
XVI, *LV*: R = 2-(4-$ClC_6H_4CH_2O$)-5-Cl
XVII, *LVI*: R = 2-(3,4-$Cl_2C_6H_3CH_2O$)-5-Cl
XVIII, *LVII*: R = 2-HO-5-Br
XIX, *LVIII*: R = 2-HO-3,5-Br_2
XX, *LIX*: R = 2-CH_3O-5-Br

XXI, *LX*: R = 2-CH_3O-3,5-Br_2
XXII, *LXI*: R = 2-C_2H_5O-5-Br
XXIII, *LXII*: R = 2-n-C_3H_7O-5-Br
XXIV, *LXIII*: R = 2-n-C_4H_9O-5-Br
XXV, *LXIV*: R = 2-i-C_4H_9O-5-Br
XXVI, *LXV*: R = 2-n-$C_5H_{11}O$-5-Br
XXVII, *LXVI*: R = 2-n-$C_6H_{13}O$-5-Br
XXVIII, *LXVII*: R = 2-n-$C_{12}H_{25}O$-5-Br
XXIX, *LXVIII*: R = 2-$CH_3OCH_2CH_2O$-5-Br
XXX, *LXIX*: R = 2-$C_6H_5CH_2O$-5-Br
XXXI, *LXX*: R = 2-(2-$ClC_6H_4CH_2O$)-5-Br
XXXII, *LXXI*: R = 2-(3-$ClC_6H_4CH_2O$)-5-Br
XXXIII, *LXXII*: R = 2-(4-$ClC_6H_4CH_2O$)-5-Br
XXXIV, *LXXIII*: R = 2-(3,4-$Cl_2C_6H_3CH_2O$)-5-Br
XXXV, *LXXIV*: R = 2-SH
XXXVI, *LXXV*: R = 2-CH_3S
XXXVII, *LXXVI*: R = 2-C_2H_5S
XXXVIII, *LXXVII*: R = 2-n-C_3H_7S
XXXIX, *LXXVIII*: R = 2-i-C_4H_9S

(method *C*) was found to be satisfactory even with other 2-alkoxy-5-chlorobenzoic acids. It has the advantage that the benzimidazole formed crystallizes out from the reaction mixture. However, acids with a free phenolic group, such as 5-chloro- and 5-bromosalicylic acids (*I*, *XVIII*) do not react with 1,2-diaminobenzene under these conditions.

The compounds prepared were tested for anthelminthic and coccidiostatic efficiency using worms *Nippostrongylus brasiliensis* and *Hymenolepis nana*, and coccidia *Eimeria tenella* (for method see[1]). A statistically significant efficiency was found against *N. brasiliensis* with *XLV*, *XLVIII*, *L*, *LII*, *LVI*, *LXIII*, *LXIV*, *LXVI*, *LXVIII*, *LXIX* and *LXX*, and against *H. nana* with *XLVI*, *LI*, *LVI* and *LXX*. A coccidiostatic effect was found only with *LIII*. Although the compounds represent a numerous set of compounds of related structure, the results of the biological tests do not permit to derive clearer relationships between structure and activity. This is due apparently to the fact that the anthelminthic and the coccidiostatic activity of the compounds tested are relatively low and the differences in their effects are obscured by the variability of response of the biological test.

EXPERIMENTAL

The melting points were determined in a Mettler FP 2 apparatus.

Method A: A mixture of 0·05 mol 1,2-diaminobenzene, 0·05 mol halogenosalicylic acid *I* (ref.[5]) *II* (ref.[6]), *III* (ref.[7]), *XVIII* (ref.[12]), *XIX* (ref.[13]), and of 0·055 mol phosphorus pentoxide[3] was slowly heated in a 100 ml flask with a thermometer. After reaching 100—105°C, the reaction took place and the temperature reached nearly 270°C. After waning of the reaction, the melt was dissolved in 70 ml 5M-NaOH at 80°C. The solution was diluted with 100 ml water and acidified with acetic acid. The precipitate formed was filtered, washed with water and recrystallized from a suitable solvent as shown in Table I.

Method B: A mixture of 0·04 mol 1,2-diaminobenzene, 0·04 mol of salicylic acid *III* (ref.[7]), *IV* (ref.[8]), *XVIII* (ref.[12]), *XXXV* (ref.[16]), *XXXVI* (ref.[17]), *XXXVII* (ref.[18]), *XXXVIII* (ref.[18]), *XXXIX* (ref.[1]) and 30 g polyphosphoric acid[4] was heated with stirring for 3 h in a 210—220°C bath, cooled and poured into 150 ml water. The precipitated powdery product was filtered, washed with water and stirred in 100 ml water. The suspension was neutralized with ammoniak, the precipitate was filtered, washed with water and crystallized from a suitable solvent (see Table I).

Method C: A mixture of 0·2 mol 1,2-diaminobenzene, 0·2 mol of the corresponding derivative of salicylic acid *VII* (ref.[9,10]), *VIII* (ref.[11]), *IX* (ref.[1]), *X* (ref.[11]), *XI* (ref.[1]), *XII* (ref.[1]), *XIII* (ref.[1]), *XIV* (ref.[1]), *XVI* (ref.[1]), *XX* (ref.[14]), *XXI* (ref.[12]), *XXII* (ref.[15]), *XXIII* (ref.[1]), *XXIV* (ref.[1]), *XXV* (ref.[1]), *XXVI* (ref.[1]), *XXVII* (ref.[1]), *XXIX* (ref.[1]), *XXX* (ref.[1]), *XXXI* (ref.[1]), *XXXII* (ref.[1]), *XXXIII* (ref.[1]), *XXXIV* (ref.[1]) and 200 ml xylene was boiled in a flask with Friedrichs extension as long as the distillate was turbid with water (8—15 h). After cooling and several hours of standing the precipitate was filtered, washed with ether and dried. The crude product was stirred with 500 ml 2% NaOH, filtered, washed with water, 2% acetic acid and water. After drying, it was crystallized from a suitable solvent (Table I). Evaporation of xylene from the crude product *in vacuo* and processing of the residue as above yielded in some cases another portion of the product.

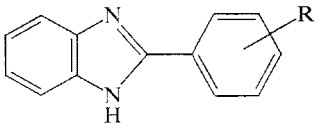

TABLE I

2-Phenylbenzimidazoles XL—LXXVIII

Compound yield, %	M.p., °C (ethanol, %)[a]	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% Br(S)
XL	303—305	$C_{13}H_9ClN_2O$	63·80	3·71	11·49	11·45	—
53·0	(100)	(244·7)	63·86	3·77	11·42	11·60	
XLI	304—306	$C_{13}H_8Cl_2N_2O$	55·94	2·89	25·40	10·04	—
60·2	(100)	(279·1)	55·95	2·92	25·03	9·92	
XLII	271·2—272·3	$C_{13}H_7Cl_3N_2O$	49·79	2·25	33·92	8·94	—
21·0	(100)	(313·6)	49·96	2·51	33·73	9·32	
XLIII	246·1—247·0	$C_{14}H_{11}ClN_2O$	64·99	4·29	13·71	10·83	—
28·0	(100)	(258·7)	65·27	4·36	13·69	11·00	
XLIV	216·6—218·6	$C_{14}H_{10}Cl_2N_2O$	57·35	3·44	24·19	9·56	—
5·6	(75)	(293·2)	57·98	3·64	24·09	9·62	
XLV	175·4—177·1	$C_{15}H_{13}ClN_2O$	66·05	4·80	13·00	10·28	—
20·1	(55)	(272·7)	65·86	4·75	13·29	10·56	
XLVI	162·1—162·7	$C_{16}H_{15}ClN_2O$	67·01	5·27	12·37	9·77	—
41·9	(70)	(286·7)	67·08	5·54	12·28	9·84	
XLVII	168·7—169·3	$C_{17}H_{17}ClN_2O$	67·88	5·70	11·79	9·31	—
22·6	(80)	(300·8)	67·89	5·98	11·93	9·52	
XLVIII	155·7—156·3	$C_{17}H_{17}ClN_2O$	67·88	5·70	11·79	9·31	—
10·8	(80)	(300·8)	67·75	5·87	11·68	9·28	
XLIX	161·8—162·4	$C_{18}H_{19}ClN_2O$	68·67	6·08	11·26	8·90	—
23·1	(90)	(314·8)	68·44	6·18	11·14	8·60	
L	148·9—149·6	$C_{19}H_{21}ClN_2O$	69·39	6·44	10·78	8·52	—
23·1	(100)	(328·8)	69·68	6·34	10·61	8·48	
LI	182·6—183·3	$C_{16}H_{15}ClN_2O_2$	63·47	4·99	11·71	9·26	—
50·5	(100)	(302·8)	63·54	5·22	11·58	9·36	
LII	192·7—193·2	$C_{20}H_{15}ClN_2O$	71·74	4·52	10·59	8·37	—
5·4	(100)	(334·8)	71·68	4·45	10·73	8·45	
LIII	149·3—149·7	$C_{20}H_{14}Cl_2N_2O$	65·05	3·82	19·20	7·59	—
13·8	(80)	(369·2)	65·07	3·79	19·26	7·75	
LIV	174·1—174·5	$C_{20}H_{14}Cl_2N_2O$	65·05	3·82	19·20	7·59	—
21·6	(100)	(369·2)	65·23	3·81	18·82	7·41	
LV	214·8—215·4	$C_{20}H_{14}Cl_2N_2O$	65·05	3·82	19·20	7·59	—
20·0	(100)	(369·2)	65·28	3·89	19·39	7·62	

TABLE I
(*Continued*)

Compound yield, %	M.p., °C (ethanol, %)[a]	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% Br(S)
LVI	197·2—197·8	$C_{20}H_{13}Cl_3N_2O$	59·50	3·25	26·35	6·94	—
5·1	(100)	(403·7)	59·47	3·16	26·56	7·10	
LVII	295·1—296·8	$C_{13}H_9BrN_2O$	54·00	3·14	—	9·69	27·64
52·3	(100)	(289·1)	54·04	3·16	—	9·54	27·82
LVIII	268·6—269·9	$C_{13}H_8Br_2N_2O$	42·42	2·19	—	7·61	43·43
4·5	(80)	(368·0)	42·12	2·14	—	7·65	43·15
LIX	255·0—256·4	$C_{14}H_{11}BrN_2O$	55·46	3·68	—	9·24	26·36
22·8	(100)	(303·2)	55·99	3·84	—	9·26	26·08
LX	222·3—224·0	$C_{14}H_{10}Br_2N_2O$	44·01	2·64	—	7·33	41·84
3·7	(100)	(382·1)	43·78	2·64	—	7·48	42·02
LXI	187·2—187·6	$C_{15}H_{13}BrN_2O$	56·79	4·13	—	8·83	25·20
34·8	(100)	(317·2)	56·81	4·18	—	8·84	25·32
LXII	165·1—165·5	$C_{16}H_{15}BrN_2O$	58·02	4·56	—	8·46	24·13
40·5	(90)	(331·2)	57·98	4·67	—	8·51	24·21
LXIII	180·2—180·5	$C_{17}H_{17}BrN_2O$	59·14	4·96	—	8·12	23·15
24·4	(90)	(345·3)	59·12	5·08	—	7·96	23·31
LXIV	145·8—146·5	$C_{17}H_{17}BrN_2O$	59·14	4·96	—	8·12	23·15
22·6	(80)	(345·3)	59·29	4·93	—	8·26	23·14
LXV	164·6—165·2	$C_{18}H_{19}BrN_2O$	60·17	5·33	—	7·80	22·25
25·8	(100)	(359·3)	60·05	5·33	—	7·97	22·38
LXVI	152·2—152·8	$C_{19}H_{21}BrN_2O$	61·13	5·67	—	7·51	21·41
32·3	(100)	(373·3)	61·25	5·10	—	7·57	21·64
LXVII	95·8—96·4	$C_{25}H_{33}BrN_2O$	65·63	7·27	—	6·13	17·47
21·7	(100)	(457·5)	65·90	7·48	—	6·06	17·56
LXVIII	175·2—175·7	$C_{16}H_{15}BrN_2O_2$	55·34	4·35	—	8·07	23·02
72·6	(100)	(347·2)	55·64	4·62	—	7·98	23·23
LXIX	202·1—202·6	$C_{20}H_{15}BrN_2O$	63·33	3·99	—	7·39	21·07
4·4	(100)	(379·3)	63·58	4·18	—	7·56	21·12
LXX	153·1—153·9	$C_{20}H_{14}BrClN_2O$	58·06	3·41	8·57	6·77	19·32
20·0	(100)	(413·7)	57·98	3·45	8·35	6·91	19·37
LXXI	192·4—192·9	$C_{20}H_{14}BrClN_2O$	58·06	3·41	8·57	6·77	19·32
28·6	(100)	(413·7)	58·06	3·49	8·61	6·64	19·24
LXXII	244·0—244·8	$C_{20}H_{14}BrClN_2O$	58·06	3·41	8·57	6·77	19·32
22·5	[b]	(413·7)	58·07	3·43	8·73	6·50	19·52

TABLE I
(*Continued*)

Compound yield, %	M.p.,°C (ethanol, %)[a]	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% H	% Br(S)
LXXIII	202·7—203·4	$C_{20}H_{13}BrCl_2N_2O$	53·60	2·92	—	6·25	—
14·5	(100)	(448·2)	53·34	2·91	—	6·17	—
LXXIV	279·1—280·5	$C_{13}H_{10}N_2S$	69·00	4·45	—	12·38	(14·17)
75·0	(100)	(226·3)	67·80	4·25	—	12·49	(14·23)
LXXV	226·8—228·0	$C_{14}H_{12}N_2S$	69·96	5·04	—	11·66	(13·34)
58·3	(100)	(240·3)	70·05	5·23	—	11·83	(13·27)
LXXVI	209·7—211·1	$C_{15}H_{14}N_2S$	70·83	5·55	—	11·01	(12·61)
65·1	(100)	(254·3)	70·37	5·93	—	10·94	(12·20)
LXXVII	164·6—165·3	$C_{16}H_{16}N_2S$	71·60	6·01	—	10·44	(11·95)
60·2	(80)	(268·4)	71·29	6·02	—	10·09	(11·80)
LXXVIII	173·1—174·1	$C_{17}H_{18}N_2S$	71·30	6·42	—	9·92	(11·36)
57·7	(80)	(282·4)	71·89	6·53	—	9·54	(11·14)

[a] Concentration of ethanol used for crystallization; [b] ethanol–dimethylformamide (9 : 1).

The anthelminthic and coccidiostatic screening was done in the Research Institute for Biofactors and Veterinary Drugs (director Prof. B. Ševčík). The elementary analyses were done in the analytical department of this institute (Dr J. Körbl).

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Translated by A. Kotyk.