benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride[15] (13.5 g, 0.05 mol) and TEA (30.3 g, 0.3 mol) was stirred at 88 °C for 8 h. After cooling, the mixture was slowly poured into 10% H_2SO_4 (500 mL), and the resulting solution was extracted with $CHCl_3$. The solvent was washed with H_2O (2 × 100 mL), dried, and evaporated. The residue was distilled to give 34 g: bp 90–93 °C (11 mm); IR ν_{max} 1720 (C=O), 1140 (CO), 1075, 1038, 990 cm^{-1}.

Pharmacology. Oral Treatment. Groups of three male conscious spontaneously hypertensive rats (SHR) rats were used. The compounds, suspended in aqueous 0.5% methocel HC 90 Dow, were administered by gavage in a volume of 2 mL/kg. Systolic blood pressure (SBP) was recorded before and 2 and 4 h after treatment. The measurements were taken by the indirect tail-cuff method (W + W BP recorder, Electronic Basel) with a sensor and pressure cuff, after heating the rats for 20 min at 37 °C. Heart rate (HR) was calculated from the pressure tracing. Regression lines were plotted for the maximum fall in blood pressure vs. 1-g dose.

Intravenous Treatment. Groups of four conscious mongrel renal hypertensive dogs were used. The compounds were dissolved in distilled water and administered at 0.5 mL/kg. SBP and HR were measured in the tail by an indirect technique with the recorder already described.

Acknowledgment. We acknowledge with thanks the contribution of Adele Depaoli for the interpretation of the NMR spectra, Valentino Milani for the microanalyses, and Dr. Romeo Ciabatti for helpful discussion on metabolism.

Registry No. 1, 89937-23-5; 2, 83491-12-7; 2·HCl, 83514-28-7; 3, 89937-24-6; 4, 66346-85-8; 5, 89937-25-7; 6, 89937-26-8; 7, 89937-27-9; 8, 89937-28-0; 9, 89937-29-1; 10, 89937-30-4; 11, 75848-36-1; 12, 89937-31-5; 13, 83491-13-8; 14, 89937-32-6; 15, 75842-13-6; 16, 76953-31-6; 17, 89937-33-7; 18, 89937-34-8; 19, 89937-35-9; 20, 37121-81-6; 21·2HCl, 75842-03-4; 22·2HCl, 75842-01-2; 23·2HCl, 75842-05-6; 24·2HCl, 75842-11-4; 25·HCl, 77510-12-4; 26·2HCl, 89937-36-0; 27, 89937-37-1; 28, 75848-33-8; 29, 75842-02-3; 30·HCl, 86703-02-8; 31, 75841-81-5; 32, 75842-04-5; 33, 89937-38-2; 34, 75841-90-6; 35, 75841-87-1; 36·HCl, 89937-39-3; 37, 75841-98-4; 38, 75841-80-4; 39, 75841-99-5; 40, 75842-12-5; 41, 89937-40-6; 42, 75842-08-9; 43, 75842-06-7; 44, 75842-00-1; 45, 89937-41-7; 46, 75841-93-9; 47, 89937-42-8; 48, 75848-35-0; 49, 89937-43-9; 50, 75841-91-7; 51, 75841-97-3; 52, 75841-86-0; 53, 75841-95-1; 54, 75841-89-3; 55, 75841-94-0; 26, 75842-10-3; 57, 89937-44-0; I ($R_3 = R_4 = H$), 141-30-0; IV (R = c-$N(CH_2CH_2)_2O$, $R_1 = CH_3$, $R_3 = R_4 = H$, $R_5 = CH_3$), 77510-10-2; V·2HCl (R = $(CH_2=CHCH_2)_2N$, $R_1 = R_3 = R_4 = H$), 28546-57-8; VII, 17259-72-2; VIII, 89937-45-1; IX, 89937-46-2; X ($R_2 = CH_3$), 110-13-4; X ($R_2 = C_2H_5$), 2955-65-9; XI (R = c-$N(CH_2CH_2)_2O$, $R_1 = CH_3$, $R_3 = R_4 = H$), 61472-02-4; $HN(CH_2CH_2OCH_3)_2$, 111-95-5; NH_2NHCO_2Bu-t, 870-46-2; C_2H_5CHO, 123-38-6; $C_2H_5COCH=CH_2$, 1629-58-9; 1-(2-methoxyphenyl)piperazine, 35386-24-4; 2,5-dimethoxytetrahydrofuran, 696-59-3.

Notes

Syntheses and Anthelmintic Activity of Alkyl 5(6)-(Substituted-carbamoyl)- and 5(6)-(Disubstituted-carbamoyl)benzimidazole-2-carbamates and Related Compounds[1]

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Received August 5, 1983

A number of alkyl 5(6)-(substituted-carbamoyl)- and 5(6)-(disubstituted-carbamoyl)benzimidazole-2-carbamates and related compounds have been synthesized, and their anthelmintic activity against various intestinal helminths of experimental animals have been evaluated. A large percentage of the compounds synthesized showed noteworthy activity against *Ancylostoma ceylanicum* and at higher doses against *Hymenolepsis nana* infections. Compared to the alkyl 5(6)-(substituted-carbamoyl)benzimidazole-2-carbamates, the disubstituted carbamoyl analogues were found to exhibit better anthelmintic activity. The most active compound of the series, namely, methyl 5(6)-[(*N*-2-pyridylpiperazino)carbamoyl]benzimidazole-2-carbamate (**90**), has been screened against intestinal helminths in higher animals and as a micro- and macrofilaricidal agent. Compound **90** has been identified as a broad-spectrum anthelmintic agent. Compound **90** has been identified as a broad-spectrum anthelmintic in view of its efficacy against *A. ceylanicum* (hamsters and dogs), *H. nana* (rats), *Nippostrongylus brasiliensis* (rats), *Syphacia obvelata* (mice), *A. tubaeformis* (cat), *Toxocara* spp. (cat), and *Litomosoides carinii* (cotton rat).

The incidence of helminth infections is alarmingly high in tropical and subtropical regions,[2,3] as a result of poor sanitation and lower standard of living. The nonavailability of minimal medical facilities for diagnosis of the specific helminth infection aggravates the situation even further. A research program was therefore initiated to obtain a broad-spectrum anthelmintic.

We report herein the syntheses and anthelmintic properties of alkyl 5(6)-(substituted- and -disubstituted-carbamoyl)benzimidazole-2-carbamates (**68–90**), 1,2-bis[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]-ethane and its phenyl derivature (**103** and **104**), bis[4-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]phenyl] sulfide or sulfone (**105** and **106**) 1,4-bis-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]benzene 1,4-bis[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]benzene (**109**).

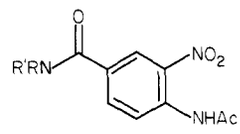
Chemistry. Nitration of 4-acetamidobenzoic acid with fuming HNO_3 at 0 °C furnished 4-acetamido-3-nitrobenzoic acid (1).[4] The reaction of **1** with $SOCl_2$ gave the

[†] Division of Medicinal Chemistry.
[‡] Division of Parisitology.

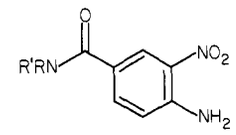
(1) CDRI communication no. 3339.
(2) P. A. J. Janssen, *Prog. Drug. Res.*, 18, 191 (1974).
(3) B. B. Gaitonde and D. M. Renapurkar, *J Assoc. Physicians India*, 27, 129 (1979).

0022-2623/84/1827-1083$01.50/0

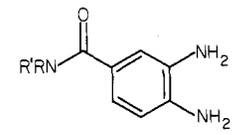
Table I. Physical Data of Various Compounds Synthesized



2-23



24-45

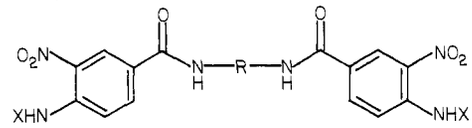


46-67

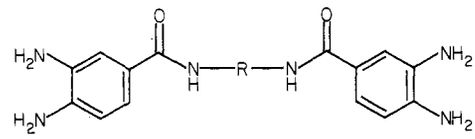
compd	R	R′	mp, °C	yield, %	mol formula[a]
2	H	CH_3	175–176	80	$C_{10}H_{11}N_3O_4$
3	H	C_4H_9	120	85	$C_{13}H_{17}N_3O_4$
4	H	C_8H_{17}	140	86	$C_{17}H_{25}N_3O_4$
5	H	cyclohexyl	190–192	90	$C_{15}H_{19}N_3O_4$
6	H	C_6H_5	220–222	90	$C_{15}H_{13}N_3O_4$
7	H	C_6H_4-F(*p*)	260	92	$C_{15}H_{12}FN_3O_4$
8	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	182	90	$C_{19}H_{21}N_3O_6$
9	H	2-thiazolyl	197	75	$C_{12}H_{10}N_4O_4S$
10	H	2-thiazolinyl	180–182	70	$C_{12}H_{12}N_4O_4S$
11	H	5-methyl-2-thiazolyl	245	70	$C_{13}H_{12}N_4O_4S$
12	H	2-pyridyl	201	75	$C_{14}H_{12}N_4O_4$
13	H	4-pyridyl	250–251	72	$C_{14}H_{12}N_4O_4$
14	H	6-methyl-2-pyridyl	188–190	80	$C_{15}H_{14}N_4O_4$
15	H	6-methoxy-2-benzothiazolyl	225–227	68	$C_{17}H_{14}N_4O_5S$
16	H	furfural	170	80	$C_{14}H_{13}N_3O_5$
17	C_2H_5	C_2H_5	85	82	$C_{13}H_{17}N_3O_4$
18	C_3H_7	C_3H_7	70	80	$C_{15}H_{21}N_3O_4$
19	$CH(CH_3)_2$	$CH(CH_3)_2$	95–98	85	$C_{15}H_{21}N_3O_4$
20	pentamethylene		115–116	80	$C_{14}H_{17}N_3O_4$
21	oxydiethylene		128–130	80	$C_{13}H_{15}N_3O_5$
22	(phenylimino)diethylene		85–86	90	$C_{19}H_{20}N_4O_4$
23	(2-pyridylimino)diethylene		115–116	85	$C_{18}H_{19}N_5O_4$
24	H	CH_3	235–237	65	$C_8H_9N_3O_3$
25	H	C_4H_9	162	70	$C_{11}H_{15}N_3O_3$
26	H	C_8H_{17}	160	70	$C_{15}H_{23}N_3O_3$
27	H	cyclohexyl	188–190	72	$C_{13}H_{17}N_3O_3$
28	H	C_6H_5	195–196	75	$C_{13}H_{11}N_3O_3$
29	H	C_6H_4-F(*p*)	225	75	$C_{13}H_{10}FN_3O_3$
30	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	176	76	$C_{17}H_{19}N_3O_5$
31	H	2-thiazolyl	230–232	60	$C_{10}H_8N_4O_3S$
32	H	2-thiazolinyl	198–200	50	$C_{10}H_{10}N_4O_3S$
33	H	5-methyl-2-thiazolyl	233–235	64	$C_{11}H_{10}N_4O_3S$
34	H	2-pyridyl	268	65	$C_{12}H_{10}N_4O_3$
35	H	4-pyridyl	208–210	65	$C_{12}H_{10}N_4O_3$
36	H	6-methyl-2-pyridyl	218–220	70	$C_{13}H_{12}N_4O_3$
37	H	6-methoxy-2-benzothiazolyl	268–270	70	$C_{15}H_{12}N_4O_4S$
38	H	furfural	205	72	$C_{12}H_{11}N_3O_4$
39	C_2H_5	C_2H_5	oil	65	$C_{11}H_{15}N_3O_3$
40	C_3H_7	C_3H_7	oil	60	$C_{13}H_{19}N_3O_3$
41	$CH(CH_3)_2$	$CH(CH_3)_2$	156–158	68	$C_{13}H_{19}N_3O_3$
42	pentamethylene		135–137	70	$C_{12}H_{15}N_3O_3$
43	oxydiethylene		182	70	$C_{11}H_{13}N_3O_4$
44	(phenylimino)diethylene		135–137	75	$C_{17}H_{18}N_4O_3$
45	(2-pyridylimino)diethylene		168	78	$C_{16}H_{17}N_5O_3$
46	H	CH_3	*b*		
47	H	C_4H_9	120	70	$C_{11}H_{17}N_3O$
48	H	C_8H_{17}	136	65	$C_{15}H_{25}N_3O$
49	H	cyclohexyl	152–154	72	$C_{13}H_{19}N_3O$
50	H	C_6H_5	156–158	70	$C_{13}H_{13}N_3O$
51	H	C_6H_4-F(*p*)	*b*		
52	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	*b*		
53	H	2-thiazolyl	234–236	60	$C_{10}H_{10}N_4OS$
54	H	2-thiazolinyl	220–223	54	$C_{10}H_{12}N_4OS$
55	H	5-methyl-2-thiazolyl	130	50	$C_{11}H_{12}N_4OS$
56	H	2-pyridyl	160	70	$C_{12}H_{12}N_4O$
57	H	4-pyridyl	282–284	60	$C_{12}H_{12}N_4O$
58	H	6-methyl-2-pyridyl	185–187	75	$C_{13}H_{14}N_4O$
59	H	6-methoxy-2-benzothiazolyl	242–244	70	$C_{15}H_{14}N_4O_2S$
60	H	furfural	170	75	$C_{12}H_{13}N_3O_2$
61	C_2H_5	C_2H_5	*b*		
62	C_3H_7	C_3H_7	*b*		
63	$CH(CH_3)_2$	$CH(CH_3)_2$	*b*		
64	pentamethylene		*b*		
65	oxydiethylene		*b*		
66	(phenylimino)diethylene		162–164	70	$C_{17}H_{20}N_4O$
67	(2-pyridylimino)diethylene		*b*		

[a] C, H, and N analyses were within ±0.4% of theory. [b] Not isolated.

Table II. Physical Data of Various Compounds Synthesized



91-94, X = $COCH_3$
95-98, X = H

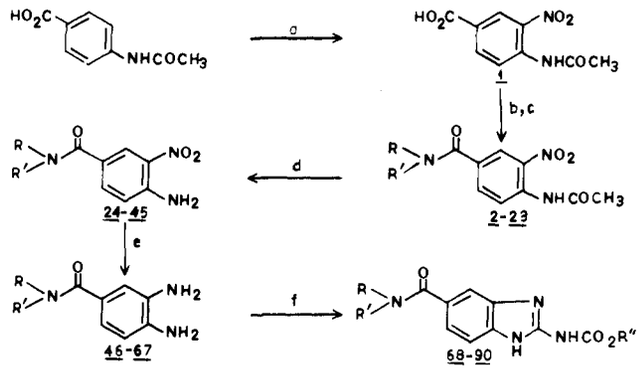


99-102

compd	R	mp, %	yield, %	mol formula[a]
91	CH_2CH_2	256–257	80	$C_{20}H_{20}N_6O_8$
92[b]	CH_2CH_2	190–192	70	$C_{26}H_{24}N_6O_8$
93	$C_6H_4SC_6H_4$	215–218	60	$C_{30}H_{24}N_6O_8S$
94	$C_6H_4SO_2C_6H_4$	258–260	65	$C_{30}H_{24}N_6O_{10}S$
95	CH_2CH_2	220–222	64	$C_{16}H_{16}N_6O_6$
96[b]	CH_2CH_2	125	69	$C_{22}H_{20}N_6O_6$
97	$C_6H_4SC_6H_4$	285–287	70	$C_{26}H_{20}N_6O_6S$
98	$C_6H_4SO_2C_6H_4$	220–222	75	$C_{26}H_{20}N_6O_8S$
99	CH_2CH_2	140–141	60	$C_{16}H_{20}N_6O_2$
100[b]	CH_2CH_2	210–212	60	$C_{22}H_{24}N_6O_2$
101	$C_6H_4SC_6H_4$	142–143	50	$C_{26}H_{24}N_6O_2S$
102	$C_6H_4SO_2C_6H_4$	190–192	50	$C_{26}H_{24}N_6O_4S$

[a] C, H, and N analyses were within ±0.4% of theory. [b] NH–R–NH is replaced by $N(C_6H_5–R–NH$.

Scheme I[a]



[a] a = fuming HNO_3; b = $SOCl_2$; c = HN(R)R′; d = ethanolic NaOH solution; e = Raney Ni/NH_2NH_2; f = $NH_2C(SMe)=NH$ and $ClCO_2R''$.

acid chloride, which, without further purification, was treated with various primary and secondary amines to yield the required amides (**2–23**). Hydrolysis of **2–23** with an aqueous ethanolic NaOH solution furnished the corresponding 4-(substituted- and disubstituted-carbamoyl)-2-nitroanilines (**24–45**). Catalytic hydrogenation of these nitroamines with Raney Ni or their reduction with hydrazine hydrate in the presence of Raney Ni gave the corresponding 4-substituted *o*-phenylenediamines (**46-67**). The reaction of these diamines (**46–67**) with *S*-methylisothiouronium sulfate and methyl or ethyl chloroformate[5] furnished the desired compounds **68–90**.

Similarly, the syntheses of 1,2-bis[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]ethane and its phenyl derivative and bis[4-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]phenyl] sulfide or sulfone were carried out by reacting **1** with $SOCl_2$, followed by treatment with various diamines. Deacetylation of amides **91–94** with aqueous alkali gave the corresponding nitroamines **95–98** (Scheme II). Catalytic hydrogenation of these compounds with Raney Ni in the presence of hydrazine hydrate furnished the desired *o*-phenylenediamines **99–102**. Reaction of these diamines with *S*-methylisothiouronium sulfate and methyl chloroformate furnished the desired compounds **103–106**.

In an extension of this study, the synthesis of 1,4-bis-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]benzene (**109**) was carried out by reacting 2-nitro-*p*-phenylenediamine with terephthaloyl chloride, followed by the catalytic hydrogenation of the amide **107** over Pd/C, and the diamine (**108**) obtained on ring closure with *S*-methylisothiouronium sulfate and methyl chloroformate furnished the required compound **109**.

Anthelmintic Activity and Structure–Activity Relationships. The anthelmintic profile of the compounds synthesized is summarized in Tables III and IV. The substituted carbamoyl residue at position 5(6) of the benzimidazole nucleus yielded compounds with lower activity, while the disubstituted carbamoyl moiety invariably improved the anthelmintic activity. Further improvement in the efficacy of the compound was observed when the disubstituted carbamoyl residue represented a heterocyclic system. Joining the two units of methyl 5(6)-carbamoylbenzimidazole-2-carbamates to two ends of a short carbon chain or to both the extreme ends of the diphenyl sulfide or sulfone residue did not improve anthelmintic activity. The most active compound of the series, namely, methyl 5(6)-(N-2-pyridylpiperazino)carbamoyl]benzimidazole-2-carbamate (**90**), however, exhibited significant activity against hookworm, roundworm, and pinworm but was ineffective against tapeworm at comparable doses. When administered intraperitoneally, compound **90** exhibited both micro- and macrofilaricidal activities (Table V). When administered orally, this compound exhibited microfilaricidal activity at higher doses. It would appear that the compound is poorly absorbed from the gastrointestinal tract. The maximum tolerated dose of **90** in mouse by ip and oral routes was 600 mg/kg and >4 g/kg, respectively. Detailed toxicity studies and pharmacological investigations of this compound are in progress.

Experimental Section

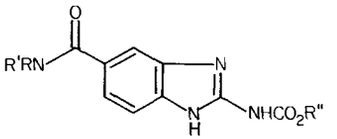
Chemistry. All the melting points were determined either on a H_2SO_4 bath or an electrically heated apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 157 or 177 grating instruments. ^1H NMR spectra were taken on Perkin-Elmer R-32 spectrometer with Me_4Si as internal reference and are expressed in δ units (parts per million). Satisfactory IR and NMR spectra were recorded for all the compounds.

4-Acetamido-3-nitrobenzoic Acid (**1**). To well-cooled (0 °C) fuming HNO_3 (*d* 1.54, 100 mL) was added 4-acetamidobenzoic acid (40 g) under stirring during a period of 1 h. Stirring was continued for another hour, and the temperature was maintained at 0 °C during the entire period of nitration. This mixture was then poured onto crushed ice, and the separated solid was filtered, washed with ice-cold water, dried, and recrystallized from DMF–H_2O: yield 80%; mp 218–20 °C (lit.[4] mp 221 °C).

4-(Substituted-carbamoyl)- and 4-(Disubstituted-carbamoyl)-2-nitroacetanilides (2–23). A mixture of **1** (5 g, 0.022 mol) dissolved in dry benzene (50 mL) and thionyl chloride (10 mL) was refluxed for 4 h. The reaction mixture was then concentrated at reduced pressure, another aliquot (20 mL) of dry benzene was added, and the solution was again concentrated under reduced pressure to remove the traces of $SOCl_2$. To this residue, redissolved in dry benzene (30 mL), was added, under stirring, the appropriate primary or secondary amine (0.022 mol) in dry benzene (10 mL) and triethylamine (0.022 mol) at room temperature. The reaction was continued for an additional period of 2 h. In cases where the solid separated out from the reaction mixture, the material was filtered, washed with water, and re-

(4) V. E. Borel and H. Deuel, *Helv. Chim. Acta.*, *36*, 801 (1953).
(5) A. H. M. Raeymaekers, J. L. H. Van Gelder, L. F. C. Roevens, and P. A. J. Janssen, *Arzneim.-Forsch.*, **28**, 586 (1978).

Table III. Physicochemical and Biological Data of Various Benzimidazole-2-carbamates Synthesized



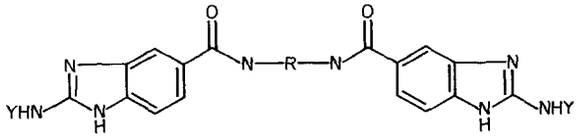
68–90

							biological activity[b]					
							A. ceylanicum		*N. brasiliensis*		*H. nana*	
compd	R	R′	R″	mp, °C	yield, %	mol formula[a]	dose, mg kg × 1	act., %	dose, mg kg × 3	act., %	dose, mg kg × 1	act., %
68	H	CH_3	CH_3	270–272	60	$C_{11}H_{12}N_4O_3$	250	95	250	*	250	100
69	H	C_4H_9	CH_3	>300	70	$C_{14}H_{18}N_4O_3$	250	100	250	*	250	100
70	H	C_8H_{17}	CH_3	292–293	75	$C_{18}H_{26}N_4O_3$	250	100	250	*	200	100
											100	100
71	H	cyclohexyl	CH_3	>300	75	$C_{16}H_{20}N_4O_3$	250	100	250	63.2	250	*
72	H	C_6H_5	CH_3	183–185	70	$C_{16}H_{14}N_4O_3$	250	87	250	*	*b*	
73	H	C_6H_5	C_2H_5	220	72	$C_{17}H_{16}N_4O_3$	250	50	250	*	250	*
74	H	C_6H_4-F(*p*)	CH_3	>300	75	$C_{16}H_{13}FN_4O_3$	250	100	250	*	250	100
75	H	$(CH_2)_2C_6H_3$-3,4-$(OCH_3)_2$	C_2H_5	285	74	$C_{21}H_{24}N_4O_5$	NT[c]		250	*	250	*
76	H	2-thiazolyl	CH_3	205	60	$C_{13}H_{11}N_5O_3S$	250	*	250	*	250	*
77	H	2-thiazolinyl	CH_3	227–230	60	$C_{13}H_{13}N_5O_3S$	250	100	250	*	250	100
							100					
							50	55.5				
78	H	5-methyl-2-thiazolyl	CH_3	240–243	65	$C_{14}H_{13}N_5O_3S$	250	100	250	*	250	100
											100	100
79	H	2-pyridyl	CH_3	237–238	70	$C_{15}H_{13}N_5O_3$	250	95	250	*	250	*
80	H	4-pyridyl	CH_3	247–248	60	$C_{15}H_{13}N_5O_3$	250	75	250	*	250	*
81	H	6-methyl-2-pyridyl	CH_3	>300	70	$C_{16}H_{15}N_5O_3$	250	100	250	*	250	100
							100	100			100	*
							50	92.5				
82	H	6-methoxy-2-benzothiazolyl	CH_3	235–236	65	$C_{18}H_{15}N_5O_4S$	250	*	250	86.6	250	*
83	H	furfuryl	CH_3	285	75	$C_{15}H_{14}N_4O_4$	250	100	250	*	250	100
							100–25	100			100	100
							10	57–82			50	100
											25	100
84	C_2H_5	C_2H_5	CH_3	222–223	65	$C_{14}H_{18}N_4O_3$	250	100	250	100	250	100
							100–50	100	100	100	100–25	100
							25	90	50	100	12.5	100
									25	50	3.12	100
85	C_3H_7	C_3H_7	CH_3	218–219	68	$C_{16}H_{22}N_4O_3$	250	100	250	*	250	100
							100	75			100	100
86	$CH(CH_3)_2$	$CH(CH_3)_2$	CH_3	225–227	70	$C_{16}H_{22}N_4O_3$	250	100	250	100	250	100
							100	100	100	100	50	100
							50	88.8				
87		pentamethylene	CH_3	233–237	70	$C_{15}H_{18}N_4O_3$	250	100	*b*		250	*
88		oxydiethylene	CH_3	223–224	65	$C_{14}H_{16}N_4O_4$	250	100	250	100	250	100
							100–6.25	100	100–50	100	100	100
							3.12	83–97	25	50–77	50	100
89		(phenylimino)diethylene	CH_3	237–240	75	$C_{20}H_{21}N_5O_3$	250	100	250	100	250	100
							100–6.25	100	100–50	100	100	100
							3.12	77–100	25	86.6	50	100

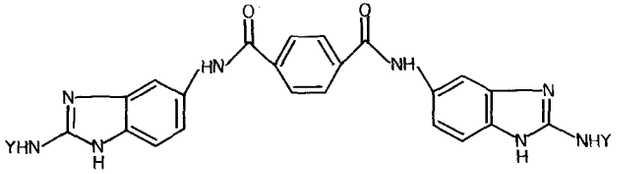
90	(2-pyridylimino)diethylene	CH_3	>240	75	$C_{19}H_{20}N_6O_3$	250	100	250	100	250	100
						100–6.25	100	100–50	100	100–50	100
						3.12	88–100	25	60	25	100
	mebendazole					2.50	100	250	100		
						1.0	100	167	33.3	400	0.0

[a] C, H, and N analyses were within ±0.4% of theory. [b] Asterisks indicate insignificant activity. [c] Not tested.

Table IV. Physicochemical and Biological Data of Various Benzimidazole-2-carbamates Synthesized



103–106, Y = CO_2CH_3



109, Y = CO_2CH_3

					biological activity					
					A. ceylanicum		*N. brasiliensis*		*H. nana*	
compd	R	mp, °C	yield, %	mol formula[a]	dose, mg/kg × 1	act., %	dose, mg/kg × 1	act., %	dose, mg/kg × 1	act., %
103	CH_2CH_2	>300	75	$C_{22}H_{22}N_8O_6$	250	50	250	*	250	*
104	$PhCH_2CH_2$	257–258	76	$C_{28}H_{26}N_8O_6$[b]	250	50	250	*	250	*
105	PhSPh	170–171	70	$C_{32}H_{26}N_8O_6S$[b]	250	48.2	250	*	250	*
106	$PhSO_2Ph$	288–291	75	$C_{32}H_{26}N_8O_8S$[b]	250	48.2	250	*	250	*
109		>300	40	$C_{26}H_{22}N_8O_6$	250	100	250	*	250	*
					50	66.6				

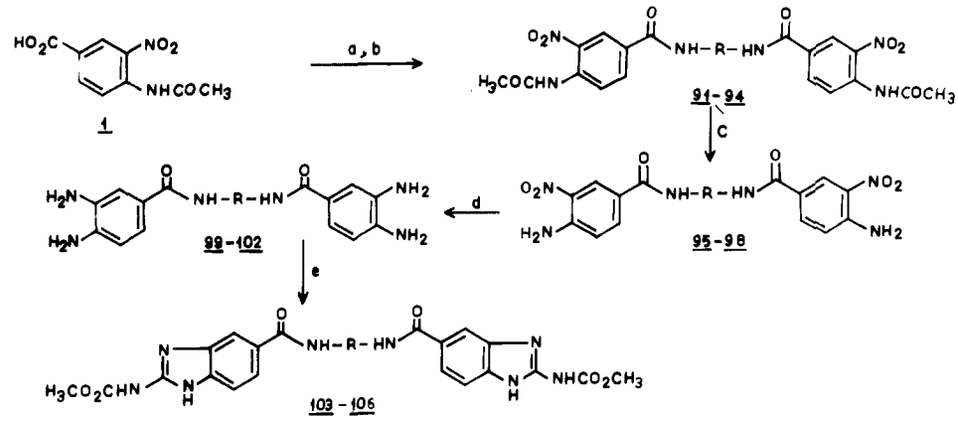
[b] Only C and H were analyzed. Asterisks indicate insignificant activity.

Table V. Efficiency of Compound **90** against Other Intestinal and Tissue Helminths

host	parasite	dose, mg/kg	results
mouse	*S. obvelata* (pinworm)	12.5 × 3	100% active
cat	*A. tubaeformis* (hookworm)	25 × 3	100% active
		10 × 3	inactive
	Toxocara spp. (ascaris)	25 × 3	100% active
	Taenia spp. (tapeworm)	25 × 3	inactive
dog	*A. ceylanicum* (hookworm)	25 × 3	100% active
		10 × 3	100% active
cotton rat	*L carinii* (filarid worm)	30 × 5 (ip)	97% effective on microfilariae
			100% effective on adults
		10 × 5 (ip)	inactive against both microfilariae and adults
		100 × 5 (po)	94.8% effective against microfilariae and inactive against adults
		50 × 5 (po)	inactive against both microfilariae and adults
		30 × 5 (ip)[a]	100% effective on adults
		10 × 5 (ip)[a]	68.5% effective on adults
		3 × 5 (ip)[a]	27.2% effective on adults
		300 × 5 (po)[a]	31.8% effective on adults

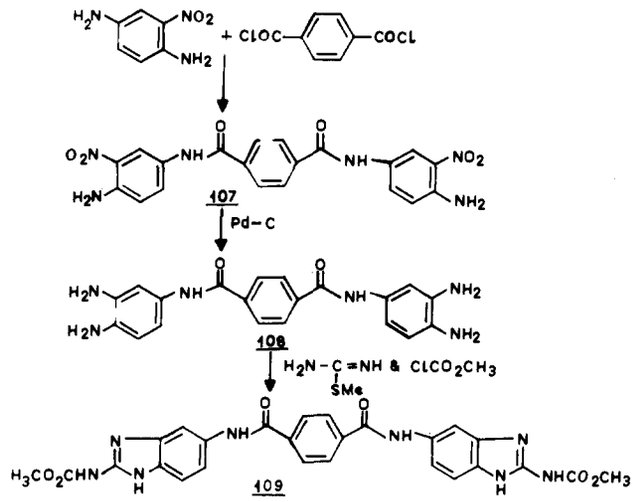
[a] Dose of mebendazole.

Scheme II[a]



[a] a = $SOCl_2$; b = NH_2RNH_2; c = ethanolic NaOH solution; d = Raney Ni/NH_2NH_2; e = $NH_2C(SMe)=NH$ and $ClCO_2CH_3$.

Scheme III



crystallized from aqueous ethanol or DMF–H_2O. In cases where the solid did not separate, the reaction mixture was extracted with ethyl acetate, and the usual workup of the organic layer furnished the desired compounds. These were recrystallized from $CHCl_3$–hexane.

4-(Substituted-carbamoyl)- and 4-(Disubstituted-carbamoyl)-2-nitroanilines (24–45). To a mixture of the appropriate 4-carboxamido-3-nitroacetanilide (**2-23**; 0.02 mol) in ethanol (25 mL) was added NaOH solution (10%, 2 mL), and the mixture was stirred at room temperature for 1 h. This was followed by the addition of dilute HCl, and the precipitated compound was filtered, washed with water, dried, and recrystallized from DMF–H_2O. In cases where the solid did not separate, the reaction mixture was extracted with appropriate organic solvent, which after usual workup furnished the desired compounds.

4-(Substituted-carbamoyl)- and 4-(Disubstituted-carbamoyl)-*o*-phenylenediamines (46–67). To a mixture of the appropriate 4-carboxamido-2-nitroaniline (**24–45**; 5 g) and Raney Ni (~5 g) in ethanol (50 mL) was added dropwise, under stirring, hydrazine hydrate (99%, 5 mL) in ethanol (5 mL), and the mixture was refluxed for 1 h. Filtration of the catalyst, followed by removal of the solvent under reduced pressure and crystallization of the solid residue from aqueous ethanol, yielded the desired compound. In cases where the solid did not separate, it was used as such for the next step without further purification, assuming the yield of hydrogenation as quantitative.

Alkyl 5(6)-(Substituted-carbamoyl)- and 5(6)-(Disubstituted-carbamoyl)benzimidazole-2-carbamates (68–90). Aqueous NaOH solution (25%) was added under stirring to a precooled mixture (10–15 °C) of *S*-methylisothiouronium sulfate (0.01 mol) and alkyl chloroformate (0.02 mol) in water (10 mL) until the pH of the solution was between 7.0 and 8.0. This was followed by the addition of glacial acetic acid for readjusting the pH to about 5.0. To this mixture was added the appropriate diamine (**46–67**; 0.01 mol) in ethanol (30 mL), and the reaction mixture was then stirred for 1 h. After the mixture was cooled, the separated solid was filtered, washed with water, and dried. These compounds were recrystallized either from DMF–H_2O or acetic acid–H_2O. Compounds **84–86** have been reported earlier.[14]

1,2-Bis[(*m*-nitro-*p*-acetamidobenzoyl)amino]ethane and Bis[4-[(*m*-nitro-*p*-acetamidobenzoyl)amino]phenyl] Sulfide and Sulfone (91-94). The experimental procedure was essentially the same as described for the syntheses of **2–24**, except that in cases of **93** and **94** dry DMF was used as solvent instead of dry benzene for the preparation of the amide.

1,2-Bis[(*m*-nitro-*p*-aminobenzoyl)amino]ethane and Bis[4-[(*m*-nitro-*p*-aminobenzoyl)amino]phenyl] Sulfide and Sulfone (95–98). The method adopted for the hydrolysis of **91–94** to obtain **95–98** was similar to the one described for the preparation of **24–45**.

Catalytic Hydrogenation of Compounds 95–98. Formation of Compounds 99–102. The method of preparation described for **46–67** was employed for the synthesis of these compounds.

1,2-Bis[[2-(carbomethoxyamino)-5-benzimidazolyl]-carboxamido]ethane and Its Phenyl Derivative and Bis-[4-[[2-(carbomethoxyamino)-5-benzimidazolyl]carboxamido]phenyl] Sulfide and Sulfone (103–106). The experimental procedure, for obtaining **103–106** from **99–102**, was essentially the same as described for the synthesis of **68–90**.

1,4-Bis[(*p*-amino-*m*-nitrophenyl)carboxamido]benzene (107). Terephthalic acid (6.64 g, 0.04 mol), $SOCl_2$ (10 mL), and PCl_5 (10 g) was heated at 240 °C for 2 h, and the clear solution so obtained was concentrated under reduced pressure. The residue was triturated with dry benzene (20 mL), and the solvent was concentrated under reduced pressure. To this residue, dissolved in dry DMF (25 mL), was added dropwise, under stirring, a solution of 2-nitro-*p*-phenylenediamine (12.25 g, 0.08 mol) in dry DMF (30 mL) and triethylamine (4 g, 0.04 mol). The reaction was allowed to continue for 4 h. This was followed by the addition of water, and the separated solid was filtered, dried, and recrystallized from DMF–H_2O: yield 5.00 g; mp >300 °C.

1,4-Bis[(*m*,*p*-Diaminophenyl)carboxamido]benzene (108). To a solution of **107** (4 g) in ethanol (50 mL) and DMF (10 mL) was added Pd/C (10%, 0.4 g), and the mixture was hydrogenated at 2.5 kg/cm^2 for a period of 6 h. The catalyst was filtered off, and the removal of solvent from the filtrate under reduced pressure gave an oil, which was used as such for the next step without further purification.

1,4-Bis[[2-(carbomethoxyamino)-5-benzimidazolyl]-carboxamido]benzene (109). The method employed to prepare this compound is similar to the one described for **68–90**: yield 40%; mp >300 °C.

Biological Methods. The anthelmintic activity of the compounds synthesized was evaluated against a variety of intestinal worms in experimental animals. Compounds that showed promise in this test were subjected to further detailed evaluation against intestinal helminths in higher animals as well as tissue helminths.

Anthelmintic Screening in Experimental Animals. ***Ancylostoma ceylanicum*** **(Hookworm).** The screening for anti *Ancylostoma ceylanicum* was carried out essentially according to Ray et al.[6] with modifications to suit the local conditions as described by Misra et al.[7] and Katiyar et al.[8] Hamsters of either sex (40–60 g) were infected orally with third-stage larvae (60 in number), and the testing of the compounds was carried out on day 20 ± 1 postinfection. The initial oral dose of the test compounds was 250 mg/kg × 1. Lower doses of active compounds were used to determine the dose–response relationship.

Hymenolepsis nana **(Tapeworm).** The cestodicidal activity in male rats (25–35 g) was assessed by following the method of Steward.[9] The animals were infected orally with 200 viable eggs, and on days 17–20 postinoculation, the infection was checked by ovoscopic examination. Rats that were found positive were treated with test compounds on day 20 ± 1 postinfection at an initial dose of 250 mg/kg × 1. The dose–response relationship for active compounds was obtained as described above.

Nippostrongylus brasiliensis **(Trichostrongylid).** The screening technique in male rats (25–40 g) was essentially that of Steward[9] and modified later by Katiyar and Sen[10] to suit local conditions. The animals received an inoculation of 500 infected larvae (from 6–8 day old fecal culture) subcutaneously, and the compounds were administered orally on day 9 postinfection in doses of 250 mg/kg × 3. Lower doses (as described above) were employed for active compounds as a follow-up study.

Syphacia obvelata **(Pinworm).** The test compounds were evaluated in adult mice of both sexes (20–30 g) according to Standon.[11] An initial oral dose of 25 mg/kg × 3 was followed by lower doses for active compounds. A positive control of mebendazole, 50 mg/kg × 3, gave 100% activity.

Litomosoides carinii **(Filariid).** The antifilarial activity of the test compounds was evaluated in recently infected cotton rats showing a progressive rise in microfilaraemia, and the technique of Hawking and Swell,[12] as modified by Misra et al.[13] was employed. In the beginning, a dose of 30 mg/kg × 5 (ip) was administered, and for the active compound, the efficacy was also assessed at 100 mg/kg × 5 po.

Assessment of Anthelmintic Efficacy in Higher Animals. The activity of compound **90** was evaluated against intestinal helminths (*A. tubaeformis*, *Toxocara* spp., *Taenia* spp., and *A. ceylanicum*) in naturally or artificially infected cat and dog as described earlier.

Registry No. 1, 1539-06-6; **2**, 89790-47-6; **3**, 89790-48-7; **4**, 89827-24-7; **5**, 89790-49-8; **6**, 89790-50-1; **7**, 89790-51-2; **8**, 89790-52-3; **9**, 89790-53-4; **10**, 89790-54-5; 11, 89790-55-6; **12**, 89790-56-7; **13**, 89790-57-8; **14**, 89790-58-9; **15**, 89790-59-0; **16**, 89790-60-3; **17**, 89790-61-4; **18**, 89790-62-5; **19**, 89790-63-6; **20**, 89790-64-7; **21**, 89790-65-8; **22**, 89790-66-9; **23**, 89790-67-0; **24**, 89790-68-1; **25**, 88638-67-9; **26**, 89790-69-2; **27**, 89790-70-5; **28**, 89790-71-6; **29**, 89790-72-7; **30**, 89790-73-8; **31**, 89790-74-9; **32**, 89790-75-0; **33**, 89790-76-1; **34**, 89790-77-2; **35**, 89790-78-3; **36**, 89790-79-4; **37**, 89790-80-7; **38**, 89790-81-8; **39**, 89790-82-9; **40**, 89790-83-0; **41**, 89790-84-1; **42**, 89790-85-2; **43**, 89790-86-3; **44**, 89790-87-4; **45**, 89790-88-5; **46**, 89790-89-6; **47**, 89790-90-9; **48**, 89790-91-0; **49**, 89790-92-1; **50**, 93-64-1; **51**, 89790-93-2; **52**, 89790-94-3; **53**, 89790-95-4; **54**, 89790-96-5; **55**, 89790-97-6; **56**, 89790-98-7; **57**, 89790-49-8; **58**, 89791-00-4; **59**, 89791-01-5; **60**, 89791-02-6; **61**, 89791-03-7; **62**, 89791-04-8; **63**, 89791-05-9; **64**, 89791-06-0; **65**, 65003-29-4; **66**, 89791-07-1; **67**, 89791-08-2; **68**, 89791-09-3; **69**, 89791-10-6; **70**, 89791-11-7; **71**, 89791-12-8; **72**, 89827-25-8; **73**, 89791-13-9; **74**, 89791-14-0; **75**, 89827-26-9; **76**, 89791-15-1; **77**, 89791-16-2; **78**, 89791-17-3; **79**, 89791-18-4; **80**, 89791-19-5; **81**, 89791-20-8; **82**, 89827-27-0; **83**, 89791-21-9; **84**, 67476-34-0; **85**, 67476-35-1; **86**, 67476-36-2; **87**, 65003-32-9; **88**, 65003-30-7; **89**, 89791-22-0; **90**, 89791-23-1; **91**, 89791-24-2; **92**, 89791-25-3; **93**, 89791-26-4; **94**, 89791-27-5; **95**, 89791-28-6; **96**, 89791-29-7; **97**, 89791-30-0; **98**, 89791-31-1; **99**, 89791-32-2; **100**, 89791-33-3; **101**, 89791-34-4; **102**, 89791-35-5; **103**, 89791-36-6; **104**, 89791-37-7; **105**, 89791-38-8; **106**, 89791-39-9; **107**, 89791-40-2; **108**, 89791-41-3; **109**, 89791-42-4; 4-acetamidobenzoic acid, 556-08-1; methanamine, 74-89-5; 1-butanamine, 109-73-9; 1-octanamine, 111-86-4; cyclohexanamine, 108-91-8; 4-fluorobenenamine, 371-40-4; 3,4-dimethoxybenzenethanamine, 120-20-7; 2-thiazolamine, 96-50-4; 2-thiazolinamine, 1779-81-3; 5-methyl-2-thiazolamine, 7305-71-7; 2-pyridinamine, 504-29-0; 4-pyridinamine, 504-24-5; 6-methyl-2-pyridinamine, 1824-81-3; 6-methoxy-2-benzothiazolamine, 1747-60-0; benzenamine, 62-53-3; 2-furanmethanamine, 617-89-0; diethylamine, 109-89-7; dipropylamine, 142-84-7; diisopropylamine, 108-18-9; piperidine, 110-89-4; morpholine, 110-91-8; 1-phenylpiperazine, 92-54-6; 1-(2-pyridyl)piperazine, 34803-66-2; ethylenediamine, 107-15-3; phenylethylenediamine, 5700-56-1; 4,4′-sulfonylbisbenzenamine, 80-08-0; 2-nitro-1,4-benzenediamine, 5307-14-2; 1,4-benzenedicarbonyl dichloride, 100-20-9; *S*-methylisothiouronium sulfate, 2260-00-6; ethyl chloroformate, 541-41-3; methyl chloroformate, 79-22-1.

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