Antiparasitic Agents. 5.[1] Synthesis and Anthelmintic Activities of Novel 2-Heteroaromatic-Substituted Isothiocyanatobenzoxazoles and Benzothiazoles

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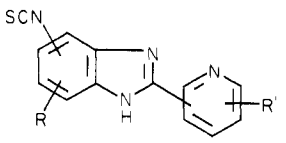
The synthesis and antiparasitic properties of 22 isothiocyanato-2-pyridinylbenzoxazoles and benzothiazoles are described; the preparation and anthelmintic activities of 14 isothiocyanato-2-thienyl-, -furyl-, and -pyrrolylbenzoxazoles are outlined. In mice experimentally infected with *Nematospiroides dubius* (nematode) and *Hymenolepis nana* (tapeworm), three derivatives, i.e., 5-isothiocyanato-2-(2-furyl)benzoxazole (**34**), 5-isothiocyanato-2-(5-methyl-2-furyl)benzoxazole (**35**), and 5-isothiocyanato-2-(1-methyl-1*H*-2-pyrrolyl)benzoxazole (**37**), show 100% nematocidal activity and two, i.e., 5- and 6-isothiocyanato-2-(3-pyridinyl)benzoxazole (**5**) and 5- and 6-isothiocyanato-2-(3-pyridinyl)benzthiazole (**21**), show 100% taeniacidal activity at 0.2% in the diet. Two derivatives (**5** and **21**) show good nematocidal activity in sheep. Maximum activity requires 3-pyridinyl derivatives for both the benzoxazole and benzothiazole series.

In an earlier paper[2] we reported the synthesis and anthelmintic activity of some novel 2-pyridinyl-5-isothiocyanatobenzimidazoles I. The most active member in this



I

series, 5-isothiocyanato-2-(2-pyridinyl)-1*H*-benzimidazole, when tested in naturally infected sheep, is potentially an effective gastrointestinal nematocide at 50 mg/kg po. This encouraging result led to the synthesis of isosteric isothiocyanatobenzoxazoles and benzothiazoles as potential anthelmintics.[3] Since our summary of pertinent published work on antiparasitic isothiocyanates,[2] additional material relevant to this paper has appeared. Thus, a variety of 2-substituted benzoxazoles have been claimed to possess antiparasitic activity against *Turbatrix aceti*,[4] *Syphacia obvelata*,[5] *Nippostronglyus brasiliensis*,[6] helminths,[7,8] *Eimeria tenella* and *Eimeria necatrix*,[9] and *S. obvelata* and *Aspicularis tetraptera*.[10] Brenneisen and co-workers describe anthelmintic isothiocyanatobenzoxazoles,[11] and Sharma's review summarizes cestocidal isothiocyanates.[12] Furthermore, several papers and patents describe antiparasitic 2-substituted benzothiazoles active against *Nematospiroides dubius*,[13] *Ascaris suum*,[14] and *Hymenolepis nana*.[15] Ciba-Geigy patents disclose isothiocyanatobenzoxazoles as anthelmintics.[16]

Chemistry. Benzoxazoles.[2,17,18] The intermediates 5- and 6-nitrobenzoxazoles VII were synthesized employing the four parallel routes developed for the benzimidazole series, namely, (a) PPA-catalyzed ring closure of *o*-aminophenols IIa with the appropriate carboxylic acids, followed by nitration of the benzoxazoles IV; (b) acylation of nitroaminophenols IIb with carboxylic acid chlorides and subsequent thermally induced cyclodehydration of the amides III; (c) oxidative cyclization of Schiff bases VI using lead(IV) acetate; and (d) reaction of imino ethers V, derived from 2-cyanopyrazine or 2-cyano-4-nitropyridine, with *o*-aminophenols IIa and nitration of IV (R^3 = 2-pyrazinyl). Reduction of nitro derivatives VII, followed by thiocarbonylation of the resulting amines using thiophosgene, completed the synthesis of 5- and/or 6-isothiocyanatobenzoxazoles VIII.

In a related study, we investigated several dialkylamino- and dialkylaminomethyl-substituted pyridine, thiophene, and furan derivatives of VIII. Alkylation of secondary amines with chloropyridines VIIa furnished VIIb. Bromination of VIIc with NBS, followed by displacement of the resulting bromomethyl derivatives with secondary amines, afforded VIIe. Finally, hydrogenation/thiocarbonylation yielded VIII (Scheme I).

Benzothiazoles.[2,19] The syntheses of the requisite nitrobenzothiazoles IX were equally straightforward: (a) PPE- or PPA-catalyzed ring closure of *o*-aminothiophenols X with heteroaromatic acids and subsequent nitration of the benzothiazole XIV; (b) base-catalyzed ring opening of 2-aminobenzothiazoles XII to yield *o*-aminothiophenols, which then were subjected to synthetic route a; (c) reaction of aniline XIII with Na_2S/S, followed by treatment with HCl. The resulting *o*-aminothiophenol XI was then converted to IX using again route a. Target compounds XV were prepared by subjecting IX to the standard hydrogenation/thiocarbonylation sequence (Scheme II).

Anthelmintic Activity. The compounds were tested as previously described[2] against mice experimentally infected with *N. dubius* (nematode) and *H. nana* (tapeworm). The results are summarized in Table I. Preliminary evaluation of anthelmintic activity in sheep naturally infected with a mixed trichostrongylid nematode popula-

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(10) U.S. Patents 3 335 052; 3 471 508.
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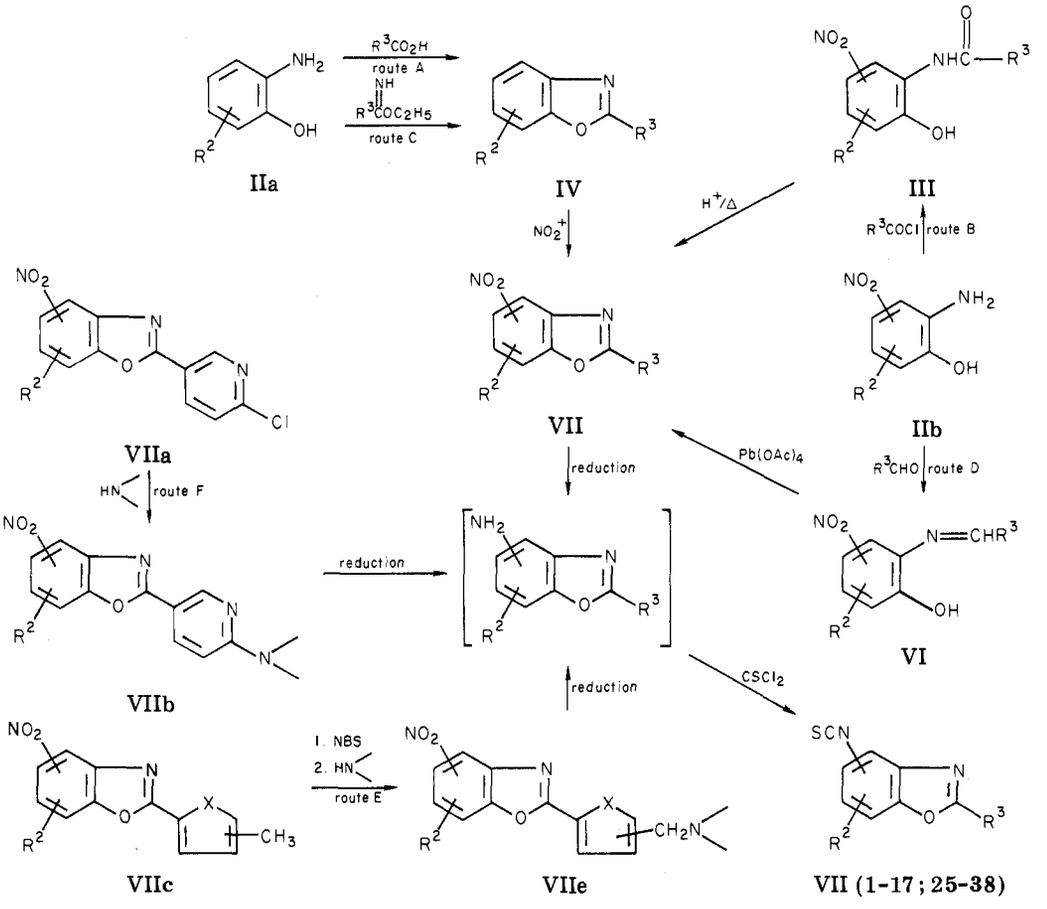
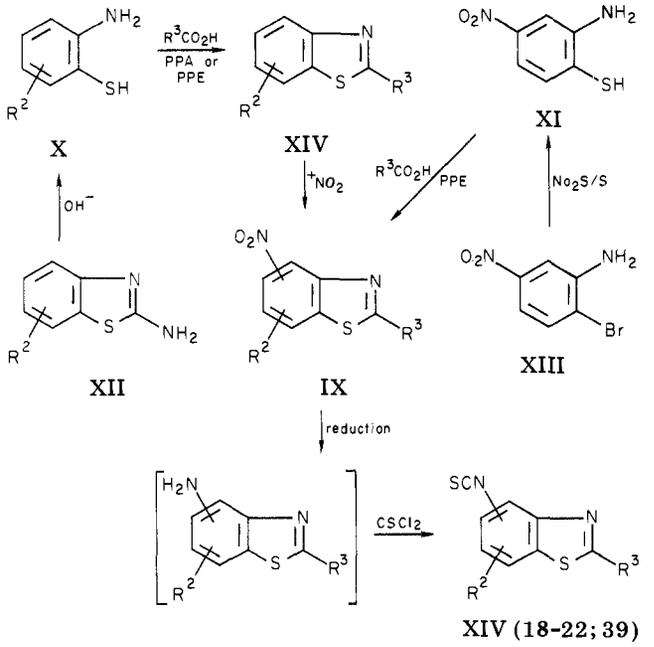
Scheme I



Scheme II

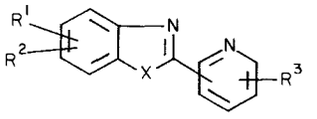


tion utilized the reduction in nematode fecal egg counts.[2]

Isothiocyanato-2-pyridinylbenzoxazoles. The low activity level of the 4-pyridinyl derivative **1** in sheep (40%) had been anticipated based on our earlier experience with benzimidazoles.[2] However, the poor activity of the 2-pyridinyl isomer **2** in sheep (35%) was unexpected. Surprising, then, was the activity in sheep of the 3-pyridinyl isomers **3**, **4**, and **5** with 69, 78, and 99% reduction in the fecal egg count, respectively. The activity of **5** was still observed at 25 mg/kg (94%). The in vivo oral activities of **4** and **5** indicated only marginal nematocidal activity in mice. The Zn-chelate **6** derived from **5** was inactive in both mice and sheep; a similar observation was made in the benzimidazole series. Switching the NCS group from the benzene ring to the pyridine ring, i.e., **7**, rendered the molecule inactive. Addition of a second nitrogen to the pyridine ring of **5**, i.e., the pyrazine derivative **8**, did not alter the anthelmintic activity in sheep to any significant degree (93%). Chlorine-substituted derivatives **9** and **13** were both inactive in the mouse screen, and **9** was also inactive when tested in sheep. The anthelmintic activity of methyl derivatives **10** (99% at 44 mg/kg) and **11** (90%) in sheep was unexpected, since this type of substitution in the benzimidazole series had led to inactive or only weekly active compounds.[2] Since none of the substituted pyridine derivatives in the benzimidazole series was active in sheep, the good activity of chloro derivative **14** was puzzling. Compounds **15**–**17** showed no activity in mice, and **15** displayed only marginal activity in sheep (27%).

Isothiocyanato-2-pyridinylbenzothiazoles. Again, the 3-pyridinyl derivative **21**, like those in the benzoxazole series, exhibited the highest activity. In the primary mouse screen, **21** demonstrated 75% reduction of *N. dubius*. Using micronized **21**, the activity against *N. dubius* increased to 99%. In addition, **21** showed 100% activity against *H. nana*. Interestingly, **21** also showed parenteral activity (76% *N. dubius*, 50% *H. nana*). In sheep, **21** was 99% effective in reducing the fecal egg count. In dogs, however, **21** was not active against *Taenia pisiformis* (tapeworm). Partial nematocidal activity was noted for the pure isomer **20** when tested in mice (58% *N. dubius*). The 2-pyridinyl derivatives **18** and **19** displayed only reduced activity in mice and in sheep (36 and 65%). The

Table I. Physical Properties and Anthelmintic Activity of Isothiocyanato-2-pyridinylbenzoxazoles (VIII) and -benzothiazoles (XV)



no.	R^1	R^2	R^3	X	pyridine attachment	yield,[a] %	crystn solvent	mp, °C	formula	anal.	mouse oral % clearance: *N. dubius*	mouse oral % clearance: *H. nana*	sheep oral[b] % reduction in fecal egg court
1	5-NCS	H	H	O	4	49	PE/Et_2O[c]	156–158	$C_{13}H_7N_3OS$	C, H, N	0	0	40
2	5- and 6-NCS	H	H	O	2	81	Et_2O[b]	148–150	$C_{13}H_7N_3OS$	C, H, N	0	50	35
3	5-NCS	H	H	O	3	34	Et_2O/EtOAc[c]	170–172	$C_{13}H_7N_3OS$	C, H, N	NT[d]	NT	69
4	6-NCS	H	H	O	3		$CHCl_3$/Et_2O[c]	149–149.5	$C_{13}H_7N_3OS$	C, H, N	46	0	78
5	5- and 6-NCS	H	H	O	3	32	PE	143–146	$C_{13}H_7N_3OS$	C, H, N	50	100	99; 94[e]
6	5- and 6-NCS	H	H	O	3 [0.5($ZnCl_2$)]	67	*f*	240–243	$C_{13}H_7N_3OS \cdot ZnCl_2$	Cl	0	0	0
7	H	H	4-NCS	O	2	55	MeCN	115–117	$C_{13}H_7N_3OS$	C, H, N	0	0	10
8	5- and 6-NCS	H	H	O	C=CHNCHCH=N	25	MeCN	167–169	$C_{12}H_6N_4OS$	C, H, N	0	NT	93
9	5-NCS	7-Cl	H	O	3	65	glyme/acetone	177–179	$C_{13}H_6ClN_3OS$	C, H, N	0	0	0
10	6-NCS	5-CH_3	H	O	3	41	MeCN	148–150	$C_{14}H_9N_3OS$	C, H, N	0	0	99[g]
11	5-NCS	6-CH_3	H	O	3	27	MeCN	193–195	$C_{14}H_9N_3OS$	C, H, N	99	0	0[e]
12	5-NCS	6-CH_3	H	O	2	68	glyme/H_2O	192–194	$C_{14}H_9N_3OS$	C, H, N	0	0	90
13	5-NCS	7-Cl	6-Cl	O	3	37	MeCN/acetone	188–190	$C_{13}H_5Cl_2N_3OS$	C, H, N	0	0	NT
14	5-NCS	H	6-Cl	O	3	47	EtOAc[c]	210–212	$C_{13}H_6ClN_3OS$	C, H, N	0	0	97
15	5- and 6-NCS	H	6-$NCH_2CH_2OCH_2CH_2$	O	3	54	glyme	207–208.5	$C_{17}H_{14}N_4O_2S$	C, H, N	0	0	27
16	5-NCS	H	6-$NCH_2CH_2N(CH_3)CH_2CH_2$	O	3	67	MeCN	191–193	$C_{18}H_{17}N_5OS$	C, H, N	0	0	0
17	5- and 6-NCS	H	6-$N(CH_3)_2$	O	3	88	PE	148–149.5	$C_{17}H_{16}N_4OS$	C, H, N	0	0	NT
18	5-NCS	H	H	S	2	20	C_6H_6/MeCN	142–143	$C_{13}H_7N_3S_2$	C, H, N	20	50	36[h]
19	6-NCS	H	H	S	2	73	C_6H_6/MeCN	185–186	$C_{13}H_7N_3S_2$	C, H, N	0	75	65
20	5-NCS	H	H	S	3	12	C_6H_6/MeCN	160–162	$C_{13}H_7N_3S_2$	C, H, N	58	0	NT
21	5- and 6-NCS	H	H	S	3	10	C_6H_6/MeCN	160–220	$C_{13}H_7N_3S_2$	C, H, N	99[i]	100[i]	99[i]
22	5-NCS	6-OCH_3	H	S	3	12	hexane/EtOAc[c]	164–166	$C_{14}H_9N_3OS_2$	C, H, N	5	0	40
23	5-NCS	H	H	NH	2						0	100	100
24	5-NCS	H	H	O	C_6H_5						60	0	57

[a] Yield calculated on hydrogenation/thiocarbonylation only. No attempt was made to optimize yields. [b] All sheep dosed at 50 mg/kg unless indicated otherwise. [c] Chromatographed. Solvent removed in vacuo to yield pure compound; PE = petroleum ether. [d] NT = not tested. [e] Dosed at 25 mg/kg. [f] Precipitated from solution and washed with Et_2O. [g] Dosed at 44 mg/kg. [h] Dosed at 58 mg/kg. [i] Micronized material.

Table II. Physical Properties and Anthelmintic Activity of Isothiocyanato-2-thienyl-, -furyl-, and -pyrrolylbenzoxazoles (VIII) and benzothiazole (39)

no.	R¹	R²	R³	X	Y	yield,[a] %	crystn solvent	mp, °C	formula	anal.	mouse oral % clearance: *N. dubius*	mouse oral % clearance: *H. nana*
25	6-NCS	H	H	O	S	17	PE	118–120	$C_{12}H_6N_2OS_2$	C, H, N	0	0
26	5-NCS	H	H	O	S	60	pentane	155–158	$C_{12}H_6N_2OS_2$	C, H, N	98	0
27	5-NCS	7-Cl	H	O	S	70	PE	150–152	$C_{12}H_5ClN_2OS_2$	C, H, N	0	0
28	5-NCS	H	3-CH_3	O	S	23	PE	112–115	$C_{13}H_8N_2OS_2$	C, H, N	78	0
29	5-NCS	H	5-CH_3	O	S	44	PE	157–160	$C_{13}H_8N_2OS_2$	C, H, N	0	33
30	5-NCS	H	5-$CH_2NCH_2CH_2OCH_2CH_2$	O	S	21	PE	130–133	$C_{17}H_{15}N_3O_2S_2$	C, H, N	0	66
31	5-NCS	H	5-$CH_2N(CH_2CH_3)_2\cdot HCl$	O	S	36	THF/Et_2O	240–243	$C_{17}H_{17}N_3OS_2\cdot HCl$	C, H, N	0	0
32	5-NCS	H	5-$CH_2NCH_2CH_2N(CH_3)CH_2CH_2$	O	S	60	PE	157–160	$C_{18}H_{18}N_4OS_2$	C, H, N	0	0
33	5-NCS	H	3-$CH_2NCH_2CH_2OCH_2CH_2$	O	S	37	PE	117–118	$C_{17}H_{15}N_3O_2S_2$	C, H, N	0	0
34	5-NCS	H	H	O	O	43	PE	135–137	$C_{12}H_6N_2O_2S$	C, H, N	100	0[b]
35	5-NCS	H	5-CH_3	O	O	16	PE	130–132	$C_{13}H_8N_2O_2S$	C, H, N	100	66[c]
36	5-NCS	H	5-$CH_2NCH_2CH_2OCH_2CH_2$	O	O	18	PE	119–122	$C_{17}H_{15}N_3O_3S$	C, H, N	0	0
37	5-NCS	H	H	O	NCH_3	54	PE	105–106	$C_{13}H_9N_3OS$	C, H, N	100	25[d]
38	5-NCS	7-Cl	H	O	NCH_3	32	PE	125–128	$C_{13}H_6ClN_3OS$	C, H, N	0	0
39	5-NCS	H	H	S	S	70	MeCN	147–149	$C_{12}H_6NS_3$	C, H, N	61	0[e]

[a] Yield calculated on hydrogenation/thiocarbonylation only. No attempt was made to optimize yields. [b] 97% reduction in egg count in sheep at 100 mg/kg. [c] 97% reduction in egg count in sheep at 100 mg/kg. [d] 34% reduction in egg count in sheep at 50 mg/kg. [e] 57% reduction in egg count in sheep at 50 mg/kg.

Table III. Titration of Anthelmintic Activity of Benzoxazoles 34 and 37 in Diet against *N. dubius* in Mice

compd	concn in diet, % 0.2	0.1	0.05	0.025	0.0125
34	100[a]	88[a]	39[a]	0	0
37	100	81	45	25	0
thiabendazole	96	89	88	47	40

[a] Percent clearance is an average of two tests.

methoxy-substituted benzothiazole **22** was inactive in the mouse screen but showed marginal activity in sheep (40%). Thiophene derivative **39** exhibited moderate activity when tested in mice (61% *N. dubius*) and in sheep (57%) (Table I).

For comparison, the anthelmintic activity of 5-isothiocyanato-2-(2-pyridinyl)-1*H*-benzimidazole (**23**) has been included in Table I, as well as that of 5-isothiocyanato-2-phenyl-benzoxazole (**24**).

Isothiocyanato-2-thienyl-, -furyl-, and -pyrrolylbenzoxazoles. Initially, we prepared a series of 5- and 6-isothioyanatobenzoxazoles, substituted at the 2-position with five-membered heterocycles.

Noteworthy were the nematocidal activities of thiophene derivative **26**, furans **34** and **35**, and the pyrrole **37** (Table II). These derivatives did not remove *H. nana* in mice but did destrobilize the tapeworms. When titrated in mice, **34** and **37** proved inferior to thiabendazole (Table III). In dogs, furan **35** demonstrated efficacies of 100% against hookworms (*Ancylostoma caninum*) and 95% against ascarids (*Toxocara canis*) at a single dose of 200 mg/kg, but it also caused emesis. No activity was observed against the whipworm *Trichuris vulpis*. When **34**, **35**, and **37** were tested at 100 mg/kg in naturally infected sheep, good reductions of the fecal egg count were observed (97, 97, and 94%), but worm recovery at necropsy indicated a narrow spectrum of activity against common trichostrongylid nematodes. Noteworthy was the lack of activity against immature forms of *Haemonchus contortus*.

These studies lead us to the conclusions that (a) the anthelmintic activities of the benzimidazole series[2] and the isosteric benzoxazoles and benzothiazoles are similar; (b) maximum activity for both the benzoxazole and benzothiazole series is noted with 3-pyridinyl derivatives (**5** and **21**); and (c) addition of chlorine to the benzene ring results in diminished activity (**9** and **13**); and (d) in contrast to the benzimidazole series, substitution of the benzene ring with a methyl group does not lead to drastic reduction of activity (**10** and **12**). The poor correlation between the screening results in mice and sheep for both series of compounds again underscores our earlier conclusion[2] regarding the merit of testing compounds in the target species.

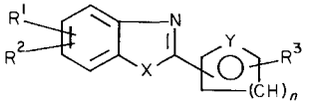
Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Neutral alumina (Woelm activity IV) was used for chromatography, except where otherwise indicated. Combustion analyses were within ±0.4% of theoretical values. The ^1H NMR spectra were obtained in Me_2SO-d_6 with Me_4Si as internal standard. IR and ^1H NMR were consistent with assigned structures for all compounds.

The following general methods were employed in the synthesis of the nitro-substituted benzoxazoles (Table IV).

Route A (Compounds 41, 43, and 47–49). A mixture of 0.3 mol of the appropriate *o*-aminophenol and 0.3 mol of the appropriate pyridinecarboxylic acid in 350 g of PPA was heated under N_2 at 200 °C for 3 h. The mixture was then cooled to 140 °C, slowly poured into 1.5 L of H_2O with rapid stirring, and neutralized with 50% NaOH solution, keeping the temperature below 30 °C by adding ice as needed. The precipitated material

Table IV. Physical Properties and Method of Preparation of Intermediate Nitrobenzoxazoles (VII) and Nitrobenzothiazoles (IX)



no.	R^1	R^2	R^3	X	Y	n	posit of attach	method	yield, %	reaction solvent	crystn	mp, °C	formula
40	5-NO_2	H	H	O	N	2	4	B	14	xylenes	EtOH	176-178	$C_{12}H_7N_3O_3$
41	5- and 6-NO_2	H	H	O	N	2	2	A	85	1. PPA 2. H_2SO_4	EtOH	205-208	$C_{12}H_7N_3O_3$
42	5-NO_2	H	H	O	N	2	3	B	17	xylenes	EtOH	184-186	$C_{12}H_7N_3O_3$
43	5- and 6-NO_2	H	H	O	N	2	3	A	47	1. PPA 2. H_2SO_4	EtOH	217-219	$C_{12}H_7N_3O_3$
44	H	H	4-NO_2	O	N	2	2	C	50	EtOH	EtOH	219-228	$C_{12}H_7N_3O_3$
45	5- and 6-NO_2	H	H	O	N	2	C=CHN=CHCH=N	C	*a*	EtOH			$C_{11}H_6N_4O_3$
46	5-NO_2	7-Cl	H	O	N	2	3	B	62	xylenes	MeOH/DMF	195-197	$C_{12}H_6ClN_3O_3$
47	6-NO_2	5-CH_3	H	O	N	2	3	A	57	1. PPA 2. H_2SO_4	MeCN	162-165	$C_{13}H_9N_3O_3$
48	5-NO_2	6-CH_3	H	O	N	2	3	A	61	1. PPA 2. H_2SO_4	MeCN	171-173	$C_{13}H_9N_3O_3$
49	5-NO_2	6-CH_3	H	O	N	2	2	A	69	1. PPA 2. H_2SO_4	EtOH	167-169	$C_{13}H_9N_3O_3$
50	5-NO_2	7-Cl	6-Cl	O	N	2	3	B	13	xylenes	MeOH/DMF	184-186	$C_{12}H_5Cl_2N_3O_3$
51	5-NO_2	H	6-Cl	O	N	2	3	B	12	xylenes	EtOH	260-261	$C_{12}H_6ClN_3O_3$
52	5- and 6-NO_2	H	6-Cl	O	N	2	3	B	65	1. xylenes 2. H_2SO_4	EtOH/DMF	232-235	$C_{12}H_6ClN_3O_3$
53	5- and 6-NO_2	H	6-$NCH_2CH_2OCH_2CH_2$	O	N	2	3	F	78	*n*-PrOH	MeCN	208-209.5	$C_{16}H_{14}N_4O_4$
54	5-NO_2	H	6-$NCH_2CH_2N(CH_3)CH_2CH_2$	O	N	2	3	F	71	*n*-PrOH	EtOH	194-196	$C_{17}H_{17}N_5O_3$
55	5- and 6-NO_2	H	6-$N(CH_3)_2$	O	N	2	3	F	83	*n*-PrOH	EtOH	138-140	$C_{14}H_{12}N_4O_3$
56	5- and 6-NO_2	H	H	S	N	2	2		30	1. PPA 2. H_2SO_4	EtOH	172-187	$C_{12}H_7N_3O_2S$
57	5-NO_2	H	H	S	N	2	3		44	$CHCl_3$/PPE	EtOH	196-198	$C_{12}H_7N_3O_2S$
58	5- and 6-NO_2	H	H	S	N	2	3		93	1. PPA 2. H_2SO_4	DMF/EtOH	227-230	$C_{12}H_7N_3O_2S$
59	6-NO_2	H	H	O	S	1	2	D	50	MeCN	MeCN	208-210	$C_{11}H_6N_2O_3S$
60	5-NO_2	H	H	O	S	1	2	D	51	HOAc	EtOH/$CHCl_3$	186-188	$C_{11}H_6N_2O_3S$
61	5-NO_2	7-Cl	H	O	S	1	2	D	58	MeCN	MeCN	161-163	$C_{11}H_5ClN_2O_3S$
62	5-NO_2	H	3-CH_3	O	S	1	2	D	42	HOAc	*b*	174-176	$C_{12}H_8N_2O_3S$
63	5-NO_2	H	3-CH_2Br	O	S	1	2	E	60	$CHCl_3$	EtOH	146-148	$C_{12}H_7BrN_2O_3S$
64	5-NO_2	H	5-CH_3	O	S	1	2	D	42	HOAc	$CHCl_3$	163-165	$C_{12}H_8N_2O_3S$
65	5-NO_2	H	5-CH_2Br	O	S	1	2	E	77	$CHCl_3$	EtOH	153-155	$C_{12}H_7BrN_2O_3S$
66	5-NO_2	H	5-$CH_2NCH_2CH_2OCH_2CH_2$	O	S	1	2	D	92	C_6H_6	EtOH	149-151	$C_{16}H_{15}N_3O_4S$
67	5-NO_2	H	5-$CH_2N(CH_2CH_3)_2$	O	S	1	2	D	81	C_6H_6	EtOH	113-115	$C_{16}H_{17}N_3O_3S$
68	5-NO_2	H	5-$CH_2NCH_2CH_2N(CH_3)CH_3CH_2$	O	S	1	2	D	74	C_6H_6	EtOH	135-137	$C_{17}H_{18}N_4O_3S$
69	5-NO_2	H	3-$CH_2NCH_2CH_2OCH_2CH_2$	O	S	1	2	E	67	C_6H_6	EtOH	143-145	$C_{16}H_{15}N_3O_4S$
70	5-NO_2	H	H	O	O	1	2	D	48	HOAc	$CHCl_3$	175-177	$C_{11}H_6N_2O_4$
71	5-NO_2	H	5-CH_3	O	O	1	2	E	50	MeCN	$CHCl_3$	182-184	$C_{12}H_8N_2O_4$
72	5-NO_2	H	5-CH_2Br	O	O	1	2	E	60	$CHCl_3$	EtOH	168-170	$C_{12}H_7BrN_2O_4$
73	5-NO_2	H	5-$CH_2NCH_2CH_2OCH_2CH_2$	O	O	1	2	E	57	C_6H_6	EtOH	188-190	$C_{16}H_{15}N_3O_5$
74	5-NO_2	H	H	O	NCH_3	1	2	D	46	MeCN	MeCN	183-185	$C_{12}H_9N_3O_3$
75	5-NO_2	7-Cl	H	O	NCH_3	1	2	D	36	HOAc	*b*	157-160	$C_{12}H_8ClN_3O_3$
76	5-NO_2	H	H	S	S	1	2		*a*	$CHCl_3$/PPE			$C_{11}H_6N_2O_2S_2$

[a] Used directly in following reaction without purification. [b] Crude product dissolved in $CHCl_3$ and dried ($MgSO_4$), and the solvent was removed in vacuo.

was filtered, washed with H_2O, and crystallized.

A stirred mixture of 0.1 mol of the benzoxazole and 150 mL of H_2SO_4 (concentrated) was cooled to 0–5 °C, and a mixture of 7.0 mL (sp gr 1.42, 0.1 mol) of HNO_3 and 20 mL of H_2SO_4 was then slowly added, maintaining the temperature below 10 °C. After the addition was completed, the mixture was allowed to reach room temperature, and the stirring was continued for 2 h. The reaction mixture was poured into 500 mL of ice–water and neutralized with 50% NaOH solution, maintaining the temperature below 25 °C. The precipitated material was collected, washed with H_2O, and crystallized to yield the pure nitrobenzoxazole.

Route B (Compounds 40, 42, 46, and 50–52). A mixture of 0.1 mol of the appropriate acid chloride in 100 mL of THF was added to a mixture of 0.1 mol of the nitro-2-aminophenol and 0.11 mol of triethylamine in 300 mL of THF, and the mixture was stirred at room temperature for 0.5 h and then refluxed for 3 h. After the mixture was cooled to room temperature, the precipitated material was filtered, washed with H_2O to remove the triethylamine hydrochloride, and crystallized from the appropriate solvent to yield the carboxamide. A suspension of 0.15 mol of the above carboxamide in 2 L of xylenes and 5 mL of H_2SO_4 (concentrated) was refluxed for 24 h using a Dean–Stark apparatus for constant removal of H_2O. The mixture became clear red-brown. The xylene solution was decanted from the polymeric deposit and evaporated in vacuo. The residue was crystallized from the appropriate solvent to yield the nitrobenzoxazole.

Route C (Compounds 44 and 45). The starting materials, 4-nitro-2-pyridinecarboximidic acid ethyl ester[2] and pyrazinecarboximidic acid ethyl ester[2] were synthesized according to known procedures. A mixture of 0.05 mol of *o*-aminophenol and 0.05 mol of the imino ether dissolved in absolute EtOH was refluxed for 2 h. The solution was cooled, and the resulting benzoxazole was filtered and crystallized. 2-Pyrazinebenzoxazole was nitrated by the procedure outlined in method A.

Route D (Compounds 59–62, 64, 70, 71, 74, and 75). To 0.02 mol of the appropriate *o*-aminophenol dissolved in 150 mL of 95% EtOH there was added a solution of 0.02 mol of the appropriate aldehyde, and the mixture was stirred at room temperature for 0.5 h. The precipitated imine was filtered and dried. A solution of 0.02 mol of the imine in 100 mL of MeCN was treated with 0.02 mol of $Pb(OAc)_4$. After heating on a steam bath for 5 min, the mixture was filtered and diluted with H_2O, and the precipitated product was filtered and crystallized. Alternatively, 0.02 mol of the imine was dissolved in HOAc, treated with 0.02 mol of $Pb(OAc)_4$, and refluxed for 2 h. The mixture was then diluted with H_2O, and the precipitated product was filtered and crystallized.

Route E (Compounds 63, 65–69, 72, and 73). A mixture of 0.01 mol of the appropriate benzoxazole (**62**, **64**, or **71**), 0.01 mol of NBS, and 0.1 g of azobisbutyronitrile in 100 mL of $CHCl_3$ was refluxed for 36–48 h. An additional 0.1 g of azobisbutyronitrile was added every 12 h. The reaction mixture was cooled to room temperature, and the precipitated succinimide was filtered off. The $CHCl_3$ solution was washed with 5% NaOH, dried, and evaporated in vacuo. The residue was crystallized from EtOH to yield the corresponding bromomethyl derivatives. A mixture of 0.015 mol of the above bromomethyl derivatives and 0.03 mol of the appropriate amine in 200 mL of benzene was refluxed for 24 h. The precipitated amine hydrobromide was filtered, the benzene was removed in vacuo, and the crude product was crystallized.

Route F (Compounds 53–55). A mixture of 0.02 mol of the appropriate benzoxazole **51** or **52** and 0.06 mol of the appropriate amine in 75 mL of *n*-propyl alcohol was refluxed for 3 h. After the mixture was cooled to room temperature, the solvent was removed in vacuo. The crude solid was washed with water and crystallized. Alternatively, a mixture of 0.015 mol of **51**, 0.06 mol of the appropriate amine, 0.03 mol of K_2CO_3, and 75 mL of DMF was refluxed for 2 h and cooled to room temperature, and 75 mL of H_2O was added. The resulting solid was filtered off and crystallized.

5- and 6-Nitro-2-(2-pyridinyl)benzothiazole (56) and 5- and 6-Nitro-2-(3-pyridinyl)benzothiazole (58). *o*-Aminophenol and the appropriate pyridinecarboxylic acid were reacted as in method A, except that the reaction temperature was maintained at 145 °C during the PPA cyclodehydration. The nitration was carried out as in method A, except that only nitric acid was added to the reaction.

The isothiocyanatobenzoxazoles and -benzothiazoles **1–39** were synthesized from the corresponding nitro compounds **40** to **76** using a general procedure for hydrogenation and thiocarbonylation. In most cases, the amines were not isolated but were used immediately in the thiocarbonylation reaction. The synthesis of **5** will serve as an example.

5- and 6-Isothiocyanato-2-(3-pyridinyl)benzoxazole (5). Hydrogenation. General Procedure. A suspension of 2.4 g (0.01 mol) of 5- and 6-nitro-2-(3-pyridinyl)benzoxazole and 0.25 g of PtO_2 in 100 mL of absolute EtOH was hydrogenated on a Parr hydrogenator at 50 psi until the required amount of H_2 was taken up. Then 50 mL of THF was added to dissolve the precipated amine, and the reaction mixture was filtered and evaporated in vacuo to yield 1.8 g of 5- and 6-amino-2-(3-pyridinyl)benzoxazole, mp 172–175 °C.

Thiocarbonylation. General Procedure.[20] A mixture of 1.5 g (0.007 mol) of 5- and 6-amino-2-(3-pyridinyl)benzoxazole, 1.5 g (0.014 mol) of triethylamine, and 125 mL of THF was cooled to 5–10 °C, and 0.81 g (0.007 mol) of thiophosgene was added dropwise with stirring. After stirring for 15 min at 5–10 °C, the mixture was allowed to warm to room temperature and stand for 3 h. The triethylamine hydrochloride was removed by filtration, and the THF was removed in vacuo to yield a tan solid. The crude material was crystallized from petroleum ether to yield 0.56 g of **5**, mp 143–146 °C.

5- and 6-Isothiocyanato-2-(3-pyridinyl)benzoxazole–Zinc Chloride Complex (2:1) (6). A solution of 2.53 g (0.01 mol) of analytically pure **5** was dissolved in 25 mL of MeCN by heating to reflux on the steam bath, and 1.5 mL of saturated methanolic solution of $ZnCl_2$ was added. The precipitated material was collected, washed with Et_2O, and dried to yield 2.14 g of **6**, mp 240–243 °C.

5- and 6-Isothiocyanato-2-(2-pyridinyl)benzothiazole (18 and 19). The mixture of 5- and 6-isothiocyanato-2-(2-pyridinyl)benzothiazoles was chromatographed on silica gel (Baker, 60–200 mesh). Elution with C_6H_6 gave the pure 5-isomer, mp 142–143 °C, followed by the pure 6-isomer, mp 185–186 °C.

5-Isothiocyanato-2-(3-pyridinyl)benzothiazole (20) and 5-Isothiocyanato-2-(2-thienyl)benzothiazole (39). A mixture of 0.1 mol of 2-amino-4-nitrothiophenol[21] and 0.15 mol of the appropriate carboxylic acid was refluxed in 100 g of PPE and 250 mL of $CHCl_3$ for 2 h. The solvent was removed in vacuo, water was added to the residue, and the pH was adjusted to 11 with 50% NaOH. The resulting solid was filtered, washed with water, and dried to yield the nitrobenzothiazoles **57** or **76**. To a solution of 0.044 mol of **57** or **76** in 45 mL of concentrated HCl there was added a solution of 35 g of $SnCl_2$ in 45 mL of hot concentrated HCl, and the mixture was heated on the steam bath for 1 h. The insoluble material was filtered, washed with cold 10% HCl, and dried. The solid was then washed with 20% NaOH solution, followed by H_2O, and dried to yield the corresponding 5-aminobenzothiazole. Thiocarbonylation yielded **20**, mp 160–162 °C, and **39**, mp 147–149 °C.

5-Isothiocyanato-6-methoxy-2-(3-pyridinyl)benzothiazole (22). A mixture of 50 g (0.28 mol) of 2-amino-6-methoxybenzothiazole (Aldrich), 250 g of KOH, and 500 mL of H_2O was refluxed for 15 h, cooled to 5 °C, and diluted with 150 mL of H_2O. The mixture was filtered and adjusted to pH 6 with concentrated HCl. The resulting white precipitate was filtered off and washed with H_2O. The precipitate was then washed with 5 × 150 mL of boiling EtOH. The ethanolic fractions were combined and evaporated to yield a residue, which was taken up in $CHCl_3$, dried ($MgSO_4$), and evaporated in vacuo to yield 25 g (58%) of 2-amino-5-methoxythiophenol. The 2-amino-5-methoxythiophenol and nicotinic acid were then cyclized in PPE, nitrated, reduced, and thiocarbonylated as described above to yield **22**, mp 164–166 °C.

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