CH_2], 2.97–3.75 (m, 8 H, other ring H), 11.22 (s, br, 2 H, imide); MS (70 eV), *m/e* 252 (M^+). Anal. ($C_{10}H_{12}N_4O_4$) C, H, N.

***cis*-Tetrahydrodipyrazino[1,2-*a*:1′,2′-*d*]pyrazine-1,3,7,9-(2*H*,4*H*,8*H*,10*H*)-tetrone (11).** Na metal (46 mg, 2 mmol) was added to 7 mL of absolute EtOH and the mixture stirred under N_2. Diamide diester *cis*-**19** (344 mg, 1 mmol) was added to the resulting solution and the mixture refluxed under N_2 for 6 h. The solvent was evaporated under reduced pressure, and the residual solid dissolved in cold H_2O (5 mL) and acidified (concentrated HCl solution) to pH 5 (approximate). The crystallized solid was stored at 4 °C overnight, filtered, washed with cold H_2O followed by Me_2CO, and dried to afford 226 mg (89.68%) of a white solid: mp >260 °C (slow decomposition >200 °C); IR (KBr) 3250 and 3105 (NH), 1730 and 1690 (imide) cm^{-1}; NMR (Me_2SO-d_6, 90 MHz) δ 2.7–2.9 (m, br, 4 H, central ring CH_2), 3.3–3.5 (m, 6 H, other ring H), 3.55 (s, 2 H, imide); MS (70 eV), *m/e* 252 (M^+). Anal. ($C_{10}H_{12}N_4O_4$) C, H, N.

***trans*-Tetrahydro-2,8-bis(4-morpholinylmethyl)dipyrazino[1,2-*a*:1′,2′-*d*]pyrazine-1,3,7,9(2*H*,4*H*,8*H*,10*H*)-tetrone (12).** To a suspension of *trans*-**10** (315 mg, 1.25 mmol) in Me_2SO (5 mL) was added morpholine (0.38 mL, 4.37 mmol) and HCHO (0.37 mL of a 37% solution, 5.0 mmol). The mixture was stirred at 55–65 °C for 5 h and then at room temperature overnight. Me_2SO was removed by distillation under reduced pressure and the residual solid triturated with EtOH, filtered, washed (EtOH), and dried to afford 488 mg (86.83') of a white solid which underwent slow decomposition above 225 °C: IR (KBr) 1735 and 1685 (imide) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.35 [deceptively simple triplet (dd), 2 H, axial H of central ring CH_2], 2.54–2.65 (m, 8 H, NCH_2 of morpholine), 3.05–3.91 (c, 16 H, other ring H), 4.78 (s, 4 H, NCH_2N). Anal. ($C_{20}H_{30}O_6N_6$) C, H, N.

***cis*-Tetrahydro-2,8-bis(4-morpholinylmethyl)dipyrazino[1,2-*a*:1′,2′-*d*]pyrazine-1,3,7,9(2*H*,4*H*,8*H*,10*H*)-tetrone (13).** To a solution of *cis*-11 (100 mg, 0.39 mmol) in Me_2SO (2 mL) was added morpholine (0.12 mL, 1.39 mmol) and HCHO (0.12 mL of a 37% solution, 1.59 mmol). The solution was stirred at 55–65 °C for 5 h and at room temperature overnight. Me_2SO was removed by distillation under reduced pressure and the residual oil crystallized from Et_2O–Me_2CO, affording 153 mg (85.95%) of a white solid: mp 179–181 °C dec; IR (KBr) 1735 and 1680 (imide) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.50–2.62 (m, 8 H, NCH_2 of morpholine), 2.83–3.89 (c, 18 H, ring H), 4.79 (s, 4 H, NCH_2N). Anal. ($C_{20}H_{30}O_6N_6$) C, H, N.

Acknowledgment. We gratefully acknowledge partial support of this work through U.S. Public Health Service Research Grant CA25445 from the National Cancer Institute. FT NMR 500-MHz spectra were obtained at The Ohio State University Chemical Instrumentation Center with use of a NT-500 spectrometer funded in part by NIH Grant No. 1-S10-RR01458-01A1. Spectra were produced by Dr. C. E. Cottrell.

Registry No. **10**, 92927-70-3; **11**, 92927-69-0; **12**, 96705-80-5; **13**, 96705-81-6; *cis*-**14**, 96705-82-7; *trans*-**14**, 96705-83-8; *trans*-**15**, 96705-84-9; *cis*-**16**, 96705-85-0; *trans*-**16**, 96705-86-1; *cis*-**18**, 96705-87-2; *trans*-**18**, 96705-88-3; *cis*-**19**, 96705-89-4; *trans*-**19**, 96705-90-7; *cis*-**20**, 96705-91-8; *trans*-**20**, 96705-92-9; *cis*-**21**, 96705-93-0; *trans*-**21**, 96728-88-0; *cis*-**22**, 96705-94-1; *trans*-**22**, 96705-95-2; *cis*-**24**, 15996-17-5; *trans*-**24**, 15996-16-4; *cis*-**25**, 96789-11-6; *trans*-**25**, 96789-12-7; *cis*-**26**, 96705-96-3; *trans*-**26**, 96705-97-4; *cis*-**27**, 96843-75-3; *trans*-**27**, 96843-76-4; *cis*-**28**, 96705-98-5; *cis*-**29**, 96705-99-6; *trans*-**29**, 96706-00-2; *cis*-**30**, 96706-01-3; *trans*-**30**, 96706-02-4; **31**, 122-05-4; **31**·2NH_3, 96728-89-1; K_2CO_3, 79-07-2; HCHO, 50-00-0; *O*-benzyl-L-serine, 4726-96-9; *O*-benzyl-L-serine methyl ester hydrochloride, 19525-87-2; iodoacetamide, 144-48-9; 2,5-dimethylpyrazine, 123-32-0; bromoacetic acid, 79-08-3; ethyl bromoacetate, 105-36-2; morpholine, 110-91-8.

Antiparasitic Agents. 6.[1] Synthesis and Anthelmintic Activities of Novel Isothiocyanatophenyl-1,2,4-oxadiazoles

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The syntheses and anthelmintic activities of 31 3- and 5-(isothiocyanatophenyl)-1,2,4-oxadiazoles are reported. In the primary anthelmintic screen, 3-(4-isothiocyanatophenyl)-1,2,4-oxadiazole (**39**) showed 100% nematocidal activity and 3-(2-furanyl)-5-(4-isothiocyanatophenyl)-1,2,4-oxadiazole (**63**), 3-(2-furanyl)-5-(2-chloro-4-isothiocyanatophenyl)-1,2,4-oxadiazole (**64**), and 3-(2-furanyl)-5-(4-chloro-3-isothiocyanatophenyl)-1,2,4-oxadiazole (**66**) showed 100% taeniacidal activity when administered orally to mice. The two most active members of this series, **39** and **63**, were active against the gastrointestinal nematodes of sheep at 100 mg/kg. In addition, **39** was also found to be active against hookworms in dogs at a single, oral dose of 200 mg/kg.

During the early stages of our anthelmintic development program, 1,2,4-oxadiazole Ia emerged as a potential lead.[2] This finding was shortly followed by the rediscovery of the antiparasitic oxadiazoles Ib[3] and Ic[4] (Figure 1). Several other 1,2,4-oxadiazoles had been reported to possess antiparasitic activity.[5-8] We decided to focus our investigation on isothiocyanatophenyl-substituted 1,2,4-oxadiazoles. Our earlier work on heterocyclic isothiocyanates had yielded compounds II and III equivalent to thiabendazole in anthelmintic activity[1,9] (Figure 2). While the main thrust of this study was directed toward the evaluation of 3- and 5-(isothiocyanatophenyl)-1,2,4-oxadiazoles[10] (Table III), numerous nitro intermediates[11] and various 3- and 5-substituted 1,2,4-oxadiazoles were also screened for an-

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(1) For paper 5 in this series, see: Haugwitz, R. D.; Angel, R. G.; Jacobs, G. A.; Maurer, B. V.; Narayanan, V. L.; Cruthers, L. R.; Szanto, J. *J. Med. Chem.* **1982**, *25*, 969.
(2) U.S. Patent 3 575 997.
(3) U.S. Patents 3 279 988 and 3 356 684.
(4) Ger. Offen, 2 050 346.
(5) Breuer, H. *J. Med. Chem.* **1969**, *12*, 708.
(6) British Patent 1 228 142.
(7) Ger. Offen. 2 310 287 and 2 312 500.
(8) U.S. Patents 2 312 411 and 3 897 447.
(9) Haugwitz, R. D.; Maurer, B. V.; Jacobs, G. A.; Narayanan, V. L.; Cruthers, L. R.; Szanto, J. *J. Med. Chem.* **1979**, *22*, 1113.
(10) U.S. Patents 3 853 893, 3 910 940, 3 910 940, 3 929 814, and 4 022 901.
(11) Jefford, C. W.; Cadby, P. A.; Smith, L. C.; Pipe, D. F. *Pharmazie* **1982**, *37*, 395.

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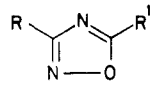
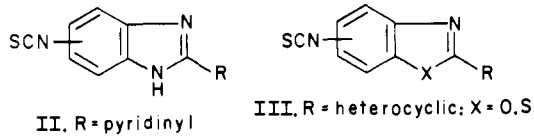


Ia, R = NH_2; R^1 = $(CH_2)_{10}CH_3$
b, R = 4-ClC_6H_4; R^1 = H
c, R = Ph; R^1 = SCH_3

Figure 1.

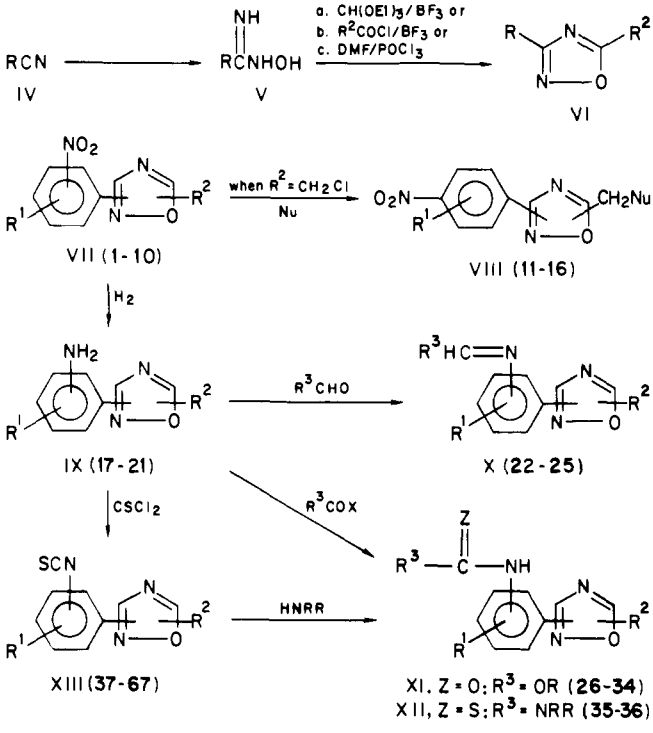


II, R = pyridinyl

III, R = heterocyclic; X = O,S

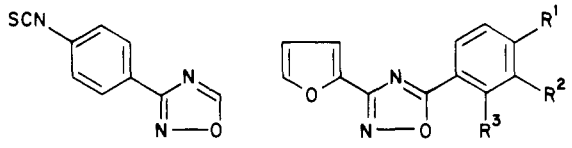
Figure 2.

Scheme I



tiparasitic activity (Tables I, II, and IV).

Chemistry. Several general methods are available for the synthesis of 3- and 5-substituted 1,2,4-oxadiazoles VI.[12-15] We found the boron trifluoride catalyzed cyclization of amidoximes V with carboxylic acid derivatives to be the most dependable route for their synthesis.[16] Catalytic hydrogenation of the nitro derivatives VII and subsequent thiocarbonylation with thiophosgene yielded the target compounds XIII. Byproducts that were frequently formed during the hydrogenation step, and which are most likely derived from the cleavage of the N–O bond[15,17], were effectively suppressed by the addition of 2–6 equiv of hydrochloric acid. The reactivity of the chloromethyl group of VII (R^2 = CH_2Cl) approaches that of benzyl chloride and displacement of the halogen with

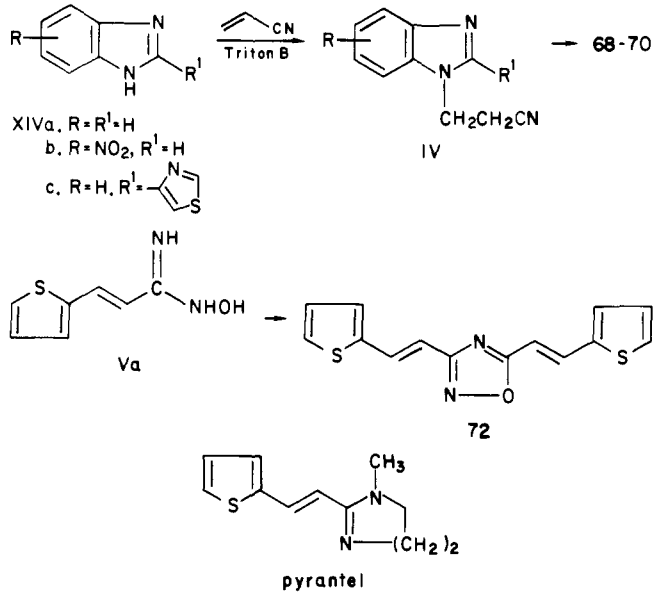


39

63, R^1 = NCS; R^2 = R^3 = H
64, R^1 = NCS; R^2 = H; R^3 = Cl
66, R^1 = Cl; R^2 = NCS; R^3 = H

Figure 3.

Scheme II

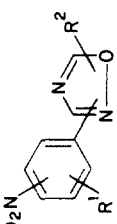


nucleophiles afforded oxadiazoles VIII. Thus, alkylation of ethanethiol with the chloromethyl derivative furnished the sulfide, which in turn was oxidized with *m*-chloroperbenzoic acid to yield the sulfone **11**. Aminoalkyl derivatives **13–15** were prepared by analogy to the reported conditions of Crovetti et al.[18] Heating a dimethyl sulfoxide solution of the chloromethyl compound and ammonium thiocyanate furnished **12**. Reaction of the amines IX with aldehydes at elevated temperature yielded the Schiff bases X; acylation of IX with chloroformates gave carbamates XI. Thioureas XII were conveniently prepared from the isothiocyanates XIII and the appropriate secondary amines. Cyanoethylation of benzimidazoles XIV in the presence of Triton B followed by ring closure of the corresponding amidoximes furnished the oxadiazoles **68–70**. The nitro derivative **71** was synthesized from benzamidoxime and 3-nitropropionyl chloride (method B). Reaction of amidoxime Va with 3-(2-thienyl)acrylic acid chloride (method B) yielded divinyl-substituted oxadiazole **72**, which shares certain structural features of the anthelmintic pyrantel. Peracid oxidation of oxadiazole **73** with *m*-chloroperbenzoic acid gave **74**.

Anthelmintic Activity. Twenty-three 3-(isothiocyanatophenyl)- and eight 5-(isothiocyanatophenyl)-1,2,4-oxadiazoles XIII were screened for anthelmintic activity against *Nematospiroides dubius* and *Hymenolepis nana* by using previously reported procedures.[9] Most of the 3-substituted oxadiazoles, with the exception of **50**, **56**, and possibly **55**, were inactive in the primary mouse screen (activity less than 50% in any one system). In sheep, **50** was inactive when tested at 100 mg/kg either orally (po) or subcutaneously (sc). The best activity in this series was

(12) Boyer, J. H. *Heterocycl. Comp.* **1962**, *7*, 462.
(13) Behr, L. C. *Chem. Heterocycl. Comp.* **1962**, *17*, 245.
(14) Elroy, F. *Fortschr. Chem. Forsch.* **1965**, *4*, 807.
(15) Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *20*, 65.
(16) Borthwick, A. D.; Foxton, M. W.; Gray, B. V.; Gregory, G. I.; Seale, P. W.; Warburton, W. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2769.
(17) Palazzo, G.; Strani, G.; Tavella, M. *Gazz. Chim. Ital.* **1961**, *91*, 1085.
(18) Crovetti, A. J.; Von Esch, A. M.; Thill, R. J. *J. Heterocycl. Chem.* **1972**, *9*, 435.

Table I. Physical Properties of Nitrophenyl-1,2,4-oxadiazoles VII and VIII



no.	NO_2 position	R^1	position of Ph attachment	R^2	mp, °C	method	yield, %	crystn soln	formula	anal.
1	4	H	3	$C_6H_4NO_2(4)$	238–240	B	63	Et_2O	$C_{14}H_8N_4O_5$	C, H, N
2	4	H	3	$(CH_2)_{10}CH_3$	51–53	B	50	95% EtOH	$C_{19}H_{27}N_3O_3$	C, H, N
3	4	H	3	$C_6H_2(OCH_3)_3(3,4,5)$	179–180	B	51	95% EtOH	$C_{17}H_{15}N_3O_6$	C, H, N
4	4	H	3	$C_6H_4F(4)$	196–197	B	67	95% EtOH	$C_{14}H_8FN_3O_3$	C, H, N
5	4	H	3	$CHCH_2CH_2CH_2CH_2CH_2$	114–116	B	60	Et_2O	$C_{14}H_{15}N_3O_3$	C, H, N
6	4	H	3	$CO_2CH_2CH_3$	118–120	B	57	EtOH	$C_{11}H_9N_3O_5$	C, H, N
7	4	H	5	$C_6H_4Cl(4)$	179–182	B	75	Et_2O	$C_{14}H_8ClN_3O_3$	C, H, N
8	3	$4\text{-}SC_6H_5$	5	$C{=}CHCH{=}CHO$	166–168	B	78	MeCN	$C_{18}H_{11}N_3O_4S^d$	C, H, N
9	3	4-Cl	5	$C{=}CHCH{=}CHO$	136–137.5	B	75	EtOH	$C_{12}H_6ClN_3O_4$	C, H, N
10	4	2-Cl	5	$C{=}CHCH{=}CHO$	124–125	B	50	EtOH	$C_{12}H_6ClN_3O_4$	C, H, N
11	4	H	3	$CH_2SO_2CH_2CH_3$	146–148	*a*	41	$CHCl_3$	$C_{11}H_{11}N_3O_5S$	C, H, N
12	4	H	3	CH_2SCN	137–139	*a*	83	$CHCl_3$	$C_{10}H_6N_9O_3S$	C, H, N
13	4	H	3	$CH_2NCH_2CH_2OCH_2CH_2$	143–144	I	76	EtOH	$C_{13}H_{14}N_4O_4$	C, H, N
14	4	H	3	$CH_2NCH_2CH_2N(CH_3)CH_2CH_2$	101–102	I	70	PE/Et_2O	$C_{14}H_{17}N_5O_3$	C, H, N
15	4	H	3	$CH_2N(CH_2CH_3)_2{\cdot}HCl$	206–208[b]	I	54	*c*	$C_{13}H_{16}N_4O_3{\cdot}HCl$	C, H, N
16	4	H	5	CH_2SCN	115–118	*a*	88	$CHCl_3$	$C_{10}H_6N_4O_3S$	C, H, N

[a] See specific procedure in the Experimental Section. [b] Free base mp 61–63 °C (PE/Et_2O). [c] Precipitated from Et_2O. [d] 35% clearance (mouse, oral).

observed with **39** (Figure 3), which when administered orally was 100% active against *N. dubius* with some taeniacidal activity as indicated by destrobilization. When administered subcutaneously, **39** was 100% active against *H. nana*. It was interesting to note that the meta isomer of **39**, namely, **37**, and its chloro analogue **38** were both inactive in the mouse screen. A similar difference in activity was noticed between the para-substituted derivative **56** and its meta isomer **57**; while the former was 72% active against *N. dubius*, the latter was devoid of any nematocidal activity. When titrated in mice infected with *N. dubius*, **39** was equipotent to thiabendazole and the three lead compounds Ia–Ic (Table V). Compounds were evaluated in dogs by using the critical test described by Hall and Foster.[19] Compound **39** was also 100% effective against *Ancylostoma caninum* (hookworms) in a dog at a single oral dose of 200 mg/kg; but no activity was detected when **39** was given subcutaneously as an aqueous suspension at the same dose. Partial activity against *A. caninum* was seen when **39** was administered to one dog and one cat at a single oral dose of 100 mg/kg (77% and 73% reduction, respectively). In a sheep naturally infected with a mixed gastrointestinal nematode population, **39** at a single, oral dose of 100 mg/kg, gave a 100% reduction of the fecal egg count.[9] Good anthelmintic activity against *Haemonchus* was observed as determined by worm count as described by Moskey and Harwood.[20] However, its spectrum of activity was narrow. On the basis of an earlier study,[21] the screening results for the 5-(isothiocyantophenyl)-1,2,4-oxadiazole series were unexpected: three of the eight compounds, **63**, **64**, and **66** exhibited 100% taeniacidal activity and **63** was also 90% active against *N. dubius* (Figure 3). While **66** was inactive in sheep at 120 mg/kg, **64** gave 73% reduction at 200 mg/kg. Oral administration of **63** to sheep at 100 mg/kg led to 99% reduction of the fecal egg count; however, only a 50% reduction was noted when **63** was administered sc. None of the nitrophenyl intermediates listed in Table I was active in the primary mouse screen. Of the anilino-substituted 1,2,4-oxadiazoles, only **26** and **27** showed nematocidal activity in mice (81% and 56%). At a single oral dose of 100 mg/kg, **26** showed moderate activity in sheep (67% reduction).

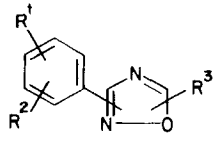
As in our earlier studies, the attachment of the isothiocyanato group to the phenyl ring of the 1,2,4-oxadiazoles confers considerable antiparasitic activity. The isothiocyanatophenyl group may be attached to either the 3- or 5-position of the oxadiazole ring to render the molecule antiparasitic. For maximum anthelmintic activity, the isothiocyanatophenyl group must be at the 3-position. The 5-isothiocyanatophenyl-substituted oxadiazoles show nematocidal activity but to a lesser degree. This latter result is in contrast to the observations by Ainsworth and co-workers, who noted nematocidal activity for 3-aryl- or 3-alkyl-1,2,4-oxadiazoles when tested in mice but stated that 5-substituted 3-aryl- or 3-alkyl-1,2,4-oxadiazoles were inactive.[21] Nevertheless, even the most active member in this series, namely, **39**, was only half as active as 5-isothiocyanato-2-(2-pyridinyl)-1*H*-benzimidazole,[9] 5- and 6-isothiocyanato-2-(3-pyridinyl)benzoxazole, or 6-isothiocyanato-2-(3-pyridinyl)benzothiazole.[1]

Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. The

(19) Hall, M. C.; Foster, W. D. *J. Agric. Res.* **1968**, *12*, 397.
(20) Moskey, H. D.; Harwood, P. D. *Am. J. Vet. Res.* **1941**, *2*, 55.
(21) Ainsworth, C.; Buting, W. E.; Davenport, J.; Callender, M. E.; McCoven, M. C. *J. Med. Chem.* **1967**, *10*, 208.

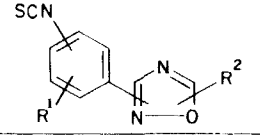
Table II. Physical Properties and Anthelmintic Activity against *N. dubius* and *H. nana* of (Aminophenyl)- and (Substituted aminophenyl)-1,2,4-oxadiazoles IX–XII



no.	R^1	R^2	Ph position of attachment	R^3	mp, °C	method	yield, %	crystn soln	formula	anal.	% clearance: mouse, oral	
											N. dubius	*H. nana*
17	4-NH_2	H	3	H	100–101	A	79	*a*	$C_8H_7N_3O$	C, H, N	0	0
18	4-NH_2	H	5	$C_6H_4F(4)$	184–185.5	B	51	MeOH	$C_{14}H_{10}FN_3O$	C, H, N	18	0
19	4-NH_2	H	5	$C_6H_4Cl(4)$	163–165	B	79	MeOH	$C_{14}H_{10}ClN_3O$	C, H, N	0	0
20	4-NH_2	2-Cl	5	C=CHCH=CHO	175–176.5	B	54	acetone/H_2O	$C_{12}H_8ClN_3O_2$	C, H, N	0	0
21	3-NH_2	4-Cl	5	C=CHCH=CHO	202.5–203.5	B	53	acetone/H_2O	$C_{12}H_8ClN_3O_2$	C, H, N	0	0
22	4-N=$CHC_6H_4Cl(4)$	H	3	H	152–155	G	47	95% EtOH	$C_{15}H_{10}ClN_3O$	C, H, N	0	0
23	4-N=CHC_6H_3Cl, $NO_2(4,3)$	H	3	H	208–211	G	50	EtOH	$C_{15}H_9ClN_4O_3$	C, H, N	0	0
24	4-N=CHC=CHCH=C(NO_2)O	H	3	H	203–205.5	G	41	EtOH/MeCN	$C_{13}H_8N_4O_4$	C, H, N	0	0
25	4-N=CHC=CHCH=CHNH	H	3	H	144–146	G	33	MeOH	$C_{13}H_{10}N_4O$	C, H, N	0	0
26	4-$NHCO_2CH_3$	H	3	H	174.5–176	H	53	C_6H_6/E	$C_{10}H_9N_3O_3$	C, H, N	81	25
27	4-$NHCO_2CH_3$	H	3	H	157–158	H	47	C_6H	$C_{15}H_{11}N_3O_3$	C, H, N	56	0
28	4-$NHCO_2C_6H_5$	H	3	H	108–110	H	55	*b*	$C_{11}H_8Cl_3N_3O_3$	C, H, N	0	0
29	4-$NHCO_2CH_3$	2-Cl	5	C=CHCH=CHO	179–180	H	53	C_6H_6	$C_{14}H_{10}ClN_3O_4$	C, H, N	0	0
30	4-$NHCO_2C_6H_5$	2-Cl	5	C=CHCH=CHO	184–185.5	H	79	C_6H_6	$C_{19}H_{12}ClN_3O_4$	C, H, N	0	0
31	4-$NHCO_2CH_2CCl_3$	2-Cl	5	C=CHCH=CHO	219–220	H	55	C_6H_6/dioxane	$C_{15}H_9Cl_4N_3O_4$	C, H, N	0	0
32	3-$NHCO_2CH_3$	4-Cl	5	C=CHCH=CHO	200–201	H	28	*a*	$C_{14}H_{10}ClN_3O_4$	C, H, N	0	0
33	3-$NHCO_2C_6H_5$	4-Cl	5	C=CHCH=CHO	177–178	H	65	C_6H_6	$C_{19}H_{12}ClN_3O_4$	C, H, N	0	0
34	3-$NHCO_2CH_2CCl_3$	4-Cl	5	C=CHCH=CHO	114–116	H	45	*a*	$C_{15}H_9Cl_4N_3O_4$	C, H, N	0	0
35	4-$NHC(=S)N(CH_2CH_3)_2$	2-Cl	5	C=CHCH=CHO	149–151	C	74	cyclohexane/C_6H_6	$C_{17}H_{17}ClN_4O_2S$	C, H, N	0	0
36	3-$NHC(=S)N(CH_2CH_3)_2$	4-Cl	5	C=CHCH=CHO	176.5–178	*c*	42	*a*	$C_{17}H_{17}ClN_4O_2S$	C, H, N	0	0

[a] Chromatographed; eluted with C_6H_6. [b] Chromatographed; eluted with 5% $CHCl_3/C_6H_6$. [c] See specific procedure in the Experimental Section.

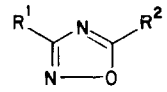
Table III. Physical Properties and Anthelmintic Activity against *N. dubius* and *H. nana* of (Isothiocyanatophenyl)-1,2,4-oxadiazoles XIII

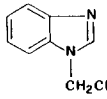
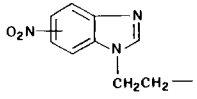
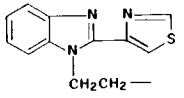
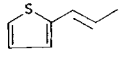
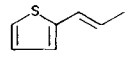
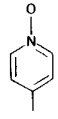


no.	SCN position	R^1	Ph position of attachment	R^2	mp, °C	method	yield,[a] %	crystn soln	formula	anal.	% clearance: mouse, oral[b] *N. dubius*	% clearance: mouse, oral[b] *H. nana*
37	3	H	3	H	59–60	E	38	PE	$C_9H_5N_3OS$	C, H, N	0	0
38	3	4-Cl	3	H	97–100	E	19	PE/Et_2O	$C_9H_4ClN_3OS$	C, H, N	0	0
39	4	H	3	H	124–127	D	52	PE	$C_9H_5N_3OS$	C, H, N	100	0,[c] 100[d]
40	4	H	3	CH_2CH_3	56–58	F	43	PE	$C_{11}H_9N_3OS$	C, H, N	30	0
41	4	H	3	$CHCH_2CH_2$	82–84	F	54	Et_2O	$C_{12}H_9N_3OS$	C, H, N	0	0
42	4	H	3	$CHCH_2CH_2CH_2CH_2CH_2$	55–57	F	50	PE	$C_{15}H_{15}N_3OS$	C, H, N	0	25
43	4	H	3	1-adamantyl	140–144	F	38	PE	$C_{19}H_{19}N_3OS$	C, H, N	0	0
44	4	H	3	CH_2Cl	108–110	D	52	PE	$C_{10}H_6ClN_3OS$	C, H, N	38	0
45	4	H	3	$CH_2CH_2OCH_3$	146–148	F	65	Et_2O	$C_{12}H_{11}N_3O_2S$	C, H, N	0	0
46	4	H	3	$CH_2CO_2CH_2CH_3$	140–142	F	63	Et_2O	$C_{12}H_{11}N_3O_3S_2$	C, H, N	0	0
47	4	H	3	$CH_2CH_2C_6H_5$	74–76	F	62	PE	$C_{17}H_{13}N_3OS$	C, H, N	0	0
48	4	H	3	$CH_2NCH_2CH_2N(CH_3)CH_2CH_2$	87–89	D	35	PE	$C_{15}H_{17}N_5OS$	C, H, N	0	0
49	4	H	3	$CO_2CH_2CH_3$	109–110	E	66	PE	$C_{12}H_9N_3O_3S$	C, H, N	0	0
50	4	H	3	C_6H_5	147–150	D	63	PE	$C_{15}H_9N_2OS$	C, H, N	80	50
51	4	H	3	$C_6H_4Cl(4)$	147–149	E	73	Et_2O	$C_{15}H_8ClN_3OS$	C, H, N	0	0
52	4	H	3	$C_6H_4F(4)$	153–154	E	96	Et_2O	$C_{15}H_8FN_3OS$	C, H, N	42	0
53	4	H	3	$C_6H_2(OCH_3)_3(3,4,5)$	159–160	D	65	Et_2O	$C_{18}H_{15}N_3O_4S$	C, H, N	0	0
54	4	H	3	$C_6H_4OCOCH_3(2)$	147–150	F	44	Et_2O	$C_{17}H_{11}N_3O_3S$	C, H, N	0	0
55	4	H	3	$C{=}CHCH{=}CHS$	148–150	D	35	PE	$C_{13}H_7N_3OS_2$	C, H, N	57	25
56	4	H	3	$C{=}CHCH{=}CHO$	137–140	D	57	PE	$C_{13}H_7N_3O_2S$	C, H, N	72	0
57	3	H	3	$C{=}CHCH{=}CHO$	97–98	E	62	PE	$C_{13}H_7N_3O_2S$	C, H, N	0	50
58	4	H	3	$C{=}CHCH{=}CHCH{=}N$	143–145	F	54	$CHCl_3/Et_2O$	$C_{14}H_8N_4OS$	C, H, N	0	0
59	4	H	3	C_6H_5	143–144.5	F	51	PE	$C_{15}H_9N_3OS$	C, H, N	0	0
60	4	H	5	$C_6H_4Cl(4)$	167–168.5	F	77	Et_2O	$C_{15}H_8ClN_3OS$	C, H, N	0	0
61	4	H	5	$C_6H_4F(4)$	144–146	F	45	PE	$C_{15}H_8FN_3OS$	C, H, N	0	0
62	4	H	5	$C{=}CHCH{=}CHS$	161–162	F	49	PE	$C_{13}H_7N_3OS_2$	C, H, N	22	33
63	4	H	5	$C{=}CHCH{=}CHO$	136–137	F	68	PE	$C_{13}H_7N_3O_2S$	C, H, N	90	100
64	4	2-Cl	5	$C{=}CHCH{=}CHO$	118–120	F	61	PE	$C_{13}H_6ClN_3O_2S$	C, H, N	0	100
65	3	4-SC_6H_5	5	$C{=}CHCH{=}CHO$	123–125	F	25	MeCN	$C_{19}H_{11}N_3O_2S_2$	C, H, N	0	0
66	3	4-Cl	5	$C{=}CHCH{=}CHO$	133.5–134.5	F	28	PE	$C_{13}H_6ClN_3O_2S$	C, H, N	0	100
67	4	H	5	$C{=}CHCH{=}CHCH{=}N$	145–146	F	54	PE	$C_{14}H_8N_4OS$	C, H, N	0	0

[a] Yield calculated on hydrogenation/thiocarbonylation only. No attempt was made to optimize yields. [b] For details, see ref 9 [c] Destrobilization. [d] Dosed subcutaneously.

Table IV. Physical Properties and Anthelmintic Activity against *N. dubius* and *H. nana* of Miscellaneous Oxadiazoles



no.	R^1	R^2	mp, °C	method	yield, %	crystn soln	formula	anal.	% clearance: mouse, oral *N. dubius*	% clearance: mouse, oral *H. nana*
68		C_6H_5	112–114	B	22	CH_3CN	$C_{17}H_{14}N_4O$	C, H, N	0	0
69		C_6H_5	206–214	B	70	CH_3CN	$C_{17}H_{13}N_5O_3$	C, H, N	0	0
70		C_6H_5	118–120	B	54	hexane	$C_{20}H_{15}N_5OS$	C, H, N	17	0
71	$-C_6H_5$	$CH_2CH_2NO_2$	53–55	B	36	PE/Et_2O	$C_{10}H_9N_3O_3$	C, H, N	0	0
72			118–121	B	10	Et_2O	$C_{14}H_{10}N_2OS_2$	C, H, N	0	0
73		H	144–147[a]	C	16	MeOH	$C_7H_5N_3O$	C, H, N	0	0
74		H	162–164	*b*	27	THF/PE	$C_7H_5N_3O_2$	C, H, N	0	0

[a] Lit.[24] mp 147–148 °C. [b] See Experimental Section for specific procedure.

Table V. Anthelmintic Activity of Oxadiazole Compounds in the Diet against *Nematospiroides dubius* in Mice

concn, %	% clearance of *N. dubius* Ia	Ib	Ic	**39**	thiabendazole
0.2	93		98	100	100
0.1	70	100	94	100	100
0.05	46	95	96	96	94
0.025	35	61	67	82	81
0.013	8	36	39	48	47

NMR spectra were obtained in Me_2SO-d_6 with Me_4Si as internal standard. IR and NMR spectra were consistent with assigned structures for all compounds. Neutral alumina (Woelm activity IV) was used for chromatography. Combustion analyses were within ±0.4% of the theoretical values.

All of the amidoximes V that were used in this study have been reported in the literature with the exception of 5- and 6-nitro-1*H*-benzimidazole-1-propionamidoxime and 2-(4-thiazolyl)-1*H*-benzimidazole-1-propionamidoxime, i.e., the intermediates for oxadiazoles **69** and **70**, which were synthesized as follows.

5- and 6-Nitro-1*H*-benzimidazole-1-propionamidoxime and 2-(4-Thiazolyl)-1*H*-benzimidazole-1-propionamidoxime. 5-Nitro-1*H*-benzimidazole was reacted with acrylonitrile in the presence of Triton B to yield 5- and 6-nitro-1*H*-benzimidazole-1-propionitrile.[9] A mixture of 0.02 mol of the nitrile, 0.02 mol of hydroxylamine hydrochloride, 0.01 mol of K_2CO_3, 10 mL of H_2O, and 50 mL of EtOH was refluxed for 24 h and cooled, and 25 mL of H_2O was added. The EtOH was evaporated in vacuo, and the resulting solid was filtered and crystallized from aqueous EtOH to yield 5- and 6-nitro-1*H*-benzimidazole-1-propionamidoxime, mp 167–169 °C (85%). This compound was used without further purification in the cyclization step. 2-(4-Thiazolyl)-1*H*-benzimidazole-1-propionamidoxime was prepared analogously.

The 1,2,4-oxadiazoles VI were synthesized by three general methods (A–C), which are illustrated below.

Method A. 3-(4-Nitrophenyl)-1,2,4-oxadiazole. A mixture of 2.5 g (0.014 mol) of 4-nitrobenzamidoxime, 0.03 mL of BF_3·Et_2O, and 6.2 g (0.042 mol) of triethyl orthoformate was heated with stirring until all of the amidoxime dissolved. Heating was continued for 10 min at which time the reaction mixture solidified. The solid was filtered off, washed with petroleum ether (bp 40–60 °C), and dried to yield 2.2 g of 3-(4-nitrophenyl)-1,2,4-oxadiazole, mp 164–165 °C (lit.[22] mp 165–166 °C).

Method B. 3,5-Bis(4-nitrophenyl)-1,2,4-oxadiazole (1). A solution of 5.4 g (0.03 mL) of 4-nitrobenzamidoxime and 5.6 g (0.03 mol) of 4-nitrobenzoyl chloride in 250 mL of dioxane was heated on the steam bath for 1 h. After addition of 1 mL of BF_3·Et_2O, the reaction mixture was refluxed overnight. The reaction mixture was cooled and the precipitated solid was filtered, washed with petroleum ether (bp 40–60 °C), and crystallized from Et_2O to yield 5.9 g of 1, mp 238–240 °C.

Method C. 3-(4-Chloro-3-nitrophenyl)-1,2,4-oxadiazole. A solution of 9.3 g (0.043 mol) of 4-chloro-3-nitrobenzamidoxime in 75 mL of THF was stirred at 10 °C for 0.5 h in the presence of DMF–$POCl_3$ complex in ether [prepared by stirring 6.3 g (0.086 mol) of DMF and 13.1 g (0.086 mL) of $POCl_3$ in 45 mL of Et_2O at 0 °C for 1 h and then decanting the solvent to give a greenish oil]. The resulting white suspension was evaporated in vacuo and 50 mL of H_2O was added. Upon cooling, a white-yellow solid precipitated; it was filtered and crystallized from MeOH to yield 3.9 g of 3-(4-chloro-3-nitrophenyl)-1,2,4-oxadiazole, mp 76–78 °C.

3-(2-Furanyl)-5-[3-nitro-4-(phenylthio)phenyl]-1,2,4-oxadiazole (8). To a solution of 4.9 g (0.017 mol) of **9** in 35 mL of DMF were added 3.4 g of K_2CO_3 and 2 mL of benzenethiol, and the mixture was refluxed for 2 h. The mixture was then poured into 400 mL of cold dilute NaOH and extracted with $CHCl_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated in vacuo to yield a brown oil. Trituration with CH_3CN yielded a solid, which was crystallized from CH_3CN to yield 4.5 g of **8**, mp 166–168 °C.

5-[(Ethylsulfonyl)methyl]-3-(4-nitrophenyl)-1,2,4-oxadiazole (11). To a solution of 1.06 g (0.01 mol) of Na_2CO_3 in 100 mL of H_2O was added 0.62 g (0.01 mol) of ethanethiol followed by a solution of 2.4 g (0.01 mol) of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole in the minimum amount of MeOH and the mixture was refluxed for 2 h. After cooling, the reaction mixture was extracted with Et_2O. The organic layers were combined, dried ($MgSO_4$), and evaporated to yield a pale yellow solid. The sulfide was dissolved in 300 mL of $CHCl_3$ and 4.0 g (85%, 0.02 mol) of MCPBA was added and the mixture was stirred overnight at room temperature. The mixture was washed with aqueous K_2CO_3, and the organic layer was separated, dried, and evaporated in vacuo to furnish a solid. Crystallization from $CHCl_3$ yielded 1.3 g of **11**, mp 146–148 °C.

Method I. 4-[[3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl]methyl]morpholine (13) (General Method for VIII). To a solution of 3.8 g (2.8 mL, 0.033 mol) of morpholine in 30 mL of DMF was added 4.0 g (0.167 mol) of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole and the mixture was stirred at room temperature overnight. Then there was added 200 mL of H_2O. The resulting solid was filtered off and crystallized from absolute EtOH to yield 3.6 g of **13**, mp 143–144 °C.

3-(4-Nitrophenyl)-5-(thiocyanatomethyl)-1,2,4-oxadiazole (12) and 5-(4-Nitrophenyl)-3-(thiocyanatomethyl)-1,2,4-oxadiazole (16). A solution of 4.8 g (0.02 mol) of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole and 4.8 g of NH_4SCN in 40 mL of Me_2SO was heated on steam bath for 1 h. Water was added and the resulting solid was filtered and dried. Crystallization from $CHCl_3$ yielded 4.3 g of **12**, mp 137–139 °C. Compound **16** was prepared analogously, mp 115–118 °C.

3-(4-Aminophenyl)-1,2,4-oxadiazole (17) (General Method for IX). A mixture of 25.6 g (0.134 mol) of 3-(4-nitrophenyl)-1,2,4-oxadiazole, 2.5 g of 10% Pd/C, and 22.8 mL (0.134 mol) of concentrated HCl in 700 mL of 95% EtOH was reduced on a Parr hydrogenator at 50 psi until the required amount of H_2 was absorbed. The catalyst and resulting amine salt were filtered and washed with a solution of 39 mL (0.268 mol) of triethylamine in 100 mL of EtOH. The filtrate and washings were combined and concentrated to dryness. THF was added to the residue and the insoluble triethylamine hydrochloride was filtered and washed with THF. The filtrate was evaporated in vacuo to yield a solid, which was dissolved in C_6H_6 and passed through an alumina column. Concentration of the eluant yielded 17 g of **17**, mp 100–101 °C.

Method G. 3-[4-[[(4-Chlorophenyl)methylene]amino]phenyl]-1,2,4-oxadiazole (22) (General Method for X). To a solution of 4.5 g (0.028 mol) of 3-(4-aminophenyl)-1,2,4-oxadiazole (17) in 75 mL of absolute EtOH was added a solution of 3.94 g (0.028 mol) of 4-chlorobenzaldehyde in 25 mL of absolute EtOH and the mixture was refluxed for 20 min. The reaction mixture was cooled and the resulting solid was filtered and recrystallized from 95% EtOH to yield 3.7 g of **22**, mp 152–155 °C.

Method H. [4-(1,2,4-Oxadiazol-3-yl)phenyl]carbamic Acid Methyl Ester (26) (General Method for XI). To a mixture of 1.9 g (0.012 mol) of 3-(4-aminophenyl)-1,2,4-oxadiazole (17) and 2.07 g (0.015 mol) of K_2CO_3 in 50 mL of dioxane was added 1.41 g (0.015 mol) of methyl chloroformate and the mixture was refluxed for 15 min. The mixture was cooled and filtered and the solvent was removed in vacuo. The residue was crystallized from C_6H_6–EtOAc to yield 1.39 g of **26**, mp 174.5–176 °C.

The isothiocyanato compounds XIII were synthesized by use of three variations D–F. The preparations of **39**, **52**, and **40** will serve as examples.

Method D.[23] **3-(4-Isothiocyanatophenyl)-1,2,4-oxadiazole (39).** To a solution of 4.0 g (0.02 mol) of **17** in 100 mL of $CHCl_3$ was added a mixture of 100 mL of H_2O and 2.0 g (0.02 mol) of $CaCO_3$ and the mixture was cooled to 5 °C. Then there was added 1.8 mL of thiophosgene and the mixture was stirred at 5 °C for 1 h and then at room temperature overnight. The organic layer was separated, washed with H_2O, dried, and evaporated to yield a solid residue. Crystallization from petroleum ether (bp 40–60 °C) yielded 2.1 g of **39**, mp 124–127 °C.

Method E. 5-(4-Fluorophenyl)-3-(4-isothiocyanatophenyl)-1,2,4-oxadiazole (52). To a solution of 3.7 g (0.02 mol of) 3-(4-aminophenyl)-5-(4-fluorophenyl)-1,2,4-oxadiazole in 200 mL of THF was added 4.0 g (0.04 mol) of TEA at 5 °C followed by 1.8 mL of thiophosgene and the mixture was stirred at 5 °C for 1 h and then at room temperature overnight. The triethylamine hydrochloride was filtered and the solvent was removed in vacuo to yield a solid residue. Crystallization from Et_2O yielded 4.3 g of **52**, mp 153–154 °C.

Method F. 5-Ethyl-3-(4-isothiocyanatophenyl)-1,2,4-oxadiazole (40). To a solution of 1.9 g (0.01 mol) of 3-(4-aminophenyl)-5-ethyl-1,2,4-oxadiazole in 120 mL of glyme and 60 mL

(22) Arbasino, M.; Gruenanger, P. *Chim. Ind. (Milan)* **1963**, *45*, 1238.

(23) Sharma, S. *Synthesis* **1978**, 803.

of H_2O was added 1.0 g (0.01 mol) of $CaCO_3$ followed by 0.8 mL (0.01 mol) of thiophosgene at 5 °C. The mixture was stirred for 1.5 h and then filtered. The glyme was removed in vacuo and the resulting solid was filtered and crystallized from petroleum ether (bp 40–60 °C) to yield 1.0 g of **40**, mp 56–58 °C.

***N'*-[3-Chloro-4-[3-(2-furanyl)-1,2,4-oxadiazol-5-yl]-phenyl]-*N*,*N*-diethylthiourea (35) and *N'*-[2-Chloro-5-[3-(2-furanyl)-1,2,4-oxadiazol-5-yl]phenyl]-*N*,*N*-diethylthiourea (36).** A solution of 1.5 g (0.005 mol) of **64** or **66** in 24 mL of diethylamine was stirred overnight at room temperature. The diethylamine was evaporated in vacuo, and in the case of **35**, the resulting solid was crystallized from cyclohexane–C_6H_6 to yield 1.4 g of pure **35**, mp 149–151 °C. In the case of **36**, the residue was chromatographed. Elution with C_6H_6 yielded 0.8 g of **36**, mp 176–178 °C.

4-(1,2,4-Oxadiazol-3-yl)pyridine *N*-Oxide (74). To a solution of 3.7 g (0.018 mol) of **73**[24] in 300 mL of $CHCl_3$ was added 3.16 g (0.018 mol) of MCPBA at room temperature and the reaction mixture was stirred at room temperature for 3 h. The solution was washed with Na_2CO_3 solution and the $CHCl_3$ layer was dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a solid, which was crystallized from THF/PE to yield 0.8 g of **74**, mp 162–164 °C.

Registry No. 1, 54608-83-2; 2, 96898-34-9; 3, 54608-85-4; 4, 96898-35-0; 5, 54608-93-4; 6, 96898-36-1; 7, 96898-37-2; 8, 96898-38-3; 9, 61084-44-4; 10, 61051-44-3; 11, 96898-39-4; 11 (sulfide), 96898-77-0; 12, 96898-40-7; 13, 6596-08-3; 14, 96898-41-8; 15, 92110-19-5; 15·HCl, 96898-42-9; 16, 96898-43-0; 17, 59908-70-2; 18, 96898-44-1; 19, 96898-45-2; 20, 61051-45-4; 21, 61051-43-2; 22, 96898-46-3; 23, 96898-47-4; 24, 96898-48-5; 25, 96898-49-6; 26, 59908-71-3; 27, 59908-73-5; 28, 59908-72-4; 29, 96898-50-9; 30, 61051-41-0; 31, 61051-42-1; 32, 61051-38-5; 33, 61051-40-9; 34, 61051-39-6; 35, 96913-34-7; 36, 96898-51-0; 37, 96898-52-1; 37 (amine), 96913-36-9; 38, 96898-53-2; 38 (amine), 96898-96-3; 39, 54608-86-5; 40, 96898-54-3; 40 (amine), 10185-71-4; 41, 54608-90-1; 41 (amine), 96898-78-1; 42, 54608-92-3; 42 (amine), 96898-79-2; 43, 54608-94-5; 43 (amine), 96898-80-5; 44, 96898-55-4; 44 (amine), 6674-17-5; 45, 96898-56-5; 45 (amine), 96898-81-6; 46, 96898-57-6; 46 (amine), 96898-82-7; 47, 96898-58-7; 47 (amine), 96898-83-8; 48, 96898-59-8; 48 (amine), 96898-84-9; 49, 96898-60-1; 49 (amine), 96898-85-0; 50, 54608-87-6; 50 (amine), 54494-08-5; 51, 54608-88-7; 51 (amine), 96898-86-1; 52, 96898-61-2; 52 (amine), 96898-87-2; 53, 54608-89-8; 53 (amine), 96898-88-3; 54, 96913-35-8; 54 (amine), 96898-89-4; 55, 54609-01-7; 55 (amine), 63318-64-9; 56, 54609-03-9; 56 (amine), 63318-65-0; 57, 96898-62-3; 57 (amine), 96898-90-7; 58, 54609-05-1; 58 (amine), 59908-75-7; 59, 54608-87-6; 59 (amine), 54494-08-5; 60, 96898-63-4; 61, 96898-64-5; 62, 96898-65-6; 62 (amine), 96898-91-8; 63, 96898-66-7; 63 (amine), 96898-92-9; 64, 96898-67-8; 65, 96898-68-9; 65 (amine), 96898-93-0; 66, 96898-69-0; 67, 96898-70-3; 67 (amine), 96898-94-1; 68, 58553-87-0; 69, 96898-33-8; 70, 58575-68-1; 71, 96898-71-4; 72, 96898-72-5; 73, 22926-60-9; 74, 96898-73-6; IVa (amidoxime), 4404-30-2; IVb (5-NO_2), 20129-34-4; IVb (6-NO_2), 58553-90-5; IVb (5-NO_2, amidoxime), 58553-91-6; IVb (6-NO_2, amidoxime), 58553-92-7; IVc, 58553-88-1; IVc (amidoxime), 58553-89-2; V (R = $C_6H_3NO_2$, SC_6H_5(3,4)), 96898-74-7; V (R = C_6H_3Cl,NO_2(4,3)), 96898-75-8; V (R = C_6H_3Cl,NO_2(2,4)), 96898-76-9; V (R = $C_6H_4NO_2$(4)), 1613-86-1; V (R = C_6H_5), 613-92-3; V (R = 4-pyridyl), 1594-57-6; Va, 24654-28-2; VI (R = $C_6H_4NO_2$(4), R^2 = CH_2Cl), 57611-19-5; VI (R = CH_2Cl, R^2 = $C_6H_4NO_2$(4)), 73217-32-0; VI (R = C_6H_4N-O_2(4), R^2 = H), 16013-14-2; VI (R = C_6H_3Cl,NO_2(4,3)), 96898-95-2; XIVa (5-NO_2), 94-52-0; XIVc, 148-79-8; CH_2=CHCN, 107-13-1; $ClCOC_6H_4NO_2$(4), 122-04-3; $ClCO(CH_2)_{10}CH_3$, 112-16-3; ClCO-$C_6H_2(OCH_3)_3$(3,4,5), 4521-61-3; $ClCOC_6H_4F$(4), 403-43-0; ClC-$O_2CH_2CH_3$, 541-41-3; $ClCOC_6H_4Cl$(4), 122-01-0; $OHCC_6H_4Cl$(4), 104-88-1; $OHCC_6H_3Cl,NO_2$(4,3), 16588-34-4; $ClCSN(CH_2CH_3)_2$, 88-11-9; $CSCl_2$, 463-71-8; $ClCO(CH_2)_2NO_2$, 51834-15-2; DMF·$POCl_3$, 18997-06-3; cyclohexanecarbonyl chloride, 2719-27-9; 2-furancarbonyl chloride, 527-69-5; 5-nitrofurfural, 698-63-5; 2-pyrrolecarboxaldehyde, 1003-29-8; β-(2-thienyl)acryloyl chloride, 28424-61-5.

(24) Fanshawe, W. J.; Bauer, V. J.; Safir, S. R.; Blickens, D. A.; Riggi, S. J. *J. Med. Chem.* **1969**, *12*, 381.