$CH_2C_6H_4OMe$), 96 (21.8), 83 (19.5). Anal. ($C_{23}H_{31}N_7O_3$) C, H, N.

The lower R_f diastereomer was assigned structure **1a** (see discussion): $[\alpha]^{25}_{589}$ −99.7°, $[\alpha]^{25}_{436}$ −223.6° (*c* 0.23, $CHCl_3$); IR, ^1H NMR, and mass spectra almost identical with those of **1b**. Anal. ($C_{23}H_{31}N_7O_3$) C, H, N.

6-Dimethylamino-9-[(*R*)-[2(*R*)-hydroxy-3(*S*)-(*p*-methoxyphenyl-L-alanylamino)]cyclohexyl]purine and 6-Dimethylamino-9-[(*S*)-[2(*S*)-hydroxy-3(*R*)-(*p*-methoxyphenyl-L-alanylamino)]cyclohexyl]purine (2a and 2b). Hydrogenolysis of a mixture of **18a** and **18b** as described above gave a mixture of **2a** and **2b** as a colorless glass (90%): TLC (10% MeOH–$CHCl_3$) shows two bands at lower R_f than starting material; IR and ^1H NMR as expected; attempts to crystallize the mixture were unsuccessful. The diastereomers were separated by preparative TLC (20% MeOH–$CHCl_3$), giving hygroscopic glasses. The greater R_f diastereomer was designated **2b**: $[\alpha]^{25}_{589}$ −78.0°, $[\alpha]^{25}_{436}$ −175.5° (*c* 0.23, $CHCl_3$); IR (KBr) 3300 (br, OH, NH, NH_2), 1655 (amide), 1595 cm^{-1} (purine); ^1H NMR ($CDCl_3$) δ 8.07 and 7.64 (both s, H-8 and H-2), 7.33 (br, NH), 6.83 (q, J = 8 Hz, $MeOC_6H_4$), remainder of spectrum showed overlapping with discernible singlets at 3.72 (OMe) and 3.38 (NMe_2); mass spectrum (probe temperature 200 °C, 70 eV) *m/e* (rel intensity) 453 (8.6, M^+), 437 (1.6), 436 (1.6), 435 (1.2), 419 (0.9), 368 (5.4), 333 (17.9), 332 (92.7, M − $CH_2C_6H_4OMe$), 315 (3.2), 314 (3.7, M − $CH_2C_6H_4OMe$ − H_2O), 304 (8.6), 303 (9.5), 285 (3.5), 276 (14.6), 261 (5.8), 256 (9.7), 244 (5.2), 218 (6.9, B + C_4H_8), 205 (10.0, B + C_3H_7), 190 (3.8, B + C_2H_4), 165 (14.5), 164 (100, B + 2H), 163 (25.7, B + H), 150 (21.5, $NH_2CHCH_2C_6H_4OMe$), 134 (17.8, B + H − CH_3N), 121 (25.7, $CH_2C_6H_4OMe$), 97 (40.7), 83 (59.2). Anal. ($C_{23}H_{31}N_7O_3 \cdot 0.5H_2O$) C, H, N.

The lower R_f diastereomer was designated **2a**: $[\alpha]^{25}_{589}$ −5.02°; $[\alpha]^{25}_{436}$ −7.53° (*c* 0.24, $CHCl_3$); IR, ^1H NMR and mass spectra almost identical with those of **2b**. Anal. ($C_{23}H_{31}N_7O_3 \cdot H_2O$) C, H, N.

6-Dimethylamino-9[(*R*)-[2(*R*)-hydroxy-3(*S*)-(*p*-methoxyphenyl-L-alanylamino)]cyclopentyl]purine and 6-Dimethylamino-9-[(*S*)-[2(*S*)-hydroxy-3(*R*)-(*p*-methoxyphenyl-L-alanylamino)]cyclopentyl]purine (19a and 19b). Hydrolysis of 2α-acetamido-5α-(6-dimethylamino-9-purinyl)-cyclopentan-1β-ol[1] with refluxing 0.5 N $Ba(OH)_2$ gave a quantitative yield of amine which was immediately coupled with *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanylamine[11] as above. The usual work-up gave a white solid foam (84%): chromatographically homogeneous; IR (KBr) almost identical with that of the *N*-benzyloxycarbonyl derivative of **20a** or **20b**.[1] Hydrogenolysis as above gave a mixture of diastereomers **19a** and **19b** (90%), which were separated by preparative TLC (15% MeOH–$CHCl_3$). The greater R_f diastereomer **19b** was isolated as a solid foam: $[\alpha]^{25}_{589}$ −61.6°, $[\alpha]^{25}_{436}$ −143.7° (*c* 0.23, $CHCl_3$); IR (KBr) 3300 (br, OH, NH, NH_2), 1650 (amide), 1600 cm^{-1} (purine); mass spectrum (probe temperature 200 °C, 70 eV) *m/e* (rel intensity) 439 (2.4, M^+), 422 (0.8), 421 (1.0), 319 (22.3), 318 (100, M − $CH_2C_6H_4OMe$), 301 (0.6), 300 (1.5, M − $CH_2C_6H_4OMe$ − H_2O), 273 (1.5), 230 (4.4), 190 (14.4, B + C_2H_4), 164 (95.2, B + 2H), 163 (16.9, B + H), 150 (14.7, $NH_2CHCH_2C_6H_4OMe$), 148 (11.1), 134 (23.4, B + H − CH_3N), 122 (7.8), 121 (33.9, $CH_2C_6H_4OMe$), 120 (6.4), 109 (2.0), 108 (2.4), 82 (5.0). Anal. ($C_{22}H_{29}N_7O_3$) C, H, N.

The lower R_f diastereomer **19a** was also a solid foam: $[\alpha]^{25}_{589}$ −25.8°, $[\alpha]^{25}_{436}$ −61.4° (*c* 0.23, $CHCl_3$); IR (KBr) and mass spectra almost identical with those of **19b**. Anal. ($C_{22}H_{29}N_7O_3$) C, H, N.

Acknowledgment. This investigation was supported by Grant No. CA 13592 and Career Development Award CA 2525A (to R.V.) from the National Cancer Institute, Department of Health, Education and Welfare.

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Isoxazole Anthelmintics

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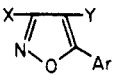
A series of 3-halo-5-phenyl- and 3-phenyl-5-haloisoxazoles has demonstrated anthelmintic activity at doses ranging from 16 to 500 mg/kg orally against the rat roundworm, *Nippostrongylus braziliensis*. In the 5-phenyl series a halogen at the 3 position of the isoxazole ring was required for activity. However, in the 3-phenyl series activity was maintained after replacement of the 5-halogen with certain alkoxyl, thioalkoxyl, or amino groups. The 3-phenyl and 5-phenyl series apparently are not acting biologically at a common receptor site. Synthetic methods and structure–activity relationships are discussed.

During the testing of selected compounds for anthelmintic activity in a rodent parasite screen, 3-chloro-5-phenylisoxazole (**1**) exhibited anthelmintic activity against the rat roundworm, *Nippostrongylus braziliensis*, equal to that of the commericial anthelmintic 2-(4-thiazolyl)-benzimidazole (thiabendazole). Although **1** is a known compound,[1] no report of anthelmintic activity for **1** or other 5-phenylisoxazoles was found.

Although the literature is replete with references to the biological activity of compounds containing the isoxazole ring as part of their structures, only in five instances were claims of anthelmintic activity made for such compounds. Sen and co-workers[2] claim cestocidal activity for a series of 3-aryl-5-(halomethyl)isoxazoles. A series of 5-amino- and 5-acylamino-3-pyridylisoxazoles has been claimed as anthelmintics and nematocides.[3,4] The corresponding 3-aryl-5-aminoisoxazoles also have been claimed as antiparasitics.[5] Anthelmintic, coccidiostatic, and growth-promoting activity has been claimed for a class of 5-amino-4-(5-nitro-2-furyl)-4-(substituted carbonyl)isoxazoles.[6]

The lack of a study of 5-phenylisoxazoles as anthelmintics prompted our investigation of this class of compounds. During the course of this work, the isomeric

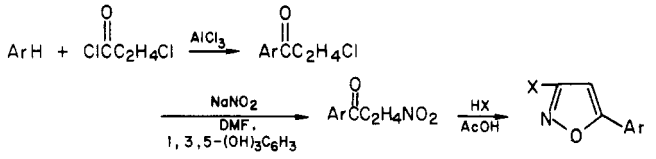
Table I. 5-Arylisoxazoles



No.	X	Y	Ar	Mp, °C	Yield, %	Formula	Analyses	MED,[a] mg/kg
1[e]	Cl	H	C_6H_5	36-37	50	C_9H_6ClNO	C, H, N, Cl	31
2	Cl	H	4-ClC_6H_4	140-141	60	$C_9H_5Cl_2NO$	C, H, N, Cl	62
3	Cl	H	2,4-$Cl_2C_6H_3$	91-92	4	$C_9H_4Cl_3NO$	C, H, N, Cl	62
4	Cl	H	3,4-$Cl_2C_6H_3$	124-125	20	$C_9H_4Cl_3NO$	C, H, N	250
5	Cl	H	4-$CH_3C_6H_4$	61-62	10	$C_{10}H_8ClNO$	C, H, N	500
6	Cl	H	4-$NO_2C_6H_4$	213-214	50	$C_9H_5ClN_2O_3$	C, H, N	*b*
7	Cl	H	3-NO_2-4-ClC_6H_3	146.5-148	35	$C_9H_4Cl_2N_2O_3$	C, H, N	*b*
8	Cl	H	2-C_4H_3S	*c*	12	C_7H_4ClNOS	C, H, N	250
9[f]	Br	H	C_6H_5	72-73	15	C_9H_6BrNO	C, H, N	31
10	Br	H	4-ClC_6H_4	154-155	30	$C_9H_5BrClNO$	C, H, N	250
11	I	H	C_6H_5	106.5-109	7	C_9H_6INO	C, H, N	250
12	CF_3	H	C_6H_5	81-81.5	67	$C_{10}H_6F_3NO$	C, H, N	*b*
13[g]	H	H	4-ClC_6H_4	77-78	3	C_9H_6ClNO	C, H, N	*b*
14[h]	OH	H	4-ClC_6H_4	217-219	75	$C_9H_6ClNO_2$	Cl	*b*
15[h]	NH_2	H	C_6H_5	133-135	50	$C_9H_8N_2O$	C, H, N	*b*
16	$CH_3NHC(O)NH$	H	C_6H_5	200-201	69	$C_{11}H_{11}N_3O_2$	C, H, N	*b*
17	$CF_3C(O)NH$	H	C_6H_5	210-210.5	95	$C_{11}H_7F_3N_2O_2$	C, H, N	*b*
18	$CH_3OC(O)NH$	H	C_6H_5	139-140	67	$C_{11}H_{10}N_2O_3$	C, H, N	*b*
19	CH_3SO_3	H	C_6H_5	94-95	70	$C_{10}H_9NO_4S$	C, H, N, S	*b*
20[i]	Cl	Cl	C_6H_5	35-35.5	70	$C_9H_5Cl_2NO$	Cl	31
21	NH_2	Cl	C_6H_5	132-133	28	$C_9H_7ClN_2O$	C, H, N	*b*
22	NH_2	Br	C_6H_5	142.5-144	23	C_9H_7BrNO	C, H, N	*b*
23	$CF_3C(O)NH$	Cl	C_6H_5	138.5-139.5	90	$C_{11}H_6ClF_3N_2O_2$	C, H, N[d]	*b*

[a] Minimum effective dose (MED), that dose which effected a 75% clearance of the rat roundworm, *Nippostrongylus braziliensis*, as compared to infected nontreated controls. [b] Inactive at 500 mg/kg. [c] Crude liquid. [d] N: calcd, 9.6; found, 10.2. [e] See ref 1. [f] See ref 7. [g] See ref 8. [h] See ref 9. [i] See ref 10.

Scheme I



5-chloro-3-phenylisoxazole (**34**) was found to possess activity equal to that of **1**. This finding prompted the extension of our study to include 3-phenylisoxazoles. This paper reports the results of these investigations.

Chemistry. 5-Arylisoxazoles. A series of 5-arylisoxazoles was synthesized (Table I) for comparison to **1** as anthelmintics. Utilizing essentially the procedure of Fusco and Rossi,[11] **1** and additional 3-chloro and 3-bromo analogues, **2–5**, **9**, and **10**, were synthesized (Scheme I) by the hydrochloric or hydrobromic acid cyclization of the appropriate 3-nitro-1-phenyl-1-propanone (Table II). Similarly, the 5-thienyl analogue **8** was prepared from **29**. An attempt to synthesize the iodo analogue with hydriodic acid in acetic acid gave instead **13**. Nesmeyanov and co-workers[10] reported the similar reductive cyclization by hydriodic acid on 3-nitro-1-phenylpropenone. In the synthesis of the 1-aryl-3-nitro-1-propanones the procedure of Fusco and Rossi[11] was modified by the addition of a 0.36 M equivalent of phloroglucinol to prevent nitrite ester formation as demonstrated by Kornblum and co-workers.[12] The 3-chloro-1-phenyl-1-propanones were synthesized by the method of Kenner and co-workers.[13] The 3-chloro-1-(2-thienyl)-1-propanone was prepared by the procedure of Janssen[14] utilizing titanium tetrachloride as the catalyst. Due to its slow decomposition upon standing, the crude product was used directly for the preparation of **29**.

The 3-trifluoromethyl analogue **12** was synthesized (Scheme II) in three steps from 1-phenylethanone and ethyl trifluoroacetate. The methods of Reid and Calvin[15] were used to obtain **30** and its oxime **31**. The formation of only the monooxime **31** of *Z* stereochemistry is attributed to the resistance of the indicated highly stabilized hydrogen bonded enol form to further reaction with hydroxylamine. The *Z* stereochemistry was assigned to **31** on the basis of the absence of a carbonyl bond in the IR and subsequent appearance of a methylene singlet at 3.7

Table II. 1-Aryl-3-nitro-1-propanones[a]

No.	R	Mp, °C	Yield, %	Formula	Analyses
24[b]	C_6H_5	79-80	93	$C_9H_9NO_3$	C, H, N
25	4-ClC_6H_4	79-80	86	$C_9H_8ClNO_3$	C, H, N
26	2,4-$Cl_2C_6H_3$	80-81	54	$C_9H_7Cl_2NO_3$	C, H, N
27	3,4-$Cl_2C_6H_3$	103-104	75	$C_9H_7Cl_2NO_3$	C, H, N
28	4-$CH_3C_6H_4$	75-76	75	$C_{10}H_{11}NO_3$	C, H, N
29	2-C_4H_3S	56-57	60	$C_7H_7NO_3S$	C, H, N

[a] Inactive at 500 mg/kg; see footnote *a*, Table I. [b] See ref 11.

Scheme II

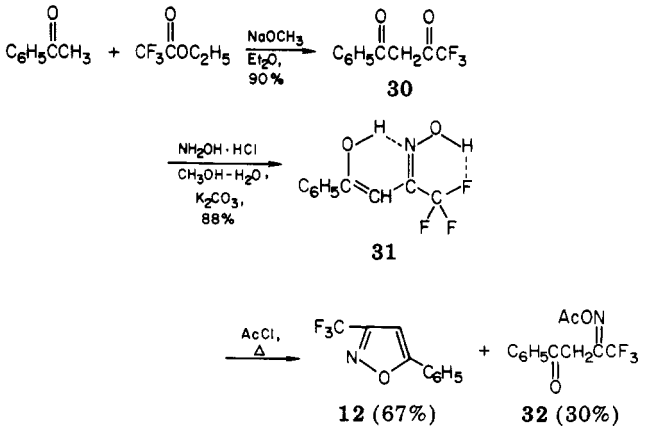
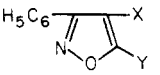


Table III. 3-Phenylisoxazoles



No.	X	Y	Mp or bp (mm), °C	Yield, %	Formula	Analyses	MED,[a] mg/kg
34[e]	H	Cl	49-50	60	C_9H_6ClNO	C, H, N	16
35[e]	H	Br	46-47	27	C_9H_6BrNO	C, H, N	16
36	H	CF_3	78-79	19	$C_{10}H_6F_3NO$	C, H, N	*b*
37[f]	H	H	46-47 (0.005)	68	C_9H_7NO	N	*b*
38[g]	H	OCH_3	77-78	67	$C_{10}H_9NO_2$	C, H, N	31
39[h]	H	OC_2H_5	75-76	74	$C_{11}H_{11}NO_2$	C, H, N	31
40	H	$OC_3H_6CH=CH_2$	55-56	20	$C_{14}H_{15}NO_2$	C, H, N	125
41	H	$OC_2H_4SC_2H_5$	64-65	64	$C_{13}H_{15}NO_2S$	C, H, N	*b*
42	H	SCH_3	41-42	77	$C_{10}H_9NOS$	C, H, N	31
43[i]	H	SC_2H_5	28-29	38	$C_{11}H_{11}NOS$	C, H, N	125
44	H	$S(O)CH_3$	87-88	78	$C_{10}H_9NO_2S$	C, H, N	*b*
45	H	$S(O)_2CH_3$	95-96	70	$C_{10}H_9NO_3S$	C, H, N	*b*
46	H	$SCH_2C_6H_5$	93-94	67	$C_{16}H_{13}NOS$	C, H, N	*b*
47[j]	H	$N(CH_3)_2$	78-79	37	$C_{11}H_{12}N_2O$	C, H, N	125
48	H	c-$N(CH_2CH_2)_2O$	99-100	60	$C_{13}H_{14}N_2O_2$	C, H, N	500
49	$CH_2CH=CH_2$	Cl	105-106 (0.2)	80	$C_{12}H_{10}ClNO$	C, H, N	*b*
50	Cl	OCH_3	*c*	94	$C_{10}H_8ClNO_2$	C, H, N	*b*
51	Cl	Cl	81-85 (0.015)	73	$C_9H_5Cl_2NO$	C, H, N	*b*
52	Cl	SCH_3	*d*	60	$C_{10}H_8ClNOS$	C, H, N	*b*

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] Undistilled product. [d] Sample chromatographed. [e] See ref 21. [f] See ref 22. [g] See ref 23. [h] See ref 24. [i] See ref 25. [j] See ref 26.

ppm in the NMR when Me_2SO-d_6 was used as the solvent. This latter observation indicates destruction of the hydrogen bonded enol form by Me_2SO-d_6. The ring closure of **31** to give **12** was effected in refluxing acetyl chloride by the procedure utilized by Bauer and Safir[16] to cyclize 4,4,4-trifluoro-1-(4-pyridyl)-1,3-butanedione 3-oxime. Apparently, acetyl chloride forms an acetylated oxime that can undergo ring closure to the isoxazole by displacement of the acetoxy group. As a by-product, the acetylated oxime **32** was isolated. Presumably, **32** arises from acetylation of the *E* isomer formed by acid-catalyzed rearrangement of **31**. The *E* stereochemistry was assigned to **32** on the basis of a carbonyl bond at 1780 cm^{-1} in the IR and a two-proton singlet at 3.8 ppm in the NMR attributable to the methylene protons, thereby indicating its existence in a nonenolizable form. This accounts for its lack of cyclization due to unfavorable stereochemistry for displacement of the acetoxy group.

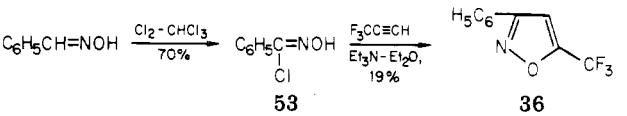
The 3-amino analogue **15** was synthesized from phenylpropionitrile[17] by the procedure of Iwai and Nakamura.[9] Diazotization of **15**, followed by reaction with potassium iodide, afforded the iodoisoxazole **11**. Reaction of **15** with methyl isocyanate, trifluoroacetic anhydride, and methyl chloroformate gave, respectively, the urea **16**, the trifluoroacetamide **17**, and the carbamate **18**.

Previous investigations of the bromination and chlorination of 5-phenylisoxazoles[7,18,19] have shown that substitution occurs at the 4 position of the isoxazole ring in preference to the phenyl ring. In agreement with these observations, chlorination of **17** and **1** with sulfuryl chloride gave, respectively, the corresponding 4-chloroisoxazoles **23** and **20**.[10] Similarly, chlorination and bromination of **15** with sulfuryl chloride or bromine in carbon tetrachloride afforded **21** and **22**.

Nitration of **1** and **2** with 90% nitric acid afforded only the phenyl ring nitrated products **6** and **7**. This agrees with the observations of Sokolov and co-workers[20] that nitration of 5-phenyl- and 5-(4-chlorophenyl)isoxazole with a concentrated nitric–sulfuric acid mixture occurred only on the phenyl ring.

3-Hydroxy-5-phenylisoxazole (**33**) and its *p*-chloro analogue **14** were synthesized according to the method of Iwai and Nakamura.[9] Methanesulfonylation of **33** gave **19**.

Scheme III



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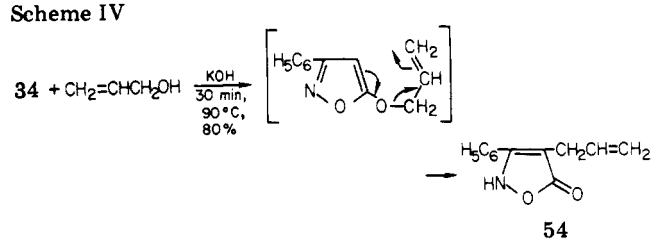
3-Arylisoxazoles. To determine if the activity of **1** and its analogue could be found in other systems, the isomeric 3-phenyl-5-chloroisoxazole[21] **34** (Table III) was prepared and found to demonstrate a high level of anthelmintic activity. This finding prompted investigation of 3-phenylisoxazoles with varying functionality at the 4 and 5 positions of the isoxazole ring.

3-Phenyl-5-chloroisoxazole (**34**) and its 5-bromo analogue **35** were synthesized by reaction of the appropriate phosphoryl halide with 3-phenyl-5(4*H*)-isoxazolone[27] according to the procedure of Adembri and Tedeschi.[21] The trifluoromethyl analogue **36** was prepared (Scheme III) by the 1,3-dipolar addition of benzonitrile oxide to 3,3,3-trifluoropropyne. The benzonitrile oxide was generated in situ by the action of triethylamine on benzhydroximidoyl chloride (**53**), which in turn was obtained by chlorination of benzaldehyde oxime according to the procedure of Bianchetti.[28] 3-Phenylisoxazole (**37**) was prepared by the 1,3-dipolar addition of benzonitrile oxide to vinyl acetate, followed by acid-catalyzed elimination of acetic acid according to the procedure of D'Alcontres and Grunanger.[22]

The analogues having alkoxyl, alkylthio, or amino substituents at the 5 position, **38–43** and **46–48**, were synthesized by displacement of the chlorine of **34** with the appropriately substituted alkoxide, mercaptide, or amine. Treatment of **42** with 1 equiv of hydrogen peroxide afforded the sulfoxide **44**, while excess hydrogen peroxide treatment gave **45**. During the reaction of **34** with allyl alcohol and potassium hydroxide, the initially formed displacement product readily underwent a Claisen rearrangement (Scheme IV) to afford 4-allyl-3-phenyl-5(4*H*)-isoxazolone **54**. Treatment of **54** with phosphoryl chloride and triethylamine afforded **49**.

Chlorination of **38** with sulfuryl chloride afforded the 4-chloro-5-methoxy analogue **50**. Nishiwaki[29] reported the thermal rearrangement of 5-alkoxy-3-phenylisoxazoles to

Scheme IV



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2-phenyl-1-azirine-3-carboxylates at atmospheric pressure. This author also claims stability for 5-alkoxyisoxazoles under reduced pressure. However, in our hands, **50** underwent partial rearrangement upon vacuum distillation to give a product mixture. Therefore, **50** was utilized as an undistilled product. Treatment of **50** with concentrated hydrochloric acid gave 4-chloro-3-phenyl-5(2*H*)-isoxazolone (**55**), which upon reaction with phosphoryl chloride and triethylamine afforded **51**. Base-mediated displacement of the 5-chlorine of **51** with methyl mercaptide gave **52**.

Biological Results and Discussion. The compounds in Tables I–III were tested for anthelmintic activity in *Nippostrongylus braziliensis* (rat roundworm) parasitized Sprague–Dawley derived albino rats as previously described,[30] except that the rats were parasitized 17 days before chemotherapeutic dosing. The relative activities are expressed in terms of their minimum effective dose (MED), i.e., that dose which effected a 75% clearance of the parasite as compared to infected nontreated controls. In general, the compounds were tolerated at a dose of 500 mg/kg po, the maximum dose tested.

Only compounds in the isoxazole series demonstrated activity. In the 5-phenyl series only the 3-bromo (**9**) and 3,4-dichloro (**20**) analogues were as active as the lead compound **1**, whereas the 4-chlorophenyl (**2**) and 2,4-dichlorophenyl (**3**) analogues were slightly less active.

Replacement of the 3-chlorine of **1** with iodine (**11**) resulted in a large decrease in activity. Replacement with trifluoromethyl (**12**), amino (**15**), 3-methylureido (**16**), trifluoroacetamido (**17**), methoxycarbamoyl (**18**), methanesulfonyloxy (**19**), or hydrogen (**13**) resulted in loss of activity. Similarly, replacement of the 3-chlorine of **2** by hydroxy (**14**) or the 3-chloro group of **20** by trifluoroacetamido (**23**) or amino (**21**) afforded inactive analogues. The 4-bromo (**22**) analogue of **21** also was inactive. In contrast to the equal activity of **1** and **9**, the 3-bromo (**10**) analogue of the 4-chlorophenyl (**2**) compound was significantly less active.

Substitution on the phenyl ring of **1** resulted in decreased activity. Whereas **2** and **3** were only slightly less active than **1**, the 3,4-dichloro (**4**) and tolyl (**5**) analogues were significantly less active. Nitro substitution on the phenyl ring (**6**, **7**) resulted in loss of activity. Replacement of the phenyl ring of **1** by thienyl (**8**) decreased activity.

In comparison to the 5-phenyl series, the most active compounds in the 3-phenyl series, the 5-chloro (**34**) and 5-bromo (**35**) compounds, are one order of dilution more active. Within the 3-phenyl series, the 5-methoxy (**38**), 5-ethoxy (**39**), and 5-methylthio (**42**) analogues are slightly less active than **34** and **35**. The 5-ethylthio (**43**), 5-(4-pentenyloxy) (**40**), 5-dimethylamino (**47**), and 5-morpholino (**48**) analogues were significantly less active. The 5-hydrogen (**37**), 5-trifluoromethyl (**36**), 5-ethylthioethoxy (**41**), and 5-benzylthio (**46**) analogues were inactive. Oxidation of the sulfur in **42** to the sulfoxide (**44**) and sulfone (**45**) resulted in loss of activity.

In contrast to the 5-phenyl series, where the 3,4-dichloro analogue (**20**) was highly active, substitution at the 4 position of the isoxazole ring in the 3-phenyl series is apparently forbidden for activity. Substitution at the 4 position of **34** with an allyl group (**49**) or chlorine (**51**) resulted in inactive compounds. Similarly the 4-chloro-5-methoxy (**50**) and 4-chloro-5-methylthio (**52**) analogues were inactive. The results presented herein imply that while certain 3-phenyl- and 5-phenylisoxazoles demonstrate anthelmintic activity against the rat roundworm, *Nippostrongylus braziliensis*, they do not act biologically at a common receptor site.

Experimental Section

Intermediates and products prepared by literature procedures had analytical and physical constants in agreement with reported values. Structural determinations of novel compounds were based on microanalyses and supported by IR and NMR spectra obtained, respectively, on a Perkin-Elmer Model 727 spectrophotometer and a Varian A-60 NMR spectrometer. Where analyses are represented only by symbols of the elements in Tables I–III, analytical results obtained for those elements were within ±0.4% of the theoretical value. In the following experimental procedures the term stripped is used to indicate solvent removal via a rotary evaporator under reduced pressure.

3-Chloro-1-(3,4-dichlorophenyl)-1-propanone was synthesized in a 70% yield of white crystals, mp 59–60 °C, by the aluminum chloride catalyzed reaction between 1,2-dichlorobenzene and 3-chloropropionyl chloride according to the procedure of Kenner and co-workers.[13] Anal. ($C_9H_7Cl_3O$) Cl.

3-Chloro-1-(2,4-dichlorophenyl)-1-propanone was synthesized from 1,3-dichlorobenzene and 3-chloropropionyl chloride in a 90% yield of molecularly distilled [125 °C (1.0 μm)] product according to the procedure of Kenner and co-workers.[13] No attempt was made to separate a minor isomer present in the distilled material since the nitro ketone **26** was obtained as a crystalline solid in the subsequent reaction.

1-(4-Chlorophenyl)-3-nitro-1-propanone (25). The following procedure, modified from that of Fusco and Rossi,[11] is representative of the synthesis of the 1-aryl-3-nitro-1-propanones (Table II).

A solution of 90 g (0.44 mol) of 3-chloro-1-(4-chlorophenyl)-1-propanone,[31] 60 g (0.87 mol) of $NaNO_2$, and 20 g (0.16 mol) of phloroglucinol in 200 mL of DMF was stirred at 25 °C for 18 h and then poured over ice. The resulting solid was collected and recrystallized from hexane to give 82 g (86%) of white **25**, mp 79–80 °C.

3-Chloro-5-phenylisoxazole[1] **(1).** The following procedure is representative of the synthesis of 3-chloro- and 3-bromoisoxazoles by the acid-mediated cyclization of 1-aryl-3-nitro-1-propanones.

A suspension of 30 g (0.168 mol) of **24** in 200 mL of concentrated HCl in a glass bomb was heated in a steam bath for 24 h. The resulting two-phase system was extracted with pentane and the combined extracts were stripped. The residual liquid was chromatographed through silica gel G (Grace, grade 62) with hexane as eluent to give, upon recrystallization from pentane, 15 g (50%) of white **1**, mp 36–37 °C (lit.[1] mp 38 °C).

5-Phenyl-3-(trifluoromethyl)isoxazole (12) and 4,4,4-Trifluoro-1-phenyl-1,3-butanedione 3-*O*-Acetyloxime (32). A solution of 17 g (0.074 mol) of **31**[15] in 75 mL of AcCl was refluxed 5 h, the excess AcCl was stripped, and the residue recrystallized from hexane to give 4 g (30%) of white **32**, mp 116 °C. The hexane mother liquor was stripped and the residue recrystallized from MeOH to give 10 g (67%) of white **12**, mp 81–81.5 °C. Anal. (**32**) ($C_{12}H_{10}F_3NO_3$) C, H, N.

3-Iodo-5-phenylisoxazole (11). A 10-mL H_2O solution of 2.35 g (0.034 mol) of $NaNO_2$ was added slowly below the surface to a stirred 25-mL concentrated HCl–25-mL H_2O solution of 5.0 g (0.031 mol) of **15**[9] while maintaining the reaction temperature at less than 5 °C. After the addition was complete, the reaction mixture was stirred for 10 min. To this mixture a 20-mL H_2O solution of 7.9 g (0.048 mol) of KI was added. The reaction mixture was stirred at ambient temperature for 20 h and then extracted with CH_2Cl_2. The extracts were washed with 25% $NaHSO_3$ and with H_2O, dried ($MgSO_4$), and stripped to give 5.2 g of crude material. Dry column chromatography of the crude material through silica gel G with THF–EtOAc–hexane (4:30:66),

followed by recrystallization from hexane, gave 0.6 g (7%) of cream-colored **11**, mp 106.5–109 °C.

1-Methyl-3-(5-phenyl-3-isoxazolyl)urea (16). A solution of 1.6 g (0.01 mol) of **15** and 0.57 g (0.01 mol) of methyl isocyanate in 50 mL of C_6H_6 was refluxed for 4 h and then allowed to stand for 16 h at ambient temperature. Recrystallization of the resulting solid from EtOH gave 1.5 g (69%) of white **16**, mp 200–201 °C.

2,2,2-Trifluoro-*N*-(5-phenyl-3-isoxazolyl)acetamide (17). To a stirred 200-mL KOH-dried C_5H_5N solution of 18.0 g (0.113 mol) of **15** at 5–10 °C was added dropwise 31.5 g (0.15 mol) of trifluoroacetic anhydride. The reaction mixture was allowed to stir at ambient temperature for 1 h and poured over ice and this mixture was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and stripped and the residue was recrystallized from EtOH–CH_2Cl_2 to give 28.8 g (95%) of tan **17**, mp 210–210.5 °C.

5-Phenyl-3-isoxazolecarbamic Acid Methyl Ester (18). To a stirred 50-mL CH_2Cl_2 solution of 8.0 g (0.05 mol) of **15** and 5.0 g (0.05 mol) of Et_3N at 0–5 °C was added dropwise 4.8 g (0.05 mol) of methyl chloroformate. The reaction mixture was refluxed for 1 h, cooled, washed with H_2O, and stripped. Recrystallization of the resulting solids from Et_2O gave 7.0 g (67%) of **18**, mp 139–140 °C.

4-Chloro-5-phenyl-3-(2,2,2-trifluoroacetamido)isoxazole (23). A 1.60-g (0.0063 mol) sample of **17** in 20 mL of SO_2Cl_2 was heated on a steam bath for 20 min. The excess SO_2Cl_2 was stripped and the residue was taken up in CH_2Cl_2, treated with charcoal, and triturated with hexane to give 1.2 g (66%) of white **23**, mp 138.5–139.5 °C.

3-Amino-4-chloro-5-phenylisoxazole (21). A 1.0-g (0.0063 mol) sample of **15** upon solution in 25 mL of SO_2Cl_2 gave an immediate exothermic evolution of gas and a white precipitate. The excess SO_2Cl_2 was stripped and the resulting solid taken up in CH_2Cl_2, washed with saturated $NaHCO_3$ solution and H_2O, dried ($MgSO_4$), and stripped to give 1.2 g of yellow gum containing two major components as evidenced by TLC (THF–EtOAc–hexane, 4:30:66). Dry column chromatography of this gum through silica gel G using the above solvent gave 350 mg of **21** and 400 mg of yellow gum whose NMR was consistent with the 3-chloroamino analogue of **21**. Heating this yellow gum in 10 mL of concentrated HCl on a steam bath, followed by dilution with H_2O, gave an additional 100 mg of crude **21**. Recrystallization of the combined samples from hexane–CH_2Cl_2 gave 350 mg (28%) of tan **21**, mp 132–133 °C.

3-Amino-4-bromo-5-phenylisoxazole (22). A solution of 1.0 g (0.006 mol) of **15** and 1.0 g (0.006 mol) of Br_2 in 40 mL of CCl_4 was refluxed for 1.5 h and cooled and the solvent decanted from the resulting solid. The solid was taken up in CH_2Cl_2, washed with 10% NaOH and H_2O, dried ($MgSO_4$), and stripped to give 0.9 g of red solid. Dry column chromatography of this solid through silica gel G using THF–EtOAc–hexane (4:16:80), followed by recrystallization from CH_2Cl_2–hexane, gave 0.35 g (23%) of white **22**, mp 142.5–144 °C.

3-Chloro-5-(4-nitrophenyl)isoxazole (6). A 10-g (0.056 mol) sample of **1** was added to 33 mL of 90% HNO_3 at 10 °C. The reaction mixture was allowed to warm to room temperature and then poured onto ice and the resulting solid collected. Recrystallization of the solid from EtOAc gave 6.0 g (48%) of cream **6**, mp 213–214 °C.

3-Chloro-5-(4-chloro-3-nitrophenyl)isoxazole (7). This compound was synthesized in 35% yield, mp 146.5–148 °C, from **2** by the procedure described for the synthesis of **6**, except that the reaction mixture stood at room temperature for 3 h.

5-Phenyl-3-isoxazolol Methanesulfonate (19). To a stirred 20 °C solution of 8 g (0.05 mol) of **33**[9] in 20 mL of 10% NaOH was added dropwise 5.72 g (0.05 mol) of methanesulfonyl chloride. The reaction mixture was stirred at ambient temperature for 30 h; the resulting solid was collected and recrystallized from hexane–Et_2O to give 8.0 g (70%) of white **19**, mp 94–95 °C.

3-Phenyl-5-(trifluoromethyl)isoxazole (36). To a stirred 250-mL anhydrous Et_2O solution of 9.0 g (0.053 mol) of benzhydroximidoyl chloride[28] at −5 °C was added dropwise 5.3 g (0.053 mol) of Et_3N. This mixture was cooled to −10 °C while 4.7 g (0.05 mol) of 3,3,3-trifluoropropyne was passed into the reaction. A dry ice condenser was used to prevent escape of the 3,3,3-trifluoropropyne. The resultant slurry was allowed to come to room temperature over a 4-h period. Water was added and the Et_2O layer was separated and stripped. The residue was extracted with hot hexane which upon cooling afforded a white solid, mp 73–76 °C. This solid was mixed with CCl_4, insolubles were filtered, and the filtrate was cooled to give crystals, mp 74–76 °C. These crystals were vacuum sublimed at 100 °C (0.1 mm) and the sublimate was recrystallized from pentane to afford 2 g (19%) of white **36**, mp 78–79 °C.

5-(Ethylthioethoxy)-3-phenylisoxazole (41). The following is representative of the procedure used to synthesize the 5-alkoxyl-, 5-alkylthio-, and 5-ethylthioethoxyisoxazoles **40**, **42**, and **46**. A 25-mL THF solution of 9.0 g (0.05 mol) of **34** was added to a stirred 20-mL THF suspension of 1.2 g (0.05 mol) of NaH, obtained by hexane washing 2.4 g of 50% NaH–mineral oil dispersion. The reaction mixture was refluxed for 10 min, allowed to stand at ambient temperature 16 h, and stripped, and H_2O was added to the residue. The insoluble crystals were collected and recrystallized from hexane to give 8.1 g (65%) of **41**, mp 64–65 °C.

5-(Methylsulfinyl)-3-phenylisoxazole (44). A solution of 5.0 g (0.026 mol) of **42** and 3.5 mL of 30% H_2O_2 in 10 mL of AcOH was heated on a steam bath for 1 h and diluted with H_2O and the resulting oil was extracted with CH_2Cl_2. The extracts were washed with Na_2CO_3 solution, dried ($MgSO_4$), and stripped. The residue was recrystallized from C_6H_6–hexane to give 4.2 g (78%) of white **44**, mp 87–88 °C.

5-(Methylsulfonyl)-3-phenylisoxazole (45). A solution of 15 g (0.079 mol) of **42** and 20 mL of 30% H_2O_2 in 50 mL of AcOH was heated at 65 °C for 17 h. The solvent was stripped and the resulting solid was recrystallized from CCl_4 to give 12 g (70%) of white **45**, mp 95–96 °C.

4-(3-Phenyl-5-isoxazolyl)morpholine (48). A mixture of 9.0 g (0.05 mol) of **34** and 10 g (0.11 mol) of morpholine was refluxed 15 min at which time the mixture solidified. The solid was washed with H_2O and recrystallized from hexane to give 7 g (60%) of tan **48**, mp 99–100 °C.

3-Phenyl-4-(2-propenyl)-5(2*H*)-isoxazolone (54). A 100-mL 2-propenol solution of 6 g (0.11 mol) of KOH was refluxed with azeotropic removal of H_2O until the head temperature reached 97 °C. To this cooled solution was added 9.0 g (0.05 mol) of **34** and the mixture refluxed 30 min. The excess 2-propenol was stripped under vacuum and the residue was extracted with C_6H_6. The C_6H_6-insoluble residue was dissolved in H_2O and then acidified with 6 N HCl and the resulting precipitate was collected. Recrystallization of the precipitate from CCl_4 afforded 8.0 g (80%) of white **54**: mp 87–88 °C; IR (CH_2Cl_2) 3310 (NH), 1810, 1750 cm^{-1} (C=O); NMR ($CDCl_3$) 2.8–3.2 (m, 2 H, CH_2), 4.0 (t, 1 H, CH), 4.8–5.9 (m, 3 H, $-CH=CH_2$), 7.6 ppm (m, 5 H, C_6H_5). The IR and NMR indicate that **54** can exist in two tautomeric forms. Anal. ($C_{12}H_{11}NO_2$) H, N; C: calcd, 71.6; found, 71.1.

5-Chloro-3-phenyl-4-(2-propenyl)isoxazole (49). This compound was synthesized in an 80% yield, bp 105–106 °C (0.2 mm), from **54**, $POCl_3$, and Et_3N by the procedure described by Adembri and Tedeshchi[21] for the synthesis of **34**.

4-Chloro-5-methoxy-3-phenylisoxazole (50). To a stirred slurry of 33 g (0.19 mol) of **38** in 100 mL of CH_2Cl_2 at 0 °C was added dropwise 15 mL (0.19 mol) of SO_2Cl_2. The temperature of the reaction mixture rose to 35 °C. When the reaction was complete, as indicated by GLC, the solution was washed with H_2O, dried ($MgSO_4$), and stripped to give 37.4 g (94%) of light yellow **50** as an oil.

4-Chloro-3-phenyl-5(2*H*)-isoxazolone (55). A mixture of 36 g (0.17 mol) of **50** and 100 mL of concentrated HCl was stirred at 80–90 °C for 30 min and cooled to 10 °C and the resulting precipitate was recrystallized from $CHCl_3$ to yield 14 g (42%) of **55**, mp 146–148 °C. Anal. ($C_9H_6ClNO_2$) C, H, N.

4,5-Dichloro-3-phenylisoxazole (51). This compound was synthesized in 73% yield, bp 81–85 °C (0.015 mm), from **55**, by the method for the synthesis of **49**.

4-Chloro-5-(methylthio)-3-phenylisoxazole (52). An excess of CH_3SH was bubbled into a 50-mL anhydrous THF suspension of 0.7 g of 50% NaH–mineral oil (0.014 mol of NaH) containing 3.0 g (0.014 mol) of **51**. The mixture was heated at 60 °C for 1 h and then the solvent volume was reduced by stripping at less than 35 °C. This mixture was poured into H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried ($MgSO_4$), and stripped. The resulting liquid was dry column chromatographed through silica gel G using hexane–THF (96:4) as solvent

to give 1.9 g (60%) of yellow liquid **52**.

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Anticoccidial 1-Substituted 4(1*H*)-Pyridinone Hydrazones

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4-Chlorobenzaldehyde 1-(4-chlorophenyl)-4(1*H*)-pyridinylidene hydrazone fluorosulfonate (**4**) was found to have excellent anticoccidial activity in chickens. The synthesis and biological evaluation of related analogues are presented. Presumably **4** shares a common mechanism of action with robenidine (**25**) since it was not active on a robenidine tolerant strain of *E. tenella*. Structural comparisons of the two molecules are presented.

As part of our continuing search for bioactive molecules, some 1-substituted 1,4-dihydro-4-iminopyridines were synthesized for screening. One derivative, 4-chlorobenzaldehyde 1-(4-chlorophenyl)-4(1*H*)-pyridinylidene hydrazone fluorosulfonate (**4**), showed broad-spectrum anticoccidial activity in chickens. Structure–activity relationships within the series were explored through the synthesis and testing of some close analogues.

Chemistry. The 1,4-dihydro-4-iminopyridines which were prepared in this study are listed in Tables I and II. Syntheses of a few 1-aryl-1,4-dihydro-4-iminopyridines had been accomplished previously.[1] The methods used involved the arylation of 4-aminopyridine with reactive aryl halides or aryliodonium halides. In the present work we developed a more general route beginning with the reaction of substituted anilines with chelidonic acid. In a typical example, reaction of 4-chloroaniline with chelidonic acid gave via decarboxylation of the intermediate chelidamic acid, 1-(4-chlorophenyl)-4(1*H*)-pyridinone (**23**).[2] Alkylation of **23** with methyl fluorosulfonate afforded the intermediate **24** which on reaction with hydrazine yielded 1-(4-chlorophenyl)-4(1*H*)-pyridinone hydrazone fluorosulfonate (**2**). Compound **2** readily condensed with 4-chlorobenzaldehyde to give **4**. A series of aldehydes and 4-chloroacetophenone was similarly allowed to react with **2** yielding analogous hydrazones. Reaction of **24** with ammonia gave 1-(4-chlorophenyl)-4(1*H*)-pyridinimine (**1**). Condensation of 4-hydrazinopyridine[3] with 4-chlorobenzaldehyde gave 4-chlorobenzaldehyde 4-pyridylhydrazone (**19**) which was alkylated with methyl iodide or 4-chlorobenzyl chloride to yield the 1-alkyl derivatives **20** and **22**.

Biological Activity. Tables I and II list the compounds which were investigated in this study. Table I summarizes results of variations of the lead structure **4** at the 4 position and Table II presents the results of variations at the 1 position.

Compounds were evaluated for anticoccidial activity in chickens[4] carrying an infection of either *E. acervulina* or *E. tenella* by standard assay methods indicated in the footnotes of Tables I and II. All but one of the active compounds showed activity against both species of coccidia, but there was a trend toward higher activity against *E. tenella* throughout the series. The most potent group of monosubstituted compounds **4**, **6–8**, **10**, and **11** contained halogen or halogen-like groups in the 4 position. Analogues containing unsubstituted phenyl (**3**), 2-chlorophenyl (**5**), or substituted 4-aminophenyl (**12**, **13**) were inactive. Likewise, replacement of the methylidyne