was treated with excess HCl and the precipitate was collected by filtration and crystallized from EtOH. 2-({3-[Bis(2-hydroxyethyl)amino]propyl}amino)-3-chloro-1,4-naphthoquinone hydrochloride (XIXb) was obtained (24.5 g, 72%) as orange crystals, mp 149–151°.

5,8-Isoquinolinedione 8-Oxime (XXXI).—5-Isoquinolinol (7.3 g, 0.05 mole) was dissolved in 50 ml of H_2O and 6.5 ml of concentrated HCl and was treated at 5–10° with a solution of 3.5 g (0.05 mole) of $NaNO_2$ in H_2O. The mixture was stirred at 5–10° for 3 hr and the product was collected by filtration and crystallized from DMF. The product (1.4 g, 16%) was obtained as olive crystals, mp 235° dec. *Anal.* ($C_9H_6N_2O_2$) C, H, N.

2-(Piperidinomethyl)-1-naphthol.—A solution of 72.0 g (0.5 mole) of 1-naphthol, 43.0 g (0.5 mole) of piperidine, and 38 ml (0.5 mole) of 40% formalin in 500 ml of EtOH was heated under reflux on a steam bath for 2.5 hr and chilled. The crystalline precipitate that separated was collected by filtration and dried at 45° *in vacuo* (70.1 g, mp 120–132°). The crude product was crystallized twice from EtOH, slurried into 500 ml of H_2O, and treated with 50 ml of concentrated HCl. The precipitate was collected and heated to 90° in 2 l. of H_2O, and the mixture was filtered. The insoluble material was discarded. The filtrate was treated with decolorizing charcoal, chilled, and made strongly alkaline with 50% NaOH. The precipitate was collected, washed with H_2O, and dried at 65° *in vacuo*. Crystallization from EtOH afforded 33.0 g (27%) of pure product, mp 134–135°. *Anal.* ($C_{16}H_{19}NO$) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Paul E. Thompson and coworkers for the antischistosome testing, Mrs. Maria L. Zamora for chemical assistance, Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for the spectral data.

Novel Anthelmintic Agents. IV. Noncyclic Amidines Related to Pyrantel

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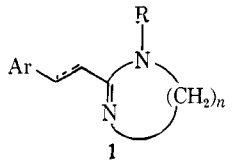
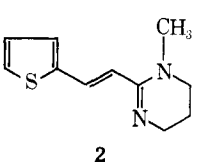
Received July 14, 1969

Anthelmintic activity has been discovered among some N,N-disubstituted thiophenepropionamidines and thiopheneacrylamidines. Activity is associated with compounds in which one N substituent is Me and the other is Me, Et, allyl, MeO, or MeNH. Substitution at the N′ position abolishes activity. Synthetic methods and structure–activity relationships are discussed.

The discovery of a new class of anthelmintic agents was reported in the first papers of this series.[1,2] It was observed that certain compounds of the type represented by **1** are highly effective against the intestinal nematode *Nematospiroides dubius* when tested in mice; indeed one member of the series, pyrantel (**2**), has undergone extensive evaluation in domestic animals and in man.



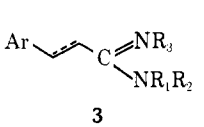
1



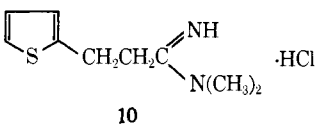
2

Ar = C_4H_3S, C_4H_3O, C_6H_5
R = H, CH_3
n = 2,3
--- = optional bond

In pursuing the structure–activity relationships in this series, we became concerned over the question of whether a cyclic amidine system was essential to good anthelmintic activity. Therefore, a number of noncyclic compounds (**3**) were prepared and tested. Very early in this work N,N-dimethyl-2-thiophenepropionamidine (**10**) emerged as an analog active not only against *N. dubius* but also against the tapeworm *Hymenolepis nana;* other active compounds were subsequently discovered. The present work will describe the structure–activity relationships within the noncyclic series of compounds, and will attempt to correlate these findings with those of the cyclic series.



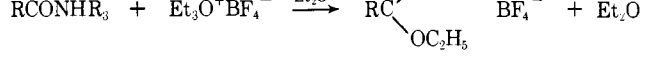
3



10

Chemistry.—Most of the compounds under discussion were prepared by the action of imidate salts on amines or aminelike substances. However, when an amine was more conveniently available as its HCl salt, an alternate combination was employed: the imidate salt was converted to its free base, and the base was then allowed to react with the amine salt.

Three general procedures were used to prepare the requisite imidate salts. Method A followed the technique of Pinner, *i.e.*, the reaction of a nitrile with dry HCl and an alcohol in dry Et_2O. This method is useful for preparing N-substituted and N,N-disubstituted amidines, but is not suitable for the preparation of N′-substituted compounds. Intermediates for the latter substances are readily prepared by method B, the formation of ethyl N-alkylimidates by the action of $Et_3O^+BF_4^-$ on an N-alkylamide. Some α,β-unsaturated nitriles tended to react very slowly or not at all in the Pinner reaction; in such instances the reaction of the corresponding amides with 1,3-propane sultone (method C) served to prepare the desired imidate salt.[3]

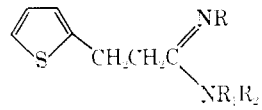


(1) W. C. Austin, W. Courtney, J. C. Danilewicz, D. H. Morgan, R. L. Cornwell, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, J. W. McFarland, and V. J. Theodorides, *Nature*, **212**, 1273 (1966).

(2) J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, **12**, 1066 (1969).

(3) W. Ried and E. Schmidt, *Ann.*, **676**, 114 (1964).

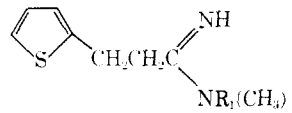
Table I



No.	R_1	R_2	R_3	Salt	Preparative method[a]	Mp, °C	Recrystn solvent	Formula[f]	MED,[d] mg/kg	Days given
2	(Pyrantel)			Tartaric					12.5	1
4	H	H	H	HCl	A1	173–175	MeOH–*i*-PrOH	$C_7H_{11}ClN_2S$[g]	>250	3
5	CH_3	H	H	Maleic	A3	129–130	MeOH–Me_2CO	$C_{12}H_{16}N_2O_4S$	>500	3
6	C_2H_5	H	H	Maleic	A3	133–135	MeCN	$C_{13}H_{18}N_2O_4S$	>250	3
7	C_3H_7	H	H	Maleic	A3	125–128	Me_2CO	$C_{14}H_{20}N_2O_4S$[e]	>500	3
8	$CH(CH_3)_2$	H	H	Maleic	A3	113–116	EtOAc–Me_2CO	$C_{14}H_{20}N_2O_4S$	>250	3
9	$C(CH_3)_3$	H	H		A2	101–104	C_6H_{14}	$C_{11}H_{18}N_2S$	>500	3
10	CH_3	CH_3	H	HCl	A1	163–165[h]	MeOH–Me_2CO	$C_9H_{15}ClN_2S$	50[e]	3
11	C_2H_5	C_2H_5	H	Fumaric	A3	107–110	MeOH–MeCN	$C_{15}H_{22}N_2O_4S$	>100	3
12	C_2H_5	H	CH_3	HBF_4	B1	130–132	EtOAc	$C_{10}H_{17}BF_4N_2S$	>250	3
13	CH_3	CH_3	CH_3	HBF_4	B1	200–202	MeOH	$C_{10}H_{17}BF_4N_2S$	>250	3
14	OH	H	H		D2	70–72	C_6H_6	$C_7H_{10}N_2OS$	>500	3
15	OCH_3	H	H	HCl	A1	122–124	MeOH–Me_2CO	$C_8H_{13}ClN_2OS$	>500	2
16	$N(CH_3)_2$	H	H		A2	102–104	i-Pr_2O	$C_8H_{15}N_3S$	>250	3

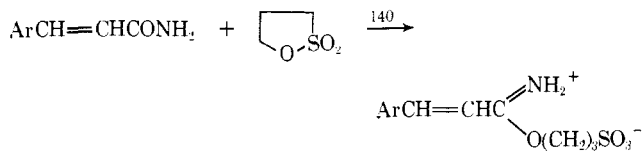
[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] A dimorphic form of this material melts at 179–182°. [c] N: calcd, 9.0; found, 8.5. [d] Minimum effective dose against *N. dubius*. [e] The MED of this compound against *H. nana* is 25 mg/kg, three daily doses. [f] All compounds were analyzed for C, H, N unless otherwise noted. [g] Not analyzed.

Table II



No.	R_1	Salt	Preparative method[b]	Mp, °C	Recrystn solvent	Formula[d]	MED,[c] mg/kg	Days given
2	(Pyrantel)	Tartaric					12.5	1
10	CH_3	HCl					50	3
17	C_2H_5	SSA[a]	A3	191–193	MeOH–EtOAc	$C_{17}H_{22}N_2O_6S_2$	100	3
18	C_3H_7	SSA[a]	A3	161–162	MeOH–Me_2CO	$C_{18}H_{24}N_2O_6S_2$	>100	3
19	$CH(CH_3)_2$	SSA[a]	A3	168–170	MeOH–Me_2CO	$C_{18}H_{24}N_2O_6S_2$	>250	3
20	C_4H_9	HCl	A1	99–101	MeOH–EtOAc	$C_{12}H_{21}ClN_2S$	>100	3
21	$CH_2CH{=}CH_2$	Fumaric	A3	116–118	MeOH–EtOAc	$C_{15}H_{20}N_2O_4S$	100	3
22	$CH_2C{\equiv}CH$	Maleic	A3	105–106	i-PrOH–i-Pr_2O	$C_{15}H_{18}N_2O_4S$	>250	1
23	CH_2CF_3	SSA[a]	A3	205–207	MeOH–i-PrOH	$C_{17}H_{19}F_3N_2O_6S_2$	>500	3
24	$CH_2CH_2N(CH_3)_2$	HCl	A1	108–110	Me_2CO	$C_{12}H_{22}ClN_3S$	>500	3
25	$CH_2CH_2SO_3H$		A2	245–251	H_2O	$C_{10}H_{16}N_2O_3S_2$	>500	3
26	OH	HCl	A1	157–159	i-PrOH	$C_8H_{13}ClN_2OS$	>250	3
27	OCH_3	HCl	A1	125–127	i-PrOH–i-Pr_2O	$C_9H_{15}ClN_2OS$	50	3
28	$NHCH_3$	HCl	A1	155–156	MeOH–Me_2CO	$C_8H_{16}ClN_3S$	125	3

[a] SSA = sulfosalicylic acid. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] Minimum effective dose against *N. dubius*. [d] See Table I, footnote *f*. [e] See Table I, footnote *g*.



The amidoxime **14** was prepared by the addition of H_2NOH to 2-thiophenepropionitrile (method D).

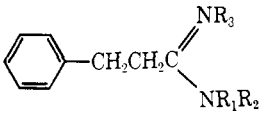
Assignment of the *trans* configuration to the double bond in **36** was based on the nmr spectrum of the compound in D_2O. It has been shown previously[2] that the coupling constant $J_{\alpha\beta}$ for the olefinic protons of *trans*-pyrantel (**2**) is 15.7 cps, and that $J_{\alpha\beta}$ for the *cis*-pyrantel isomer is 12.5 cps. The coupling constant $J_{\alpha\beta}$ for **36** is 15.8 cps, and is therefore consistent with the *trans* configuration.

Biological Evaluation.—Compounds were tested for anthelmintic activity in worm-infested mice. Each mouse harbored a natural infection of the pinworm *Syphacia obvelata*, and experimentally induced infections of the roundworm *Nematospiroides dubius* and the tapeworm *Hymenolepis nana*. Different substances were dissolved or suspended in a 1% carboxymethylcellulose solution at such a concentration that 0.4 ml delivered an appropriate dose to a 20-g mouse. Treated mice were dosed once each day for 1–3 days. Initially, a high dose (25–500 mg/kg depending on the compound's toxicity) was given to a group of four infected male mice. If anthelmintic activity was detected, the compound was tested at successively lower doses until a minimum effective dose (MED) was established. The MED is considered to be the lowest dose which causes at least a 90% reduction in the *N. dubius* worm burden as compared to untreated infected controls, or the lowest dose which will cause 100% clearance of *H. nana* or *S. obvelata*.

Further details of these testing methods are given by Howes and Lynch.[4] The results of these tests with

(4) H. L. Howes, Jr., and J. E. Lynch, *J. Parasitol.*, **53**, 1085 (1967).

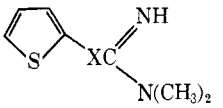
TABLE III



No.	R_1	R_2	R_3	Salt	Preparative method[a]	Mp, °C	Recrystn solvent	Formula[c]	MED,[b] mg/kg	Days given
29	H	H	H	HCl	A1	177–179	*i*-PrOH–Et_2O	$C_9H_{13}ClN_2$	>500	3
30	CH_3	CH_3	H	HCl	A1	164–166	MeCN–Me_2CO	$C_{11}H_{17}ClN_2$	>100	2
31	CH_3	H	CH_3	HBF_4	B1	137–139	MeOH–*i*-Pr_2O	$C_{11}H_{17}BF_4N_2$	>250	3
32	C_2H_5	H	CH_3	HBF_4	B1	153–155	Me_2CO	$C_{12}H_{19}BF_4N_2$	>250	3
33	CH_3	CH_3	CH_3	HBF_4	B1	209–211	H_2O–MeOH	$C_{12}H_{19}BF_4N_2$	>250	3

[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] Minimum effective dose against *N. dubius*. [c] See Table I, footnote *f*.

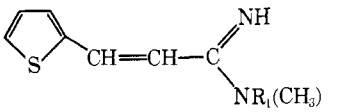
TABLE IV



No.	X	Salt	Preparative method[a]	Mp, °C	Recrystn solvent	Formula[c]	MED,[b] mg/kg	Days given
34	CH_2	HCl	A1	204–206	*i*-PrOH	$C_8H_{13}ClN_2S$	>100	3
10	$(CH_2)_2$	HCl				*d*	50	3
35	$(CH_2)_3$	HCl	A1	168–171	*i*-PrOH	$C_{10}H_{17}ClN_2S$	>100	1
36	*trans*-CH=CH	HCl	A1	254–257	MeOH–*i*-PrOH	$C_9H_{13}ClN_2S$	25	1

[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] Minimum effective dose against *N. dubius*. [c] See Table I, footnote *f*. [d] See Table I, footnote *g*.

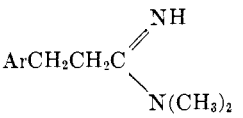
TABLE V



No.	R_1	Salt	Preparative method[b]	Mp, °C	Recrystn solvent	Formula[c]	MED,[d] mg/kg	Days given
2	(Pyrantel)	Tartaric					12.5	1
36	CH_3	HCl	A1	254–257	MeOH–*i*-PrOH	$C_9H_{13}ClN_2S$	25	1
37	C_2H_5	HCl	A1	193–195	MeOH–Me_2CO	$C_{10}H_{15}ClN_2S$	50	3
38	C_3H_7	SSA[a]	A3	183–186	MeOH–*i*-PrOH	$C_{18}H_{22}N_2O_6S_2$[e]	>250	3
39	C_4H_9	SSA[a]	A3	162–164	MeOH–*i*-PrOH	$C_{19}H_{24}N_2O_6S_2$	>250	3
40	$NHCH_3$	HPF_6	A4	144–146	EtOH	$C_9H_{14}F_6N_3PS$	250	3

[a] SSA = sulfosalicylic acid. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] C: calcd, 50.7; found, 51.2. [d] Minimum effective dose against *N. dubius*. [e] See Table I, footnote *f*.

TABLE VI



No.	Ar	Salt	Preparative method[a]	Mp, °C	Recrystn solvent	Formula[d]	MED,[b] mg/kg	Days given
2	(Pyrantel)	Tartaric				*g*	12.5	1
10	2-Thienyl	HCl				*g*	50	3
41	3-Methyl-2-thienyl	HCl	A1	180–181	*i*-PrOH	$C_{10}H_{17}ClN_2S$	100	1
30	Phenyl	HCl				*g*	>100	2
42	*o*-Tolyl	HCl	A1	165–166	*i*-PrOH	$C_{12}H_{19}ClN_2$	>100	1
43	2-Furyl	HCl	A1	150–152	MeOH–Me_2CO	$C_9H_{15}ClN_2O$	>250[c]	3

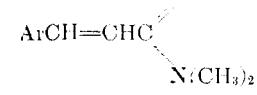
[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] Minimum effective dose against *N. dubius*. [c] The minimum effective dose against *H. nana* is, however, 125 mg/kg. [d] See Table I, footnote *f*. [e] See Table I, footnote *g*.

noncyclic amidines are reported in the last columns of Tables I–VII.

Structure–Activity Relationships.—Except where noted, all discussions of anthelmintic activity in this section refer to activity against *N. dubius*.

The noncyclic amidines described in this paper all bear gross structural resemblances to pyrantel. Each compound possesses (i) a simple aromatic system, (ii) an amidine function, and (iii) a chain of atoms connecting the aromatic ring with the amidine moiety (compare **1** and **3**). Because of this, many similarities in the structure–activity relationships between the cyclic and noncyclic amidines should be expected and are indeed found. Differences exist as well.

Table VII



No.	Ar	Salt	Preparative method[a]	Mp, °C	Recrystn solvent	Formula[c]	MED,[b] mg/kg	Days given
2	(Pyrantel)	Tartaric				*d*	12.5	1
36	2-Thienyl	HCl				*d*	25	1
44	3-Thienyl	HPF_6	A4	232–233	Me_2CO–C_6H_{14}	$C_9H_{13}F_6N_2PS$	250	3
45	3-Methyl-2-thienyl	HCl	A1	244–245	*i*-PrOH	$C_{10}H_{15}ClN_2S$	25	1
46	5-Methyl-2-thienyl	HCl	A1	263–265	MeOH–Me_2CO	$C_{10}H_{15}ClN_2S$	>125	3
47	Phenyl	HCl	C3	239–240	MeOH–Me_2CO	$C_{11}H_{15}ClN_2$	>25	3
48	*o*-Tolyl	HCl	A1	230–231	*i*-PrOH	$C_{12}H_{17}ClN_2$	>50	1
49	2-Furyl	HCl	C3	219–221	MeOH–Me_2CO	$C_9H_{13}ClN_2O$	>100	3

[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] Minimum effective dose against *N. dubius*. [c] See Table I, footnote *f*. [d] See Table I, footnote *g*.

Among the similarities the following should be noted. (1) In each series, 2-thienyl is the aromatic system most favorable for anthelmintic activity; the 3-thienyl system is also effective, but the corresponding 2-thienyl compounds are more potent. (2) Activity is found in compounds in which the aromatic and amidine systems are connected by ethylene (CH_2CH_2) or *trans*-vinylene (CH=CH) bridges; extending the bridge to trimethylene ($(CH_2)_3$) or shortening it to CH_2 leads to a decrease in activity (see Table IV). (3) Only a narrow range of structural changes may be made in the amidine system without loss of activity.

In order to investigate this latter point, we systematically prepared and tested the compounds described in Tables I, II, and V. The results show that (a) substitution of the amidine system is necessary for activity, (b) a single substituent is not sufficient, (c) N′ substitution is unfavorable for activity, and (d) N,N disubstitution leads to activity, but one substituent must be Me, and the second may be Me, Et, MeO, MeNH, or allyl. In keeping with observations made in the cyclic series, there appears to be an optimum value of lipophilicity associated with the more potent members of this acyclic series. Thus compounds insufficiently substituted on N are too hydrophilic to be active [conditions a and b above], while compounds with substituents larger than the Me/allyl combination are too lipophilic to be active (see examples in Table II). Other factors, possibly steric, must also play a role, because it is difficult to see why the allyl compound **21** is active, and why the related Pr (**18**), *i*-Pr (**19**), and propargyl (**22**) analogs are not. Similarly, the inactivity of the N-Et-N′-Me compound **12** is difficult to resolve with lipophilicity arguments alone (compare with **17**).

The principal difference to be found between the cyclic and noncyclic series is that among the cyclic amidines several phenyl analogs are active, and some are even highly potent; the corresponding compounds in the noncyclic series are not active at subtoxic doses (see Table VII). Other and more subtle differences between the two series exist, but discussion of these at this time does not seem profitable.

Generally, the noncyclic amidines do not exhibit significant activity against *S. obvelata*. Only **10** and its furyl analog **43** are active against *H. nana*, but **43** is inactive against *N. dubius*.

The results of this investigation show that noncyclic amidines can possess good anthelmintic activity.

Experimental Section

Boiling points are uncorrected; melting points were determined on a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.) and are corrected. The nitriles used as intermediates have been described elsewhere.[2] With one exception, the amines used were commercially available; 2,2,2-trifluoro-N-methylethylamine was prepared by a modification[5] of the method of Bissell and Finger.[6]

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The meaning of the symbol used under the heading "Preparative Method" in the various tables is as follows. The alphabetic character refers to the general synthetic methods illustrated in the Experimental Section; the arabic numeral refers to one of the following routines used to isolate or purify the final product: (1) isolate the salt directly from the reaction mixture and recrystallize; (2) isolate the product as a free base and recrystallize; (3) isolate the product as a free base, convert it to an appropriate salt, and recrystallize; (4) precipitate the HPF_6 salt from an aqueous solution of the crude HCl salt by the addition of 65% HPF_6.

Method A. N,N-Dimethyl-2-thiophenepropionamidine Hydrochloride (10).—To a stirred, ice-cooled solution of 2.5 *N* Me_2NH in MeOH (125 ml, 0.31 mole) was added portionwise 22.0 g (0.1 mole) of ethyl 2-thiophenepropioniminidate hydrochloride.[2] The mixture was allowed to warm to room temperature and, after standing overnight, the volatile components were evaporated under reduced pressure to furnish a yellow crystalline mass. One recrystallization from EtOH–Et_2O afforded colorless crystals, mp 156–162°, yield 11.9 g. A second crop afforded 4.3 g of material, mp 162–164°; the total yield was 16.2 g (74%). One recrystallization from MeOH–Et_2O afforded analytically pure **10**, mp 163–165°.

N-Methyl-2-thiophenepropionamide.—An ice-cooled, stirred solution of 31.6 g (0.2 mole) of 2-thiophenepropionic acid[7] and 125 ml of CH_2Cl_2 was treated portionwise with 25.4 g (0.2 mole) of $(COCl)_2$. After standing overnight at room temperature, the solution was evaporated under reduced pressure to furnish an oil which was stirred immediately into 100 ml of ice-cooled 25% aqueous $MeNH_2$. An oil precipitated, and after work-up there was obtained 17.4 g (51%) of the crude amide. The product was distilled to give material which solidified on standing, bp 140–145° (0.1 mm), mp 51–53°. *Anal.* ($C_8H_{11}NOS$) C, H; N: calcd, 8.3; found, 7.8.

Method B. N,N,N′-Trimethyl-2-thiophenepropionamidine Tetrafluoroborate (13).—An ice-cooled, stirred solution of 8.5 g (0.05 mole) of N-methyl-2-thiophenepropionamide and 100 ml of dry Et_2O was treated portionwise with 11.4 g (0.06 mole) of

(5) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).
(6) E. R. Bissell and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).
(7) J. Sam and A. C. Thompson, *J. Pharm. Sci.*, **52**, 898 (1963).

$Et_3O^+ BF_4^-$.[8] After 1 hr at 0°, the reaction mixture was allowed to warm to room temperature and stirring was continued for 4 hr. The solvent was evaporated under reduced pressure, and the residue was taken up in a minimum of MeOH and treated with 40 ml of 2.5 *N* Me_2NH in MeOH. Colorless crystals precipitated after 40 min, and after 3 hr the desired product was filtered: yield 2.17 g, mp 190–196°. One recrystallization from MeOH afforded 1.31 g of **13**, mp 200–202°. A second crop was obtained: yield 0.15 g, mp 199–201°; total yield 1.46 g (10%).

Method C. N,N-Dimethyl-2-furanacrylamidine Hydrochloride (49).—A stirred, ice-cooled solution of 2 *N* Me_2NH in MeOH (50 ml) was treated portionwise with 13.0 g (0.05 moles) of crude 3-(2-furanacrylimidoyloxy)propanesulfonic acid,[2] prepared from 2-furanacrylamide and 1,3-propane sultone.[3] The resulting solution was allowed to warm to room temperature, and to stand for 2 days. The volatiles were evaporated under reduced pressure, and the residue was taken up in H_2O and poured into a rapidly stirred mixture of 100 ml of 10% NaOH and 100 ml of Et_2O. The ether phase was dried, filtered, and evaporated to furnish 3.1 g of the crude base. The base was dissolved with 20 ml of 1 *N* HCl in MeOH, and the resulting solution was treated with Et_2O to precipitate the desired **49** as an oil. The solvents were evaporated and the product crystallized on standing. One recrystallization from MeOH–Me_2CO afforded the pure product, yield 1.93 g (19%), mp 219–221°. One more recrystallization from MeOH–Me_2CO gave an analytical sample, mp 219–221°.

Method D. 2-Thiophenepropionamidoxime (14).—A stirred mixture of 8.3 g (0.12 mole) of $HONH_2 \cdot HCl$ and 50 ml of MeOH was treated with 48 ml (0.12 mole) of 2.5 *N* NaOMe in MeOH. Et_2O (100 ml) was added and the insoluble matter was filtered. The filtrate was concentrated to about 100 ml and 13.7 g (0.1 mole) of 2-thiophenepropionitrile was added. The resulting solution was heated under reflux for 2 days, and then allowed to cool. The solvents were evaporated under reduced pressure to afford a mixture of oil and crystals. The mixture was triturated with Et_2O, and filtered. On concentrating the filtrate a yellow crystalline solid was obtained, yield 15.7 g. The product was recrystallized from PhH to afford colorless prisms of the desired amidoxime (**14**), yield 6.03 g (35%), mp 67–72°. One further recrystallization afforded analytically pure material, mp 70–72°.

(8) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

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Novel Anthelmintic Agents. V. Thiazoline and Dihydrothiazine Analogs of Pyrantel

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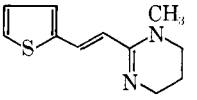
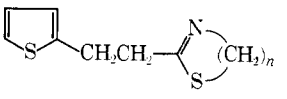
Some 2-thiazoline and 5,6-dihydro-4H-1,3-thiazine analogs of pyrantel exhibit highly significant activity against the round worm *Nematospiroides dubius*. Only a few members of the thiazoline group are active, and then only at high doses; the dihydrothiazine group, however, has many highly potent members. In the latter, the structural requirements for activity are less restricted than in the tetrahydropyrimidine (pyrantel) series. The structure–activity relationships within the tetrahydropyrimidine and dihydrothiazine series are similar, but certain relationships found in the former series are inverted or are absent in the latter. One compound, 5,6-dihydro-2-[2-(2-thienyl)ethyl]-4H-1,3-thiazine (**6**), has been shown to be active against not only *N. dubius*, but also against *Nippostrongylus muris, Syphacia obvelata, Trichinella spiralis, Ascaris suum, Ancylostoma caninum,* and *Toxocara canis*. Other highly potent compounds in this series are 5,6-dihydro-2-[2-(3-methyl-2-thienyl)-ethyl]-4H-1,3-thiazine (**9**), 5,6-dihydro-2-phenethyl-4H-1,3-thiazine (**10**), and 2-[2-(2-furyl)ethyl]-5,6-dihydro-4H-1,3-thiazine (**21**).

The recent discovery of the broad spectrum anthelmintic agent pyrantel has opened new fields of inquiry for those seeking novel agents to treat worm-caused diseases.[1] Other amidines, both cyclic and acyclic, closely similar in structure to pyrantel possess anthelmintic activity with varying degrees of potency.[2,3] In the course of investigating the structure–activity relationships among these compounds, we became interested in finding alternatives to the amidine moiety.[4]

Very early in our studies we observed that the thiazoline **1**, when administered at 250 mg/kg orally to a mouse, is highly effective against the round worm *Nematospiroides dubius*. Later, the dihydrothiazine homolog **6** was found to be not only effective but also highly potent: the *N. dubius* burden in mice is reduced greater than 90% by a single dose of only 3.1 mg/kg.



pyrantel



1, $n = 2$
6, $n = 3$

A large number of compounds were prepared in this new series of cyclic thiomidates and were tested in our primary screen. The present report will discuss the structure–activity relationships which emerged within the series, and will compare and contrast these with the corresponding relationships found in the cyclic amidine series.

Chemistry.—The synthetic methods used to prepare the thiazolines and dihydrothiazines followed standard

(1) W. C. Austin, W. Courtney, J. C. Danilewicz, D. H. Morgan, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, J. W. McFarland, R. L. Cornwell, and V. J. Theodorides, *Nature*, **212**, 1273 (1966).

(2) J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, **12**, 1066 (1969).

(3) J. W. McFarland and H. L. Howes, Jr., *ibid.*, **13**, 109 (1970).

(4) One such alternative is the 1-substituted pyridine system, *e.g.*, 1-[2-(2-thienyl)vinyl]pyridinium bromide: see J. W. McFarland and H. L. Howes, Jr., *ibid.*, **12**, 1079 (1969).