$Et_3O^+ BF_4^-$.[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).

Acknowledgments.—Thanks are due to Mr. R. B. James for valuable assistance in preparing the compounds mentioned in this article, to Mr. G. F. Smith for his help in evaluating their anthelmintic activity, and to Drs. L. H. Conover and J. E. Lynch for their encouragement and advice during the course of this investigation.

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

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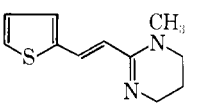
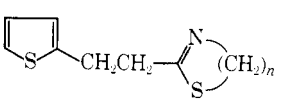
Some 2-thiazoline and 5,6-dihydro-4H-1,3-thiazine analogs of pyrantel exhibit highly significant activity against the round worm *Nematospiroides dubius*. Only a few members of the thiazoline group are active, and then only at high doses; the dihydrothiazine group, however, has many highly potent members. 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).

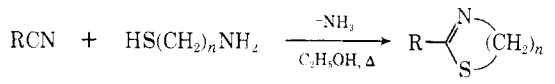
(2) J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, **12**, 1066 (1969).

(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).

procedures described in the literature. These are summarized briefly below.

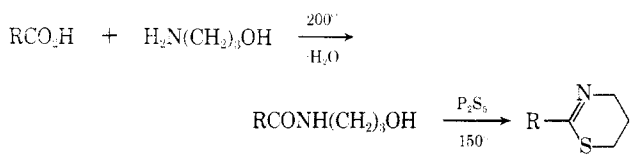
Method A.—The reaction of a nitrile with cysteamine or 3-amino-1-propanethiol to produce, respectively, a thiazoline or a dihydrothiazine proceeds well under mild conditions to give excellent yields of product.[5] This reaction is particularly advantageous for compounds which cannot withstand the more vigorous reaction conditions of method B. The major disadvantages are



$n = 2, 3$

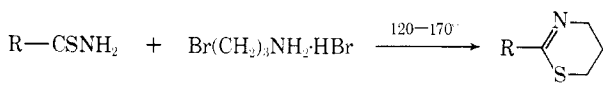
(i) 3-amino-1-propanethiol is prepared by a multistep synthesis,[6] and (ii) 2-arylacrylonitriles cannot be employed owing to the reactivity of the thiol function with the double bond system.

Method B.—Carboxylic acids or esters condense with 3-amino-1-propanol to give N-(3-hydroxypropyl)carboxamides. When these amides are heated at approximately 150° with P_2S_5 the corresponding dihydrothiazines are obtained in yields up to 50%.[7,8] This

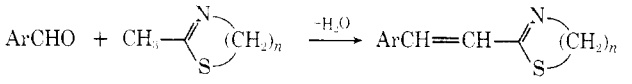


technique is convenient because of the ready availability of starting materials, and because both amide formation and the subsequent P_2S_5 treatment can be done in a single reaction vessel. However, certain delicate molecules, *e.g.*, furan derivatives, will not survive the vigorous conditions of this reaction, and (as with method A) acrylic acid derivatives cannot be employed.

Method C.—Thioamides will condense with 3-bromo-1-propylamine to furnish dihydrothiazines.[9] This method was used to synthesize **32**.



Method D.—The previously described methods are not suitable for the preparation of 2-(2-arylvinyl)thiazolines or 2-(2-arylvinyl)dihydrothiazines. However, these compounds are readily accessible by the direct condensation of aromatic aldehydes with 2-methyl-2-thiazoline or with 5,6-dihydro-2-methyl-4H-1,3-thiazine.[7] This reaction was first reported in 1954,[5] but



$n = 2, 3$

its utility has not been widely recognized.

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 round worm *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 (62–2000 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. In general, the better compounds in this series exhibited activity against *S. obvelata*, but no compound described here was active against *H. nana*. In the following discussion structure–activity relationships will be developed from the *N. dubius* activity alone.

Further details of these testing methods are given by Howes and Lynch.[10] The results of these tests are reported in the last columns of Tables I–VI.

Structure–Activity Relationships. Although the cyclic thioimidates described in this report are structural analogs of the cyclic amidines described by McFarland, *et al.*,[2] it is not entirely obvious that these compounds should possess similar biological activities. The amidines are 10^6–10^8 times stronger bases than the cyclic thioimidates, and for this reason grossly different biological properties might be anticipated. In spite of this big difference in an important physical parameter, anthelmintic activity nevertheless is observed. Certain structure–activity relationships found within one series are also found within the other; however, other relationships found within one series have no parallel within the other. The details of these observations are given below.

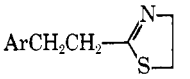
The Basic Ring System.—One of the most striking effects in the cyclic thioimidate series is that of ring size on potency (see Tables VII and VIII). Regardless of the nature of the connecting side chain or of the aromatic ring system, a dihydrothiazine is invariably more potent than the corresponding thiazoline. In contrast, related compounds in the cyclic amidine series appear to show no such marked differences (see Table IX). Actually, a closer examination of the amidine series[2] reveals that in instances where a difference in activity between an imidazoline and a comparable tetrahydropyrimidine exists, the tetrahydropyrimidine is invariably the more potent compound. The difference, however, is usually much smaller than that observed in the cyclic thioimidate series.

The range of structures associated with activity in the thiazoline series is also much narrower than in the dihydrothiazine series. Taking this and the lower potency of the thiazolines into account, we will emphasize the dihydrothiazine series of compounds in the following discussion.

The Connecting Chain.—In both the dihydrothiazine and tetrahydropyrimidine series, anthelmintic activity is dependent on the length and on the nature of the chain of atoms connecting the basic function with the aromatic system. In both series this activity is optimal when the chain is 2 C; shortening the chain or

(5) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).
(6) S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson, *J. Org. Chem.*, **27**, 2846 (1962).
(7) F. M. Hamer and R. J. Rathbone, *J. Chem. Soc.*, 243 (1943).
(8) G. Bach and M. Zahn, *J. Prakt. Chem.*, **8**, 68 (1959).
(9) C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **15**, 694 (1950).
(10) H. L. Howes, Jr., and J. E. Lynch, *J. Parasitol.*, **53**, 1085 (1967).

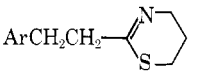
TABLE I



No.	Ar	Salt	Preparative method	Bp (mm) or mp, °C	Recrystn solvent or $n^{25}D$	Formula[a]	MED,[c] mg/kg	Days given
	(Pyrantel)	Tartaric					12.5	1
1	2-Thienyl		A	118 (0.5)	1.5911	$C_9H_{11}NS_2$[b]	250	3
2	2-Thienyl	TsOH		77–78	Me_2CO–C_6H_{14}	$C_{16}H_{19}NO_3S_3$	>800	3
3	3-Methyl-2-thienyl	HCl	A	146–147	MeOH–EtOAc	$C_{10}H_{14}ClNS_2$	500	1
4	Ph		A	90 (0.1)	1.5755	$C_{11}H_{13}NS$	>500	3
5	2-Furyl		A	66 (0.1)	1.5435	$C_8H_{11}NOS$	250	3

[a] All compounds were analyzed for C, H, N unless otherwise noted. [b] Not analyzed; vapor phase chromatography showed this material to be >97% pure. [c] Minimum effective dose against *N. dubius*.

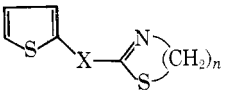
TABLE II



No.	Ar	Salt	Preparative method	Bp (mm) or mp, °C	Recrystn solvent or $n^{25}D$	Formula[d]	MED,[c] mg/kg	Days given
	(Pyrantel)	Tartaric					12.5	1
6	2-Thienyl		A	102 (0.2)	1.5910	$C_{10}H_{13}NS_2$	3.1	1
7	2-Thienyl	HCl		108–110	Me_2CO	$C_{10}H_{14}ClNS_2$	6.2	1
8	2-Thienyl	CH_3I		121–123	MeOH–*i*-PrOH	$C_{11}H_{16}INS_2$	500	3
9	3-Methyl-2-thienyl	HCl	B	137–138	*i*-PrOH–*i*-Pr_2O	$C_{11}H_{16}ClNS_2$	1.3	1
10	Ph		B	95 (0.08)	1.5775	$C_{12}H_{15}NS$	6.2	1
11	Ph	Citric		97–98	MeOH–Me_2CO	$C_{18}H_{23}NO_7S$	12	1
12	*o*-MeC_6H_4	HCl	B	160–162	MeOH–Me_2CO	$C_{13}H_{18}ClNS$	15	1
13	*m*-MeC_6H_4	HCl	A	103–104	Me_2CO	$C_{13}H_{18}ClNS$	>250	1
14	*p*-MeC_6H_4	HCl	A	124–125	Me_2CO–C_6H_{14}	$C_{13}H_{18}ClNS$[a]	>200	1
15	3-FC_6H_4	HPF_6	A	96–97	EtOAc–C_6H_{14}	$C_{12}H_{15}F_7NPS$[b]	62	1
16	4-FC_6H_4	HPF_6	A	93–94	H_2O	$C_{12}H_{15}F_7NPS$	>250	1
17	2-ClC_6H_4	HCl	B	155–157	*i*-PrOH	$C_{12}H_{15}Cl_2NS$	31	1
18	4-BrC_6H_4	HPF_6	B	161–163	*i*-PrOH	$C_{12}H_{15}BrF_6NPS$	>500	1
19	2-$MeOC_6H_4$	HCl	A	151–152	MeOH–EtOAc	$C_{13}H_{18}ClNOS$	>62	1
20	4-$MeOC_6H_4$	HPF_6	A	105–106	*i*-PrOH	$C_{13}H_{18}F_6NOPS$	>500	1
21	2-Furyl		A	100 (0.06)	1.5512	$C_{10}H_{13}NOS$	1.5	1
22	2-Furyl	1.5Fumaric		125–126	MeOH	$C_{16}H_{19}NO_7S$	3.1	1

[a] H: calcd, 7.7; found, 8.1. [b] C: calcd, 39.0; found, 39.7. [c] Minimum effective dose against *N. dubius*. [d] See footnote *a*, Table I.

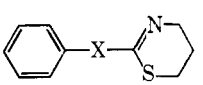
TABLE III



No.	X	*n*	Salt	Preparative method	Bp, (mm) or mp, °C	Recrystn solvent or $n^{25}D$	Formula[a]	MED,[b] mg/kg	Days given
23		3	HPF_6	B	170–175	EtOH	$C_8H_{10}F_6NPS_2$	>500	3
24	CH_2	2		A	90 (0.2)	1.6064	$C_8H_9NS_2$	>500	3
25	CH_2	2	HCl	B	132–133	Me_2CO	$C_9H_{12}ClNS_2$	500	3
26	$(CH_2)_2$	3		B	110 (0.04)	1.5807	$C_{11}H_{15}NS_2$	62	2

[a] See footnote *a*, Table I. [b] Minimum effective dose against *N. dubius*.

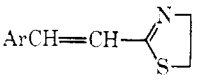
TABLE IV



No.	X	Salt	Preparative method	Bp (mm) or mp, °C	Recrystn solvent or $n^{25}D$	Formula[d]	MED,[e] mg/kg	Days given
27[a]		HPF_6	B	175–176	*i*-PrOH	$C_{10}H_{12}F_6NPS$	>500	3
28[b]	CH_2		B	104 (0.3)[b]	1.5893	$C_{11}H_{13}NS$	250	3
29	$CH_2CH(CH_3)$	HCl	B	109–111	MeCN–EtOAc	$C_{13}H_{18}ClNS$	>250	3
30	$CH(CH_3)CH_2$	HCl	B	122–124	Me_2CO	$C_{13}H_{18}ClNS$	>250	1
31	$(CH_2)_3$		B	126 (0.08)	1.5670	$C_{13}H_{17}NS$	>100	3
32[c]	OCH_2	HCl	C	161–164[c]	EtOH–C_6H_6	$C_{11}H_{14}ClNOS$	>250	3

[a] P. A. S. Smith and J. M. Sullivan [*J. Org. Chem.*, **26**, 1132 (1961)] and G. Pinkus [*Ber.*, **26**, 1077 (1893)] report the free base. [b] Pinkus[a] reports only the density and N and S analyses. [c] C. Djerassi and C. R. Scholz [*J. Org. Chem.*, **15**, 694 (1950)] report mp 162–164°. [d] See footnote *a*, Table I. [e] Minimum effective dose against *N. dubius*.

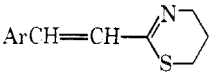
Table V



No.	Ar	Salt	Preparative method	Mp, °C	Recrystn solvent	Formula	Analyses	MED,[d] mg/kg	Days given
33	2-Thienyl		D	119–120	CCl_4	$C_9H_9NS_2$	H, N; C[c]	>500	3
34	3-Methyl-2-thienyl	HCl	D	224–225	MeOH	$C_{10}H_{12}ClNS_2$	C, H, N	>500	1
35[a]	Ph		D	100–101[a]	CCl_4	$C_{11}H_{11}NS$	N	>250	3
36[b]	2-Hydroxyphenyl		D	192–193[b]	C_6H_6	$C_{11}H_{11}NOS$	N	>500	3
37	2-Furyl		D	82–85	C_6H_{14}	C_9H_9NOS	C, H, N	>500	2

[a] Lit.[5] 101–102°. [b] Lit.[5] 191–192°. [c] C: calcd, 55.3; found, 54.3. [d] Minimum effective dose against *N. dubius*.

Table VI

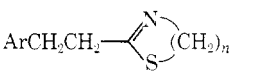


No.	Ar	Salt	Preparative method	Mp, °C	Recrystn solvent	Formula[a]	MED,[b] mg/kg	Days given
	(Pyrantel)	Tartaric					12.5	1
38	2-Thienyl		D	60–61	C_6H_{14}	$C_{10}H_{11}NS_2$	15	1
39	2-Thienyl	Fumaric	D	169–171	MeOH	$C_{14}H_{15}NO_4S_2$	25	1
40	3-Thienyl	HPF_6	D	149–150	*i*-PrOH	$C_{10}H_{12}F_6NPS_2$	250	1
41	3-Methyl-2-thienyl	HCl	D	252–254	EtOH	$C_{11}H_{14}ClNS_2$	12.5	1
42	4-Methyl-2-thienyl	HCl	D	197–198	*i*-PrOH	$C_{11}H_{14}ClNS_2$	250	1
43	5-Methyl-2-thienyl	HPF_6	D	144–146	$CHCl_3$	$C_{11}H_{14}F_6NPS_2$	250	3
44	Ph	HPF_6	D	151–155	*i*-PrOH	$C_{12}H_{14}F_6NPS$	125	3
45	*o*-MeC_6H_4	HCl	D	219–221	Me_2CO	$C_{13}H_{16}ClNS$	62.5	3
46	*m*-MeC_6H_4	HPF_6	D	120–124	$CHCl_3$–C_6H_6	$C_{13}H_{16}F_6NPS$	>2000	1
47	*p*-MeC_6H_4	HCl	D	189–192	Me_2CO	$C_{13}H_{16}ClNS$	250	3
48	2-EtC_6H_4	HCl	D	208–210	MeCN	$C_{14}H_{18}ClNS$	250	1
49	2-FC_6H_4	HPF_6	D	176–178	EtOH	$C_{12}H_{13}F_7NPS$	250	3
50	3-FC_6H_4	HCl	D	172–175	MeCN	$C_{12}H_{13}ClFNS$	250	1
51	4-FC_6H_4	HCl	D	208–210	*i*-PrOH–Et_2O	$C_{12}H_{13}ClFNS$	250	3
52	C_6F_5	HCl	D	163–165	EtOH–Et_2O	$C_{12}H_9F_5ClNS$	>1000	1
53	2-ClC_6H_4	HCl	D	218–220	EtOH	$C_{12}H_{13}Cl_2NS$	250	1
54	3-ClC_6H_4	HCl	D	161–162	*i*-PrOH	$C_{12}H_{13}Cl_2NS$	250	3
55	4-ClC_6H_4	HPF_6	D	160–163	*i*-PrOH	$C_{12}H_{13}ClF_6NPS$	500	3
56	2-BrC_6H_4	HCl	D	218–220	EtOH	$C_{12}H_{13}BrClNS$	250	3
57	3-BrC_6H_4	HCl	D	194–195	MeCN	$C_{12}H_{13}BrClNS$	>250	3
58	4-BrC_6H_4	HCl	D	187–188	MeCN	$C_{12}H_{13}BrClNS$	250	1
59	2-$MeOC_6H_4$	HPF_6	D	182–184	MeOH	$C_{13}H_{16}F_6NOPS$	>500	3
60	3-$MeOC_6H_4$	HPF_6	D	167–170	MeOH	$C_{13}H_{16}F_6NOPS$	>500	3
61	4-$MeOC_6H_4$	HCl	D	214–217	*i*-PrOH	$C_{13}H_{16}ClNOS$	250	3
62	3,4,5-$(MeO)_3C_6H_2$	HCl	D	198–200	*i*-PrOH–Et_2O	$C_{15}H_{20}ClNO_3S$	>250	3
63	2-$O_2NC_6H_4$	HPF_6	D	190–192	MeOH	$C_{12}H_{13}F_6N_2O_2PS$	250	3
64	4-$O_2NC_6H_4$		D	178–180	C_6H_6	$C_{12}H_{12}N_2O_2S$	>500	2
65	4-$Me_2NC_6H_4$		D	156–158	C_6H_6	$C_{14}H_{18}N_2S$	>250	3
66	2-Furyl	HPF_6	D	130–131	*i*-PrOH	$C_{10}H_{12}F_6NOPS$	250	1
67	2-Pyridyl		D	78–80	Et_2O	$C_{11}H_{12}N_2S$	>250	1
68	3-Pyridyl	HPF_6	D	190–194	MeCN	$C_{11}H_{13}F_6N_2PS$	>250	3
69	4-Pyridyl		D	80–81	Et_2O	$C_{11}H_{12}N_2S$	>250	3
70	*t*-Bu	HCl	D	157–158	Me_2CO	$C_{10}H_{18}ClNS$	>250	3

[a] See footnote *a*, Table I. [b] Minimum effective dose againt *N. dubius*.

Table VII

Effect of Ring Size on Potency. Part 1

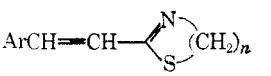


n	MED,[a] mg/kg, *vs. N. dubius*: Ar = Phenyl	Ar = 2-Thienyl	Ar = 2-Furyl
2	>500	250	250
3	6	3	1.6

[a] Based on per cent of active material present in the various salt forms.

Table VIII

Effect of Ring Size on Potency. Part 2



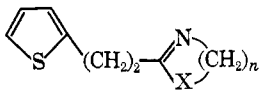
n	MED,[a] mg/kg, *vs. N. dubius*: Ar = Phenyl	Ar = 2-Thienyl	Ar = 2-Furyl
2	>250	>500	>500
3	70	16	140

[a] Based on per cent of active material present in the various salt forms.

lengthening it results in a sharp reduction of potency (see Table X).

An interesting inverse relationship between the two series is illustrated by the data in Table XI. In the tetrahydropyrimidine series, *trans*-vinylene compounds are generally more potent than the corresponding

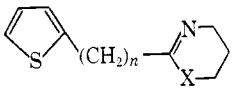
TABLE IX
EFFECT OF RING SIZE ON POTENCY. PART 3



	MED,[a] mg/kg, *vs. N. dubius*	
	X	
n	S	NCH_3
2	250	25
3	3	25

[a] Based on per cent of active material present in the various salt forms.

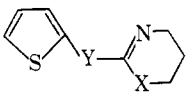
TABLE X
EFFECT OF CHAIN LENGTH ON POTENCY



	MED[a] mg/kg *vs. N. dubius*			
	n			
X	0	1	2	3
S	>280	420	3	62
NH	>85	>300	85	>420

[a] Based on per cent of active material present in the various salt forms.

TABLE XI
EFFECT OF THE NATURE OF THE CHAIN ON POTENCY



	MED,[a] mg/kg *vs. N. dubius*		
	Y		
X	CH_2CH_2	CH=CH (*trans*)	CH=CH (*cis*)
S	3	15	~15
NCH_3	25	5	150

[a] Based on per cent of active material present in the various salt forms.

ethylene derivatives. In the dihydrothiazine series the converse is true.

A still more curious observation concerns the effect upon activity associated with the transformation *trans* → *cis*. In the tetrahydropyrimidine series a large reduction in potency occurs, but in the dihydrothiazine series the efficacy of the *cis* isomer is indistinguishable from that of the *trans* (see Table XI). The *cis* isomer of pyrantel is readily prepared by the action of sunlight on a methanolic solution of its tartrate salt. This isomer is reasonably stable and can be purified by fractional crystallization to obtain a salt which is easily characterized by nmr, uv, and ir spectroscopy. It must be admitted, however, that the *cis* isomer of the dihydrothiazine analog (**38**) has not yet been isolated in the pure state. This compound has a marked tendency to reisomerize to the more stable *trans* compound, and so far attempts to purify crude preparations have led to the isolation of only the *trans* isomer. Nevertheless, experiments have been conducted which indicate that the *cis* isomer of **38** is equipotent to the *trans* (see Experimental Section).

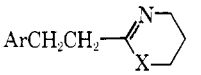
Similar experiments conducted with **41** gave the same result, *i.e.*, the *cis* isomer is just as potent as the *trans*. There are at least two explanations for this phenomenon: (i) the *cis* isomers are intrinsically just as potent as the *trans*, or (ii) *in vivo* the *cis* isomers are rapidly and quantitatively isomerized to the corresponding *trans* compounds. At the present time, it is difficult to conceive of simple experiments to differentiate these possibilities.

The Aromatic System.—The structure–activity relationships in the aromatic portion of pyrantel analogs depend considerably upon the nature of the basic function and whether the connecting chain is ethylene or *trans*-vinylene (see Tables VII, VIII, XII, and XIII). In the amidine series and in the 2-(2-arylvinyl) subgroup of the dihydrothiazines, 2-thienyl is dramatically superior to other aromatic systems (see Tables XII and XIII). However, in the 2-(2-arylethyl) subgroup of the dihydrothiazine series, phenyl is only slightly inferior to 2-thienyl and in one instance (**21**) 2-furyl is superior.

As in the amidine series, substitution of the "*ortho*" position (*i.e.*, the position adjacent to where the connecting chain is attached to the aromatic ring) by a group with approximately the same degree of lipophilicity as methyl is usually not harmful to activity and frequently results in enhanced potency. In the amidine series, substitution at other aromatic positions almost always results in the loss of activity. However, such is not the case with dihydrothiazines. As is particularly evident from the data in Table VI, "*meta*" and "*para*" substitution may result in reduced potency, but activity is only occasionally abolished.

Spectra of Activities.—Among the compounds which have been discussed, pyrantel is the one most widely tested against other helminth species and in hosts other than the mouse. Among the dihydrothiazines, **6** in various salt forms has received the most attention. Both pyrantel and **6** are representative of their own classes, and a comparison of their activities against various parasites would be indicative of the similarity or differences of the spectra of activity between the two

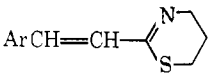
TABLE XII
EFFECT OF VARIOUS AROMATIC SYSTEMS ON POTENCY. PART 1



	MED,[a] mg/kg, *vs. N. dubius*		
	Ar		
X	Phenyl	2-Thienyl	2-Furyl
S	6	3	1.6
NH	>100	85	>85
NCH_3	>100	25	

[a] Based on per cent of active material present in the various salt forms.

TABLE XIII
EFFECT OF VARIOUS AROMATIC SYSTEMS ON POTENCY. PART 2



	MED,[a] mg/kg, *vs. N. dubius*			
	Ar			
X	Phenyl	2-Thienyl	3-Thienyl	2-Furyl
S	70	16	140	140
NCH_3	35	5	15	77

[a] Based on per cent of active material present in the various salt forms.

Table XIV

Potency of Pyrantel *vs.* Compound **6** against Various Parasites

Host	Parasite	Stage	MED,[a] mg/kg		MEC,[a,b] % in feed	
			Pyrantel	6	Pyrantel	6
Mouse	*Nematospiroides dubius*	Adult	5.0	3.0	0.006	0.007
	Nippostrongylus muris	Adult	12.0	16.0	0.006	
	Syphacia obvelata	Adult	34.0	8.5	0.006	0.012
		Immature	116.0	17.0	0.006	>0.012
	Trichinella spiralis	Enteral	25.0	68.0	0.120	
	Ascaris suum	Larval	0.5	35.0	0.006	>0.034
	Hymenolepis nana	Adult	Inactive	Inactive	Inactive	Inactive
Dog	*Ancylostoma caninum*	Adult	2.5	8.0		
	Toxocara canis	Adult	5.0	8.0		
	Trichuris vulpis	Adult	Inactive	Inactive		
	Dipylidium caninum	Adult	Inactive	Inactive		
	Taenia pisoformis	Adult	Inactive	Inactive		

[a] Based on per cent of active material in the various salt forms. [b] Minimum effective concentration.

series. For this purpose, see Table XIV. In general, each compound is active against the same organisms, but there is no parallel between the MED's. Against some organisms **6** is more potent than pyrantel, but more often than not the reverse is true. In fact, the potency of a compound is also sometimes dependent on the method of administration. By direct dose **6** is more potent than pyrantel against *Syphacia obvelata*, but in the feed pyrantel is the more potent compound.

In conclusion, it appears that the spectrum of compounds which show activity in the *N. dubius* test is broader for the dihydrothiazine series than for the tetrahydropyrimidine series. Although there are quantitative differences in potency, each series has a similar spectrum of sensitive helminths.

Experimental Section

Boiling points are uncorrected; melting points were determined on a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.) and are corrected. Many of the nitriles used as intermediates have been described elsewhere.[2] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were with ±0.4% of the theoretical values.

Method A. Reaction of a Nitrile with Cysteamine or 3-Amino-1-propanethiol. The procedure of Kuhn and Drawert[5] was followed.

Method B. Reaction of an N-(3-Hydroxypropyl)amide with P_2S_5. 5,6-Dihydro-2-[2-(3-methyl-2-thienyl)ethyl]-4H-1,3-thiazine Hydrochloride (9).—A stirred mixture of 23.5 g (0.138 mole) of 3-methyl-2-thiophenepropionic acid, and 10.4 g (0.138 mole) of 3-amino-1-propanol was heated slowly to 200°. Toward the end of the heating period, a slow stream of dry N_2 was blown over the melt to remove traces of H_2O. The mixture was allowed to cool to 150°, and 6.7 g of P_2S_5 was added portionwise. The flask was fitted with vacuum distillation equipment. The more volatile components were removed at 15–20 mm, and 5,6-dihydro-2-[2-(3-methyl-2-thienyl)ethyl]-4H-1,3-thiazine was then distilled: yield 15.3 g (49%), bp 150–160° (0.1 mm), n^{24}D 1.5829. A solution of the free base so obtained and 100 ml of 5 *N* dry HCl in MeOH was evaporated under reduced pressure. The residue was recrystallized to furnish analytically pure **9**.

3-Methyl-2-thiophenepropionic acid (71) was prepared from 3-methyl-2-thiopheneacrylic acid by a modification of the method of Sam and Thompson,[11] yield 91%, mp 64–66° (from H_2O). *Anal.* ($C_8H_{10}O_2S$) C, H, S.

Method C. Reaction of a Thioamide with 3-Bromo-1-propylamine. 5,6-Dihydro-2-phenoxymethyl-4H-1,3-thiazine (32).—The procedure of Djerassi and Scholz[9] was followed.

Method D. Condensation of 2-Methyl-5,6-dihydro-4H-1,3-thiazine and an Aldehyde. 5,6-Dihydro-2-[2-(2-thienyl)vinyl]-4H-1,3-thiazine Hydrogen Fumarate (39).—A solution of 11.5 g (0.1 mole) of 5,6-dihydro-2-methyl-4H-1,3-thiazine,[7] 11.2 g (0.1 mole) of 2-thiophenecarboxaldehyde, and 40 ml of xylene was heated under reflux in an apparatus which included a Dean–Stark moisture trap. After 12 hr, 1.1 ml of H_2O had collected in the trap, and heating was stopped. The xylene was evaporated at approximately 1 mm (bath temperature 40–60°) in a rotary film apparatus, and the residue was taken up in 40 ml of Me_2CO. A solution of 5.1 g (0.044 mole) of fumaric acid in 100 ml of MeOH was added portionwise to the Me_2CO solution. Yellow crystals of **39** formed. The product was recrystallized to furnish analytically pure **39**, yield 3.9 g (12%).

3-Methylhydrocinnamonitrile (72) was prepared by the hydrogenation[2] of 3-methylcinnamonitrile: yield 70%, bp 64–68° (0.1 mm), n^{22}D 1.5183. *Anal.* ($C_{10}H_{11}N$) C, N, H: calcd, 7.6; found, 10.0.

3-Fluorohydrocinnamonitrile (73) was prepared by the action of $C_6H_5SO_2Cl$ on 3-fluorohydrocinnamamide in pyridine:[2] yield 83%, bp 140–144° (20 mm). *Anal.* (C_9H_8FN) C, H, N.

4-Fluorohydrocinnamonitrile (74) was prepared in a manner analogous to that of the 3 isomer; yield 83%, bp 73–76° (0.05 mm), n^{23}D 1.4980. *Anal.* (C_9H_8FN) C, H, N.

4-Fluorohydrocinnamamide (75).—The acid chloride was prepared by the action of $SOCl_2$ on 4-fluorohydrocinnamic acid in C_6H_6. With vigorous stirring and ice bath cooling, the acid chloride was poured into NH_4OH to furnish the amide, yield 56%, mp 100–102° (from H_2O–MeOH). *Anal.* ($C_9H_{10}FNO$) C, H, N.

Anthelmintic Activity of *cis*-5,6-Dihydro-2-[2-(2-thienyl)vinyl]-4H-1,3-thiazine.—A solution of 125 mg of *trans*-5,6-dihydro-2-[2-(2-thienyl)vinyl]-4H-1,3-thiazine hydrochloride hydrate [**76**; mp 184–186° (MeOH–Me_2CO). *Anal.* ($C_{10}H_{11}NS_2$·HCl·H_2O) C, H, N] and 100.0 ml of H_2O was divided into two equal portions, each stored in a Pyrex glass volumetric flask. One portion was placed in a box which effectively excluded light from the sample. The box and the other portion of the solution were then placed on a shelf which was lighted by a window (northern exposure, *i.e.*, no direct sunlight fell on the sample) and by fluorescent lighting. The concentration of **76** was such that 0.5 ml delivered a dose of 25 mg/kg to a 20-g mouse, and such that when diluted 200:1 a reasonable uv spectrum could be obtained. Since 25 mg/kg is the MED of **76** the loss of anthelmintic activity can be readily detected in this system. At various intervals, uv spectra from both the light-exposed and unexposed solutions were measured (see Table XV). After 3 days a very dramatic change in the uv spectum of the light-exposed solution was observed, and after 10 and 17 days further exposure only smaller, less significant changes occurred. The control sample stored in the dark exhibited no significant change in its uv spectrum during the entire course of the experiment (31 days). In a parallel experiment, 125 mg of pyrantel citrate in 100.0 ml of H_2O was treated in a manner analogous to that described above.

At days 1, 3, and 17 mice infested with *N. dubius* were given 0.5 ml of the various light-exposed and dark (control) solutions. Each treatment group consisted of four male mice; 3 days after treatment the mice were sacrificed and the worm burdens counted. The burdens were then compared to those of infected untreated controls. Table XVI summarizes the results obtained. As is apparent from Table XVI, the aqueous solution of **76**, after prolonged exposure to light, has not lost significant anthelmintic activity, even though **76** has obviously undergone a

(11) J. Sam and A. C. Thompson, *J. Pharm. Sci.*, **52**, 898 (1963).

TABLE XV[a]

Exposure	Day	ϵ_{355}[b]	ϵ_{290}[c]	$\epsilon_{355}/\epsilon_{290}$
Light	1	20,600	8250	2.5
Light	3	10,200	7700	1.3
Light	10	10,300	7480	1.4
Light	17	8,250	7100	1.2
Dark	24	10,100	7050	1.4
Dark	31	13,000	7090	1.8

[a] Changes in the uv spectrum of *trans*-**76** on exposure to (i) diffuse daylight, fluorescent lighting for 17 days, and (ii) after exposure to light and storage in the dark for 14 days. [b] Calculated ϵ value at 355 mμ, a maximum in spectrum of **76**. [c] Calculated ϵ value at 290 mμ, another maximum in the spectrum.

TABLE XVI[a]

Sample	Exposure	% redn of *N. dubius* burden at 25 mg/kg — Day 1	Day 3	Day 17
76	Dark	99	93	82
	Light	99	90	89
Pyrantel	Dark	99	99	96
	Light	99	78	15

[a] Table is explained in the text.

dramatic change in chemical structure. In the parallel experiment, the pyrantel solution lost activity upon exposure to light. From previous experience[2] it is known that pyrantel is readily converted to its *cis* isomer by the action of light, and that the *cis* isomer is only about 0.03 times as potent as the *trans* isomer.

That the apparent isomerization of **76** is reversible is indicated by the continuation of the experiment. The light-exposed solution was placed in the dark box, and was allowed to stand there at room temperature for 2 weeks. The uv spectrum was determined after 7 and 14 days in the dark. Although little change was observed after 1 week, it was apparent that by 2 weeks the original spectrum of the *trans* isomer was beginning to emerge (see Table XV). However, the uncatalyzed rate of conversion back to the *trans* isomer is too slow to account for the observed activity of the presumed *cis* isomer. In one effort to isolate the *cis* isomer of the free base **38**, an oil was obtained; an attempt to crystallize this material resulted only in the isolation of unchanged *trans* isomer.[12] Thus, it appears that whatever change **76** undergoes on exposure to light, it is readily reversible and is therefore unlikely to involve an oxidative cyclization or a similar irreversible change of structure. The common experience that light induces the isomerization of *trans*-olefins to the *cis* isomers and the analogy to pyrantel's reaction to light strongly suggest that the light-induced change in **76** is also to the *cis* isomer.

Acknowledgments.—The authors wish to thank Messrs. P. N. Gordon, R. B. James, G. F. Smith, R. W. Sumner, and T. F. Estabrooks of the Pfizer Medical Research Laboratories for valuable assistance rendered during the course of this investigation.

(12) P. N. Gordon, private communication.

Quinoxaline Studies. XV.[1a] Potential Antimalarials. Some (*RS*)-α-(Dialkylaminomethyl)-2-quinoxalinemethanols[1b]

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Six (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols were prepared from 2-tetrahydroxybutylquinoxaline *via* an eight-step sequence. Neither intermediates nor target compounds (diethylamino through di-*n*-heptylamino derivatives) possessed antimalarial activity against *Plasmodium berghei* in mice.

Certain quinolinemethanols,[2] long used as antimalarial agents, frequently have less activity toward newer strains of malaria organisms. Because of the similarity of quinoline and quinoxaline, as well as the presence of the quinoxaline moiety in some broad spectrum (but toxic) antibiotics,[3] it was hoped that quinoxaline analogs of quinoline antimalarials would exhibit antimalarial activity. The purpose of this paper is to report the synthesis of a series of (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols, incorporating diethylamino through di-*n*-heptylamino groups, for testing as antimalarials.

Chemistry.—The desired synthetic objective was attained *via* the sequence D-*arabino*-2-tetrahydroxybutylquinoxaline (**1**),[4] 2-quinoxalinecarboxylic acid (**2**),[4] 2-quinoxaloyl choride (**3**),[4] 2-diazoacetylquinoxaline (**4**), 2-chloroacetylquinoxaline (**5**), (*RS*)-α-(chloromethyl)-2-quinoxalinemethanol (not analyzed) (**6**), (*RS*)-2-quinoxalinepoxyethane (**7**), and (*RS*)-α-(dialkylaminomethyl)-2-quinoxalinemethanols (**8**).

2-Quinoxalinecarboxylic acid was prepared from **1** by a considerable improvement of existing procedures, the material being isolated and purified as its Na salt. Treatment of **3** with CH_2N_2 gave **4** (not isolated), which was transformed by standard methods into **5**. A variety of reaction conditions failed to transform secondary amines and **5** into the corresponding amino ketones; only red, irresolvable tars were obtained.

The reduction of **5** with $NaBH_4$ gave **6**, unstable, flaring within 1–10 hr of drying to black ash, from which small flakes of 2-acetylquinoxaline were isolated manually. Nonetheless, freshly isolated **6** was treated immediately with Et_2NH in an attempt to form a target compound **8**, either *via* a substitution reaction on **6**, or *via* transformation *in situ* of **6** into **7**, which in turn could react with Et_2NH to yield **8**. However, only 2-acetylquinoxaline was obtained, possibly by a reaction mechanistically related to the hydramine fission (Scheme I). Alternatively, elimination of HCl from **6** may have been spontaneous (*vide supra*), or promoted by basic N atoms of the quinoxaline nucleus.

The amino ketone or chlorohydrin (**6**) derivatives of quinoxaline were thus eliminated as direct intermediates

(1) (a) Paper XIV of this series: S. Gerchakov and H. P. Schultz, *J. Med. Chem.*, **12**, 141 (1969). (b) Contribution No. 691 from the Army Research Program on Malaria, supported by the U. S. Army Medical Research and Development Command *via* Contract DADA 17-67-C-7064.

(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, Survey of Antimalarial Agents, Public Health Monograph No. 9, U. S. Government Printing Office, Washington, D. C., 1953.

(3) H. Otsuka and J. Shoji, *Tetrahedron*, **23**, 1535 (1967), and references therein.

(4) S. Gerchakov, P. J. Whitman, and H. P. Schultz, *J. Med. Chem.*, **9**, 266 (1966). 2-Quinoxaloyl chloride is now commercially available.