Novel Anthelmintic Agents. II. Pyrantel and Other Cyclic Amidines[1]

J. W. McFarland,[2] L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm,

Pfizer Medical Research Laboratories, Groton, Connecticut

W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan

Pfizer Limited Research Laboratories, Sandwich, Kent, United Kingdom

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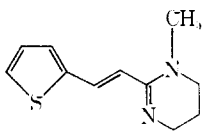
Broad-spectrum anthelmintic activity has been discovered in a novel series of imidazolines and tetrahydropyrimidines substituted variously at the 2 positions by 2-arylethyl or 2-arylvinyl groups. One member of this series, *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine tartrate (pyrantel tartrate, **71**) has gained acceptance as a veterinary anthelmintic agent in many areas of the world. The decreasing order of potency for the various aryl systems is 2-thienyl > 3-thienyl > phenyl > 2-furyl. The arylvinyl analog is usually more potent than the corresponding arylethyl compound. N-Methyl substitution on the cyclic amidine system invariably results in increased potency; substitution at almost any other position results in the loss of potency or of activity altogether. One notable exception is that certain substituents can be placed at the *ortho* position of the aryl system without detriment to anthelmintic activity, and in some cases enhanced potency is achieved. Thus, besides pyrantel, some of the more potent compounds in this series are *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine (**74**), *trans*-1,4,5,6-tetrahydro-1-methyl-2-(2-methylstyryl)pyrimidine (**84**), *trans*-2-(2-bromostyryl)-1,4,5,6-tetrahydro-1-methylpyrimidine (**97**), and *trans*-2-(2-chlorostyryl)-1,4,5,6-tetrahydro-1-methylpyrimidine (**93**).

A new class of anthelmintic agents has been discovered. An outstanding member is *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine (pyrantel,[3] **71**) which is effective in eliminating many of the various nematodes which infest mice, rats, dogs, horses, sheep, cattle, swine, and man.



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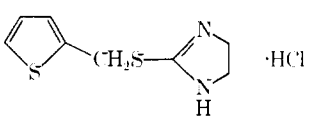

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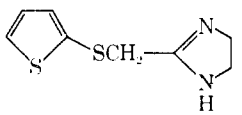
Earlier work in our laboratories[4,5] had shown that in mice the isothiuronium salt **1** possesses anthelmintic activity against the nematode *Nematospiroides dubius*, one of the principal organisms of our primary screen. However, when administered orally to sheep, **1** shows little activity. This behavior probably follows from the fact that **1** readily hydrolyzes to the inactive products 2-thenylthiol and 2-imidazolidone.



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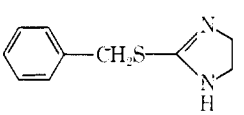

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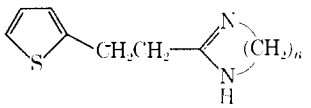


8, $n = 2$
10, $n = 3$

Certain simple analogs of **1**, as for example **4** and **157**, are inactive against *N. dubius*. The detection of activity in compounds **8** and **10**, however, led to the rapid discovery of many new active anthelmintic agents.

Chemistry.—The procedures used to prepare various cyclic amidines were adopted from a wide selection already reported in the literature. For our purposes the most useful methods were (i) the reaction of a diamine with an imidate salt, (ii) the reaction of nitriles with diamines catalyzed by H_2S,[6,7] and (iii) the condensation of nitriles, diamines, and toluenesulfonic acid at high temperatures.[8]

The imidate salts used in method i were conveniently prepared either by the action of dry HCl upon an ether solution of a nitrile and an alcohol (the Pinner synthesis) or by the reaction of 1,3-propane sultone upon an amide at elevated temperatures according to the method of Ried and Schmidt.[9] In many instances α,β-unsaturated nitriles tended to react sluggishly or not at all in the Pinner synthesis; therefore, the Ried Schmidt method was a useful complementary technique, although the yields of desired products tended to be rather low.

Method ii was particularly useful for preparing large amounts of certain cyclic amidines, but its scope was somewhat limited because α,β-unsaturated nitriles could not be employed. The addition of H_2S to the conjugated double bond of the starting nitrile, and possibly also to some of the initially formed products led to complex reaction mixtures from which little, if any, of the desired product could be isolated.

Even more restricted was method iii. It was found that when either α,β-unsaturated nitriles or N-substituted diamines were the reactants, the yields were unsatisfactory. Nevertheless, at various stages of the synthetic program each of these methods was used to advantage.

Although the synthesis of 2-thiophenepropionitrile (**124**) had already been described by Cagniant and coworkers,[10] there arose a need for a more convenient preparation of this key intermediate. Cagniant, *et al.*, employed a multistep sequence using 2-thienylmag-

(1) Paper I of this series: 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) To whom inquiries should be addressed.

(3) Pyrantel, Banminth®.

(4) J. E. Lynch and B. Nelson, *J. Parasitol.*, **45**, 659 (1959).

(5) See also W. J. Farrington, *Aust. J. Chem.*, **17**, 230 (1964).

(6) H. Isler, U. S. Patent 2,505,217 (1950).

(7) A. Marxer, *J. Am. Chem. Soc.*, **79**, 467 (1957).

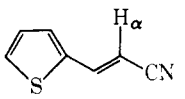
(8) P. Oxley and W. H. Short, *J. Chem. Soc.*, 497 (1947).

(9) W. Ried and E. Schmidt, *Ann.*, **676**, 134 (1964).

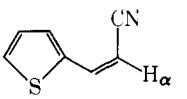
(10) P. Cagniant, D. Cagniant, and A. Delozarede, *Bull. Soc. Chim. France*, 1083 (1948).

nesium iodide as the starting material, but in our hands this method was unsuitable for making large amounts of material. What was needed was an inexpensive means of reducing 2-thiopheneacrylonitrile (**134**) on a large scale, since this latter compound is readily available from a Knoevenagel condensation of 2-thiophenecarboxaldehyde and cyanoacetic acid. After following several unrewarding approaches, we discovered that catalytic hydrogenation cleanly reduces the double bond of 2-thiopheneacrylonitrile to afford 2-thiophenepropionitrile in high yield. Normal ratios of 5% Pd–C catalyst were employed, and it was found that the presence of NaOH in the hydrogenation mixture increased the reaction rate. At about the same time this work was being carried out, Sam and Thompson[11] observed that 2-thiopheneacrylic acid can be reduced by H_2 over 10% Pd–C catalyst to furnish 2-thiophenepropionic acid in 80% yield. In the past thiopheneacrylic acids have been more generally reduced by agents such as NaHg[12,13] and Na–Pb alloy.[11] Apparently some thiophene compounds are far more stable to certain catalytic hydrogenation conditions than would be expected normally.[14]

As obtained from the reaction of cyanoacetic acid and 2-thiophenecarboxaldehyde, 2-thiopheneacrylonitrile consists of a 32:68 mixture of isomers. By means of preparative gas chromatography, the isomeric nitriles were separated and identified by their respective nmr spectra. As shown below, the coupling constant $J_{\alpha,\beta}$ and the chemical shifts for the α-protons of the isomeric nitriles are diagnostic. The doublet for the α-proton



δ = 5.6 ppm
$J_{\alpha\beta}$ = 16.4 cps

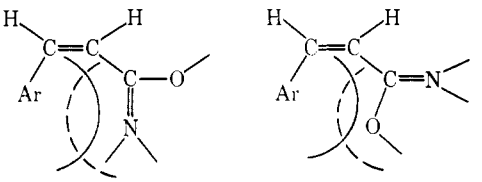


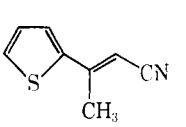
δ = 5.2 ppm
$J_{\alpha\beta}$ = 11.8 cps

of the minor component exhibits a smaller coupling constant and a smaller chemical shift than that of the major component; therefore, the minor component was assigned the *cis* configuration, while the major component the *trans*.[15]

A study of the Pinner reaction on the mixed isomers of 2-thiopheneacrylonitrile revealed an interesting case of stereoselectivity. Of the two possible isomeric imidate hydrochlorides, only the *trans* isomer was isolated. The $J_{\alpha\beta}$ for the imidate salt was 15.5 cps and no absorption peaks were found which could have been attributed to the presence of the *cis* isomer. No doubt strong repulsive nonbonded 1,3 interactions of the type illustrated below play an important role in determining this stereoselectivity.[16]

The Pinner reaction of β-methyl-2-thiopheneacrylonitrile (**140**) and the reaction between α-methyl-2-thiopheneacrylamide (**143**) and 1,3-propane sultone under the Ried–Schmidt conditions failed to produce detectable amounts of imidate salts. In both cases, 1,3 nonbonded interactions cannot be avoided. Imidate salts were prepared, however, by the action of $Et_3O^+BF_4^-$ on **143** and on β-methyl-2-thiopheneacrylamide (**141**). These latter imidates were converted to the corresponding tetrahydropyrimidines **144** and **142** (see Table I). A comparison of the uv spectra of the substances in Table I reveals that the maxima of **142** and **144** are shifted to shorter wavelengths with respect to the parent compound **71**, indicating that simple substitution on the link results in nonplanar molecules (compare **74** and **139**). Again, the repulsive 1,3 nonbonded interactions appear to be responsible.





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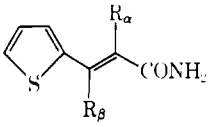
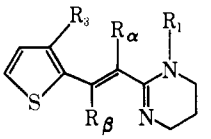


143, $R_\alpha = CH_3$; $R_\beta = H$
141, $R_\alpha = H$; $R_\beta = CH_3$

TABLE I
UV SPECTRA IN H_2O



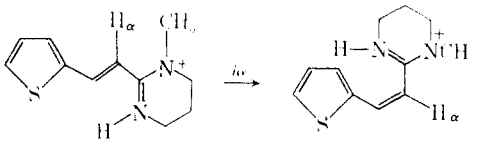
Compd no.	R_3	R_β	R_α	R_1	λ_{max}, mμ	Log ε	MED,[a] mg/kg
71	H	H	H	CH_3	312	4.27	7
74	CH_3	H	H	CH_3	318	4.26	3
142	H	CH_3	H	CH_3	292	4.10	30
144	H	H	CH_3	CH_3	287	4.24	>150
139	H	H	CH_2–CH_2		318	4.38	>86

[a] Based on per cent of active material (free base) present.

Except where noted, compounds in Tables XXI and XXII are believed to be the *trans* isomers. This belief rests mainly on the greater probability that the *trans* isomers would be the more thermodynamically stable, and on the nmr spectra of selected compounds. For example, the nmr spectrum of **71** exhibits in the olefinic proton region a doublet with a coupling constant of 15.7 cps. This value agrees well with that found for *trans*-2-thiopheneacrylonitrile, and agrees poorly with that of the *cis* nitrile. Further confirmation of the stereochemical assignment was found when the *cis* isomer **72** was prepared by the action of sunlight on **71**. The pertinent nmr data for the α-proton absorptions of the two isomers are summarized below. Because the photoisomer exhibits the smaller chemical shift and smaller coupling constant, it is assigned the *cis* configuration. Similar results were obtained with the *trans*–*cis* pairs **74**/**75** and **89**/**90**.

Owing to problems discussed previously, the 2-(2-arylvinyl) cyclic amidines exemplified in Tables XXI and XXII are relatively difficult to prepare by routes

(11) J. Sam and A. C. Thompson, *J. Pharm. Sci.*, **52**, 898 (1963).
(12) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938).
(13) M. L. Mihailovic and M. Tot, *J. Org. Chem.*, **22**, 652 (1957).
(14) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p 167 ff.
(15) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p 82 ff.
(16) A similar observation on the chemistry of cinnamonitriles has been made by M. Harfenist and A. P. Phillips, *J. Am. Chem. Soc.*, **80**, 6261 (1958).

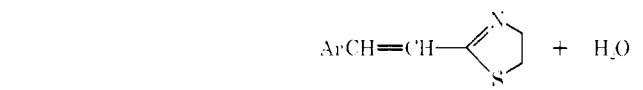


71 72 photoisomer

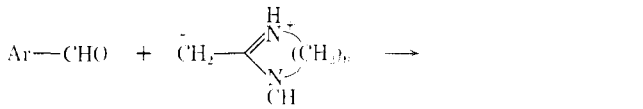
δ = 6.47 ppm δ = 6.02 ppm
$J_{\alpha\beta}$ = 15.7 cps $J_{\alpha\beta}$ = 12.5 cps

employing imidate salts as intermediates. Because some of the more highly potent compounds are found in this sub group, alternate synthetic methods were sought.

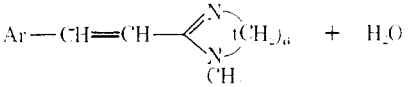
A line of investigation that proved particularly fruitful was based on Kuhn and Drawert's observation[17] that 2-methylthiazoline condenses readily with aromatic aldehydes to furnish 2-(2-arylvinyl)-2-thiazolines; such reactions are catalyzed by piperidine or piperidine acetate. Similar condensations are known to occur between aldehydes and *aromatic* heterocycles such as 2-picoline, 4-picoline, and 2-methylthiazole, but Kuhn



and Drawert speculated that for heterocyclic ring systems containing N and S, the presence of one double bond was sufficient to activate a neighboring CH_3.[17] It appeared that perhaps this principle could also be applied to other nonaromatic heterocyclic systems, in particular to 1,2-dimethyl-2-imidazoline and 1,4,5,6-tetrahydro-1,2 dimethylpyrimidine. Both of these compounds were prepared, and it was discovered that each reacted with aromatic aldehydes to produce various 2-(2-arylvinyl) cyclic amidines (see Tables XXI and XXII, compounds by method J).



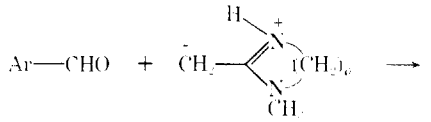
n = 2,3



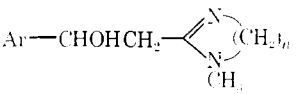
n = 2,3

Because the cyclic amidines are such strong bases themselves it was found unnecessary to use basic catalysts such as piperidine. Indeed, the zwitterion indicated above is the most probable reactive species. Usually, a solution of the 1,2-dimethyl cyclic amidine, the aldehyde, and a solvent such as benzene or toluene is heated under reflux, and as the reaction proceeds H_2O is removed from the mixture by means of a moisture trap. These conditions are quite satisfactory for small-scale preparations, *e.g.*, 0.1 mole, but it was found that as the size of the reaction mixture increases, the yield of desired product decreases. The problem seems to be that, in the larger preparations, H_2O is not removed rapidly enough from the reaction mixture to avoid its subsequent interaction with various cyclic amidines. It has been shown by Harnsberger and Riebsomer[18] that 1,2-dialkyl-2-imidazolines are rapidly hydrolyzed under strongly basic conditions, and it has been demonstrated in these laboratories that the cyclic amidines **21** and **37** also are hydrolyzed rapidly in the presence of H_2O to the corresponding amides.[19] The strongly basic amidines will generate a sufficiently high OH^- concentration in the presence of H_2O to catalyze their own hydrolysis. Harnsberger and Riebsomer[18] noted that 2-imidazolines are quite stable in aqueous solution below pH 7. From our own experience this observation applies equally well to tetrahydropyrimidines.

The problem of hydrolysis during condensation was overcome by employing the following (wo-step sequence: (i) an aldehyde and a 1,2-dimethyl cyclic amidine were allowed to react under mild conditions in an aprotic solvent or without solvent to furnish an aldol type adduct, and (ii) the aldol was then heated in the presence of an acid catalyst to effect the elimina-



n = 2,3



n = 2,3

tion of water. By breaking the condensation into these steps, exposure of cyclic amidine to H_2O under basic conditions is avoided. A number of variations on this theme are described in the Experimental Section. Table XXIII summarizes the physical properties and analytical data of the various adducts which were isolated in the course of this work. Another solution to the problem was found, when it was discovered that the presence of methyl or ethyl formate in the reaction mixture will suppress the hydrolysis of the amidine ring (see second example of method J in the Experimental Section).

Biological Evaluation. Compounds were tested in mice for anthelmintic activity against experimentally induced infections of the intestinal round worm *N. dubias*.[4,20,21] Although only the results of the *N. dubias* test are used to establish the structure–activity relationships in the present work, selected compounds have been examined for activity against a large number of nematode species in several hosts including dogs, horses, swine, sheep, cattle, and man. The results of these studies have been published elsewhere.[21,22]

(17) R. Kuhn and F. Drawert, *Ann.*, **590**, 55 (1954).

(18) R. G. Harnsberger and J. L. Riebsomer, *J. Heterocycl. Chem.*, **1**, 188 (1964).

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

(20) O. D. Standen, "Experimental Chemotherapy," Vol. 1, R. J. Schnitzer and F. Hawking, Ed., Academic Press, New York, N. Y., 1963, p 701 ff.

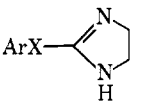
(21) H. L. Howes, Jr., and J. E. Lynch, *J. Parasitol.*, **53**, 1085 (1967).

(22) (a) R. L. Cornwell, *Vet. Record*, **79**, 590 (1966); (b) R. L. Cornwell, J. Berry, T. C. Light, E. A. Mercer, and G. Phillips, *ibid.*, **79**, 626 (1966); (c) R. L. Cornwell, J. Berry, T. C. Light, E. A. Mercer, G. Phillips, and D. A. Pullen, *ibid.*, **79**, 723 (1966); (d) R. L. Cornwell, R. M. Jones, J. Berry, T. Jordan, E. A. Mercer, D. A. Pullen, and C. J. Riley, *ibid.*, **80**, 434 (1967); (e) R. L. Cornwell, R. M. Jones, J. Berry, T. Jordan, E. A. Mercer, D. A. Pullen, and C. J. Riley, *ibid.*, **80**, 676 (1967); (f) R. L. Cornwell and R. M. Jones, *ibid.*, **82**, 183, 585 (1968); (g) J.-P. Raymond, *Rec. Med. Vet.*, **119**, 115, 213 (1968); (h) T. E. Gibson and J. W. Parfoot, *Brit. Vet. J.*, **124**, 69 (1968); (i) R. L. Cornwell and R. M. Jones, *J. Trop. Med. Hyg.*, **71**, 165 (1968); (j) D. P. Conway, unpublished results.

The rat nematode *Nippostrongylus muris* proved to be less sensitive than *N. dubius* to drugs in the pyrantel class. This observation was particularly useful in the secondary evaluation of the active compounds discovered in the primary screen. In general, the activity against *N. muris* correlated fairly well to that observed against the more drug-resistant nematodes of sheep.

The minimum effective dose (MED) of each compound reported in Tables I–XXIII is considered to be the lowest dose which will reduce the average *N. dubius* worm burden by at least 90% when administered to a group of four to six infected male mice. The different substances were dissolved or suspended in either peanut oil or 1% aqueous carboxymethylcellulose 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 (50–500 mg/kg depending upon the compound's toxicity) was given to the mice. If anthelmintic activity was detected then the compound was tested at successively lower doses until the MED was established. Sets of infected, untreated mice were used as controls. Additional details of these and similar procedures are given in the literature.[4,20,21]

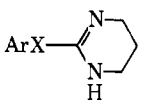
TABLE II



Ar	MED, mg/kg[a] X: $-CH_2CH_2-$	MED, mg/kg[a] X: $>C=C<^{H}_{H}$
2-C_4H_3S	100	>60
3-CH_3-2-C_4H_2S	105	
C_6H_5	>200	
2-C_4H_3O	100	

[a] Based on per cent of active material (free base) present.

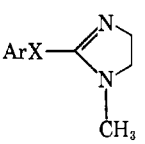
TABLE III



Ar	MED, mg/kg[a] X: $-CH_2CH_2-$	MED, mg/kg[a] X: $>C=C<^{H}_{H}$
2-C_4H_3S	100	31
3-CH_3-2-C_4H_2S		106
C_6H_5	>150	>154
2-$CH_3C_6H_4$		>106
2-C_4H_3O	>83	

[a] Based on per cent of active material (free base) present.

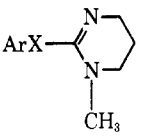
TABLE IV



Ar	MED, mg/kg[a] X: $-CH_2CH_2-$	MED, mg/kg[a] X: $>C=C<^{H}_{H}$
2-C_4H_3S	25	26
3-CH_3-2-C_4H_2S	25	21
2-$CH_3C_6H_4$		36
2-C_4H_3O		>206

[a] Based on per cent of active material (free base) present.

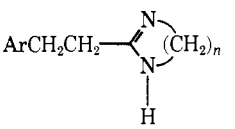
TABLE V



Ar	MED, mg/kg[a] X: $-CH_2CH_2-$	MED, mg/kg[a] X: $>C=C<^{H}_{H}$
2-C_4H_3S	25	7
3-CH_3-2-C_4H_2S	38	3
C_6H_5	>100	20
2-$CH_3C_6H_4$	>75	4
2-C_4H_3O		62

[a] Based on per cent of active material (free base) present.

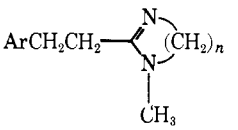
TABLE VI



Ar	MED, mg/kg[a] $n = 2$	MED, mg/kg[a] $n = 3$
2-C_4H_3S	100	100
3-CH_3-2-C_4H_2S	105	
C_6H_5	>200	>150
2-C_4H_3O	>100	>83

[a] Based on per cent of active material (free base) present.

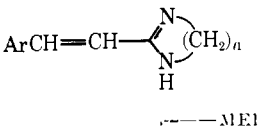
TABLE VII



Ar	MED, mg/kg[a] $n = 2$	MED, mg/kg[a] $n = 3$
2-C_4H_3S	25	25
3-CH_3-2-C_4H_2S	25	38
C_6H_5		>100
2-$CH_3C_6H_4$		>75

[a] Based on per cent of active material (free base) present.

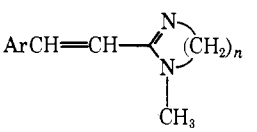
TABLE VIII



Ar	MED, mg/kg[a] $n = 2$	MED, mg/kg[a] $n = 3$
2-C_4H_3S	>60	31
3-CH_3-2-C_4H_2S		>106
C_6H_5		>154
2-$CH_3C_6H_4$		>106

[a] Based on per cent of active material (free base) present.

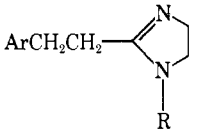
TABLE IX



Ar	MED, mg/kg[a] $n = 2$	MED, mg/kg[a] $n = 3$
2-C_4H_3S	26	7
3-CH_3-2-C_4H_2S	21	3
C_6H_5		20
2-$CH_3C_6H_4$	36	4
2-C_4H_3O	>206	62

[a] Based on per cent of active material (free base) present.

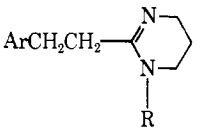
Table X



Ar	MED, mg/kg[a] R = H	MED, mg/kg[a] R = CH_3
2-C_4H_3S	100	25
3-CH_3-2-C_4H_2S	105	25
C_6H_5	>200	
2-C_4H_3O	>100	

[a] Based on per cent of active material (free base) present.

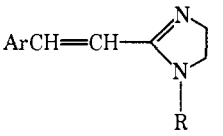
Table XI



Ar	MED, mg/kg[a] R = H	MED, mg/kg[a] R = CH_3
2-C_4H_3S	100	25
3-CH_3-2-C_4H_2S		38
C_6H_5	>150	>100
2-$CH_3C_6H_4$		>75
2-C_4H_3O	>83	

[a] Based on per cent of active material (free base) present.

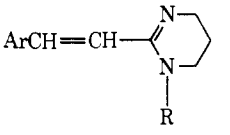
Table XII



Ar	MED, mg/kg[a] R = H	MED, mg/kg[a] R = CH_3
2-C_4H_3S	>100	26
3-CH_3-2-C_4H_2S		21
2-$CH_3C_6H_4$		36
2-C_4H_3O		>206

[a] Based on per cent of active material (free base) present.

Table XIII



Ar	MED, mg/kg[a] R = H	MED, mg/kg[a] R = CH_3
2-C_4H_3S	31	7
3-CH_3-2-C_4H_2S	>106	3
C_6H_5	>154	20
2-$CH_3C_6H_4$	>106	4
2-C_4H_3O		152

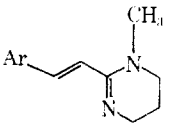
[a] Based on per cent of active material (free base) present.

Structure–Activity Relationships.—For purposes of discussion, all compounds which reduce the *N. dubius* worm burden in a mouse by >90% are considered to be active; to differentiate these compounds further a comparison of their relative potencies (*i.e.*, their minimum effective doses or MED's) is made. Inactive compounds are considered to be those which exhibit no activity at subtoxic doses.

In discussing the structure–activity relationships in this series of compounds, it is convenient to consider separately the three major structural elements: (i) the aromatic ring, (ii) the cyclic amidine portion, and (iii) the chain of atoms or link connecting the two ring systems. Statements can be made concerning requirements for activity in each of these units, but there are subtle interactions between the systems which interfere with ready predictions of relative potencies in many instances.

Table XIV

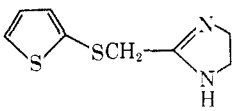
The Effect of Aromatic Substitution on Potency



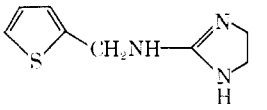
Position	No.	Ar	MED,[a] mg/kg	π[b]
Unsubstituted	71	2-C_4H_3S	7	
	82	C_6H_5	20	0.00
	108	2-C_4H_3O	62	
ortho	74	3-CH_3-2-C_4H_2S	3	
	78	3-C_2H_5-2-C_4H_2S	17	
	79	3-Br-2-C_4H_2S	16	
	84	2-$CH_3C_6H_4$	4	0.68
	88	2-$C_2H_5C_6H_4$	30	1.22
	89	2-FC_6H_4	28	0.14
	93	2-ClC_6H_4	6	0.59
	97	2-BrC_6H_4	6	0.75
	98	2-IC_6H_4	55	0.92
	920	2-HOC_6H_4	>150	−0.54[c]
	101	2-$CH_3OC_6H_4$	>76	−0.55[c]
	103	2-$C_2H_5OC_6H_4$	>62	
	104	2-$C_3H_7OC_6H_4$	>126	
	105	2-$C_4H_9OC_6H_4$	>61	
	106	2-$NO_2C_6H_4$	30	−0.28
	109	3-CH_3-2-C_4H_3O	73	
meta	76	4-CH_3-2-C_4H_2S	107	
	85	3-$CH_3C_6H_4$	>213	
	91	3-FC_6H_4	>37	
	94	3-ClC_6H_4	>61	
	102	3-$CH_3OC_6H_4$	>79	
	107	3-$NO_2C_6H_4$	>217	
para	77	5-CH_3-2-C_4H_2S	>150	
	86	4-$CH_3C_6H_4$	>297	
	92	4-FC_6H_4	>150	
	95	4-ClC_6H_4	>155	
	100	4-HOC_6H_4	>145	
Di-*ortho*	87	2,6-$(CH_3)_2C_6H_4$	>151	
	96	2,6-$Cl_2C_6H_3$	>64	

[a] Based on per cent of active material (free base) present. [b] T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964); phenoxyacetic acid series employed. [c] Phenylacetic acid series.

The Link.—As was indicated at the beginning of this paper the active isothiuronium salt **1** readily hydrolyzes to 2-thenylthiol and 2-imidazolidone. To circumvent this difficulty, compounds resembling **1** in structure, but possessing greater chemical stability in the link, were prepared and tested. Neither of the isosteres **4** and **6,** is active.



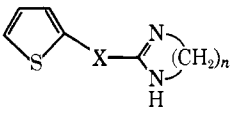
4



6

In due course, however, a stable linkage compatible with activity was discovered. This link was ethylene ($-CH_2CH_2-$) and **8** and **10** are representative active

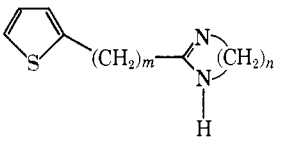
TABLE XV



No.	X	n	Salt	Preparative method[c]	Mp, °C	Recrystn solvent	Formula	Analyses	MED, mg/kg	Days given
1[a,b]	CH_2S	2	HCl	A1	173–175 dec	MeOH–*i*-PrOH	$C_8H_{11}ClN_2S_2$	C, H, N	25	3
2[b]	CH_2S	3	HCl	A1	160–162 dec	*i*-PrOH	$C_9H_{13}ClN_2S_2$	C, H, N	100	3
3	CH_2S	4	HCl	A1	158–159	MeCN	$C_{10}H_{15}ClN_2S_2$	C, H, N	>100	3
4	SCH_2	2	HCl	B1	147–149	MeOH–Me_2CO	$C_8H_{11}ClN_2S_2$	C, H, N	>350	3
5	SCH_2	3	HCl	B1	112–114	MeOH–Me_2CO	$C_9H_{13}ClN_2S_2$	C, H; N[d]	>200	3
6	CH_2NH	2	HI	C1	120–122	EtOH–Et_2O	$C_8H_{12}IN_3S$	C, H, N	250	3
7	CH_2CH_2	2	Base	B3	99–101	Me_2CO–C_6H_{14}	$C_9H_{12}N_2S$	C, H; N[e]	100	3
8	CH_2CH_2	2	HCl	B1	142–144	*i*-PrOH–Et_2O	$C_9H_{13}ClN_2S$	C, H, N	100	3
9	CH_2CH_2	3	Base	B3	94–96	PhH–C_6H_{14}	$C_{10}H_{14}N_2S$	C, H, N	100	3
10	CH_2CH_2	3	HCl	B1	171–172	MeCN	$C_{10}H_{15}ClN_2S$	C, H; N[f]	100	3
11	CH_2CH_2	4	TsOH	D1	180–182	MeOH–Me_2CO	$C_{18}H_{24}N_2O_3S_2$	C, H, N	>100	3
12	$CH_2CH(CH_3)$	3	HCl	B1	156–157	*i*-PrOH–Et_2O	$C_{11}H_{17}ClN_2S$	C, H, N	>250	3

[a] R. E. Kent, U. S. Patent 2,956,923 (1960). [b] W. H. Hensley and J. A. Lambrech, U. S. Patent 3,186,990 (1965). [c] The symbols used in this column are explained at the beginning of the Experimental Section. [d] N: calcd, 11.3; found, 10.8. [e] N: calcd, 15.5; found, 14.9. [f] N: calcd, 12.1; found, 12.8.

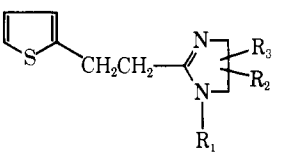
TABLE XVI



No.	m	n	Salt	Preparative method[b]	Mp, °C	Recrystn solvent	Formula	Analyses	MED, mg/kg	Days given
13	0	2	TsOH	D1	188–191	MeOH-*i*-PrOH	$C_{14}H_{16}N_2O_3S_2$	C, H, N	>100	3
14	0	3	Base	D3	183–185	MeOH–Me_2CO	$C_8H_{10}N_2S$	C, H, N	>100	3
15	0	4	TsOH	D1	165–168	*i*-PrOH	$C_{16}H_{20}N_2O_3S_2$	C, H, N	>100	3
16[a]	1	2	Maleic	B4	136–138	*i*-PrOH	$C_{12}H_{14}N_2O_4S$	C, H, N	>500	3
17	1	3	Maleic	B4	127–128	*i*-PrOH	$C_{13}H_{16}N_2O_4S$	C, H, N	>500	3
18	3	3	HCl	B1	138–139	*i*-PrOH–Et_2O	$C_{11}H_{17}ClN_2S$	C, H, N	>250	3

[a] L. P. Kyrides [U. S. Patent 2,457,047 (1948)] reported the synthesis of the free base. [b] The symbols used in this column are explained at the beginning of the Experimental Section.

TABLE XVII

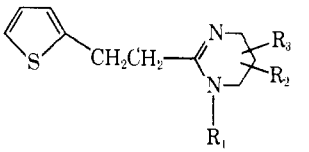


No.	R_1	R_2	R_3	Salt	Preparative method[a]	Mp or bp (mm), °C	Recrystn solvent or $n^{24}D$	Formula	Analyses	MED, mg/kg	Days given
19	H	4-CH_3	H	Base	B3	141 (1.3)	1.5611	$C_{10}H_{14}N_2S$	C, H, N	>250	3
20	H	4-CH_3	4-CH_3	Maleic	B2	117–118	Me_2CO	$C_{15}H_{20}N_2O_4S$	C, H, N	>200	3
21	CH_3	H	H	Base	B3	114 (0.7)		$C_{10}H_{14}N_2S$	H, N; C[c]	25	1
22	CH_3	H	H	Tartaric	B4	167–169	[b]	$C_{14}H_{20}N_2O_6S$	N	50	1
23	CH_3	H	H	$CH_3I \cdot H_2O$	B4	169–171	EtOH	$C_{11}H_{19}IN_2OS$	C, H, N	>250	3
24	C_2H_5	H	H	Base	B3	116 (0.2)	1.5511	$C_{11}H_{16}N_2S$	C, H, N	>100	3
25	C_3H_7	H	H	Base	B3	104 (0.1)	1.5430	$C_{12}H_{18}N_2S$	C, H, N	>62.5	3
26	*i*-C_3H_7	H	H	Base	B3	104 (0.1)	1.5435	$C_{12}H_{18}N_2S$	C, H; N[d]	>125	2
27	*i*-C_3H_7	H	H	Citric	B4	104–106	MeOH–*i*-PrOH	$C_{18}H_{26}N_2O_7S$	C, H, N	>100	3
28	C_4H_9	H	H	Base	B3	136 (2)	1.5358	$C_{13}H_{20}N_2S$	C, H, N	>250	1
29	$C_{16}H_{21}$	H	H	Base	B3	178 (0.005)	1.5109	$C_{19}H_{32}N_2S$	C, H, N	>100	3
30	$CH_2CH{=}CH_2$	H	H	HCl	B1	124–126	*i*-PrOH–Et_2O	$C_{12}H_{17}ClN_2S$	C, H, N	>100	3
31	C_6H_5	H	H	Base	B3	156 (0.15)	1.6100	$C_{15}H_{16}N_2S$	C, H, N	>250	1
32	CH_2CH_2OH	H	H	Base	B3	184 (0.5)		$C_{11}H_{16}N_2OS$	C, H, N	>125	3

[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] Precipitated from Me_2CO; triturated under cold MeOH. [c] C: calcd, 61.8; found, 61.1. [d] N: calcd, 12.6; found, 12.1.

compounds. Shortening the chain to methylene or lengthening it to trimethylene leads to a reduction of activity (see Table XVI). Later, *trans*-vinylene (–CH=CH–) was also found to be compatible with activity, and indeed some of the most potent compounds in this series possess this linkage (see Tables XXI and XXII). In fact, the data of Tables III and V suggest that *trans*-vinylene is superior to $(CH_2)_2$ as a connecting chain where the amidine system is tetrahydropyrimidine. However, no such special effect is observed among the imidazolines of Tables II and IV. The *cis* isomers are always less potent that the corresponding

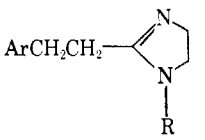
TABLE XVIII



No.	R_1	R_2	R_3	Salt	Preparative method[b]	Mp or bp (mm), °C	Recrystn solvent or $n^{25}D$	Formula	Analyses	MED, mg/kg	Days given
33	H	4-CH_3	H	Base	B3	122 (0.05)	1.5661	$C_{13}H_{16}N_2S$	C, H, N	>250	3
34	H	5-CH_3	H	HCl	B1	174–176	*i*-PrOH–Et_2O	$C_{13}H_{17}ClN_2S$	H, N; C[d]	>250	3
35	H	5-CH_3	5-CH_3	SSA[c]	B2	225–227	EtOH	$C_{26}H_{28}N_2O_6S_2$	C, H, N	>200	3
36	H	5-OH	H	HCl	B1	131–132	MeOH	$C_{12}H_{15}ClN_2OS$	C, H, N	>500	3
37	CH_3	H	H	Base	B3	130 (0.15)	1.5648	$C_{13}H_{16}N_2S$	C, H, N	25	1
38	CH_3	H	H	Tartaric	B4	140–142	[e]	$C_{15}H_{22}N_2O_8S$	N	50	1
39	CH_3	H	H	CH_3I	B3	164–166	*i*-PrOH	$C_{14}H_{19}IN_2S$	C, H, N	>200	3
40	C_2H_5	H	H	Citric	E2	102–106	Me_2CO	$C_{19}H_{26}N_2O_7S$	N	>200	3
41	C_3H_7	H	H	Citric	E2	90–93	Me_2CO	$C_{20}H_{28}N_2O_7S$	N	>200	3
42	*i*-C_3H_7	H	H	Base	B3	123 (0.2)	1.5484	$C_{15}H_{20}N_2S$	H, N; C[f]	>125	3
43	CH_2=$CHCH_2$	H	H	HCl	B1	161–163	*i*-PrOH–Et_2O	$C_{14}H_{17}ClN_2S$	C, H, N	>100	3
44	$C_6H_5CH_2$	H	H	HCl	B1	154–156	*i*-PrOH–Et_2O	$C_{19}H_{21}ClN_2S$	C, H, N	>250	3

[a] SSA = sulfosalicylic acid. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] Precipitated from Me_2CO–Et_2O; triturated under cold MeOH. [d] C: calcd, 53.9; found, 54.5. [e] C: calcd, 66.1; found, 64.9.

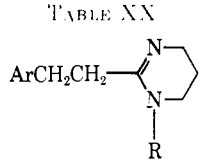
TABLE XIX



No.	Ar	R	Salt	Preparative method[b]	Mp or bp (mm), °C	Recrystn solvent or $n^{25}D$	Formula	Analyses	MED, mg/kg	Days given
45	3-CH_3-2-C_4H_2S	H	Base	B3	130 (0.2)	1.5732	$C_{10}H_{14}N_2S$	H, N; C[c]		
46	3-CH_3-2-C_4H_2S	H	HCl	B4	149–151	*i*-PrOH–IPE	$C_{10}H_{15}ClN_2S$	C, H, N	125	1
47	3-CH_3-2-C_4H_2S	CH_2	HCl	B4	143–144	Me_2CO	$C_{11}H_{17}ClN_2S$	C, H, N	30	1
48[d]	C_6H_5	H	Base	D3	106–108	PhH–C_6H_{14}	$C_{11}H_{14}N_2$	C, H, N	>200	3
49	2-C_4H_3O	H	Base	D3	105–107	EtOAc	$C_9H_{12}N_2O$	C, H, N	>100	3
50	1-Pyrrolyl	H	TsOH	D1	134–135	MeOH–Me_2CO	$C_{16}H_{21}N_3O_3S$	C, H, N	>250	3

[a] M. Hartmann and H. Isler, *Arch. Exptl. Pathol. Pharmakol.*, **192,** 141 (1939); these authors report mp 103–104°. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] C: calcd, 61.8; found, 61.1.

TABLE XX



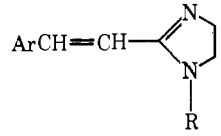
No.	Ar	R	Salt	Preparative method[b]	Mp or bp (mm), °C	Recrystn solvent or $n^{25}D$	Formula	Analyses	MED, mg/kg	Days given
51	3-CH_3-2-C_4H_2S	CH_3	HPF_6	B4	116–118	*i*-PrOH	$C_{12}H_{18}F_6N_2PS$	C, H, N	62.5	1
52	4-Br-2-C_4H_2S	H	HCl	B1	164–165	*i*-PrOH–Et_2O	$C_{10}H_{14}BrClN_2S$	H, N; C[c]	>250	3
53[d]	C_6H_5	H	Base	D3	105–106	*i*-PrOH–*i*-Pr_2O	$C_{12}H_{16}N_2$	C, H, N	>150	3
54	C_6H_5	H	HCl	B1	188–190	*i*-PrOH–Et_2O	$C_{12}H_{17}ClN_2$	C, H, N	>100	1
55	C_6H_5	CH_3	Base	B3	100 (0.16)	1.5552	$C_{13}H_{18}N_2$	C, H; N[e]	>100	3
56	2-$CH_3C_6H_4$	CH_3	HPF_6	B2	141–142	EtOH	$C_{14}H_{19}F_6N_2P$	C, H, N	>125	1
57	2-C_4H_3O	H	HCl	B1	165–167	*i*-PrOH–*i*-Pr_2O	$C_{10}H_{15}ClN_2O$	C, H, N	>100	3
58	2-Pyridyl	H	TsOH	D1	112–113	Me_2CO	$C_{18}H_{23}N_3O_3S$	C, H, N	>200	3
59	1-Pyrrolyl	H	TsOH	D1	149–151	*i*-PrOH	$C_{17}H_{23}N_3O_3S$	C, H, N	>500	3
60	1-Pyrazolyl	H	TsOH	D1	153–155	EtOH	$C_{16}H_{22}N_4O_3S$	C, H, N	>500	3
61	1-Pyrazolyl	CH_3	Citric	E2	148–150	EtOH	$C_{16}H_{24}N_4O_7$	C, H, N	>500	3
62	2-Thiazolyl	CH_3	Fumaric	E2	125–126	EtOH–Et_2O	$C_{19}H_{19}N_3O_4S$	C, H, N	>250	2
63	C_6H_5	CH_2	HPF_6	E5	84–85	H_2O	$C_{18}H_{18}F_6N_2P$	C, H, N	>250	1
64	*c*-C_3H_7	CH_3	HPF_6	E5	73–74	H_2O	$C_{16}H_{24}F_6N_2P$	C, H, N	>125	1

[a] G. S. Skinner and P. R. Wuuz [*J. Am. Chem. Soc.*, **73,** 3814 (1951)] report mp 107–109°. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] C: calcd, 38.8; found, 38.2. [d] N: calcd, 13.4; found, 13.9.

trans compounds (see Table XXII, compound pairs **71**/**72**, **74**/**75**, **89**/**90**).

The uv spectra of **142**, **144**, and **139** have been discussed in the Chemistry Section (see Table I); the α-methyl isomer **144** is inactive, while the β-methyl compound **142** is active but less potent than pyrantel. The tricyclic compound **139**, a planar analog of **144**, is also inactive. There does not appear to be any obvious relationship between the planarity of a molecule and its biological activity. The cyclopropane derivatives **145** and **146**, analogs of *trans*-vinylene compounds, were also prepared, but they were found to be inactive. In the

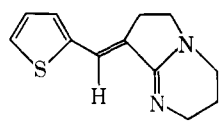
TABLE XXI



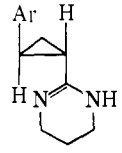
No.	Ar	R	Salt	Preparative method	Mp, °C	Recrystn solvent	Formula	Analyses	MED, mg/kg	Days given
65	2-C_4H_3S	H	Maleic	F2	162–163	*i*-PrOH	$C_{13}H_{14}N_2O_4S$	C, H, N	>100	3
66	2-C_4H_3S	CH_3	TsOH	F2	162–164	*i*-PrOH	$C_{17}H_{20}N_2O_3S$	C, H, N	50	1
67[a]	3-CH_3-2-C_4H_2S	CH_3	HCl	J2	243–244	*i*-PrOH	$C_{10}H_{15}ClN_2S$	C, H, N	25	1
68	2-$CH_3C_6H_4$	CH_3	HPF_6	J5	189–190	MeOH	$C_{13}H_{17}F_6N_2P$	C, H, N	62.5	1
69	2-C_4H_3O	CH_3	HCl	J2	93–94	*i*-PrOH–*i*-Pr_2O	$C_{10}H_{13}ClN_2O$	C, H, N	>250	1

[a] The 4-methyl isomer was present in this preparation to the extent of 5–10% as determined by the nmr spectrum; an 80:20 mixture of 3-methyl- and 4-methyl-2-thiophenecarboxaldehydes was used. [b] The symbols used in this column are explained at the beginning of the Experimental Section.

ethylene series. β substitution of the link by hydroxy leads to inactive compounds (see Table XXIII).

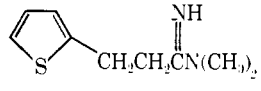


139

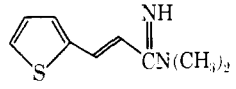


146, Ar = phenyl
145, Ar = 2-thienyl

The Cyclic Amidine System.—A cyclic amidine system is not essential for anthelmintic activity. The noncyclic pyrantel analogs **158** and **159** are active.[23] However, among the cyclic amidines, the influence of



158



159

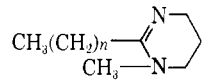
ring size upon activity or potency is important; for example, the tetrahydro-1,3-diazepines **3** and **11** are inactive at the test levels indicated in Table XV.

The majority of the compounds in the present paper are 2-imidazolines or 1,4,5,6-tetrahydropyrimidines. It was of interest to see if there was any reason to prefer one system over the other. A comparison of the data in Tables VI and VII would indicate no marked differences between the five- and six-membered ring systems where ethylene is the connecting chain. However, the data in Tables VIII and IX suggest that the tetrahydropyrimidine moiety affords more potent compounds where *trans*-vinylene is the link. This observation is actually the same as that made previously in the discussion of the link, only here the emphasis is different.

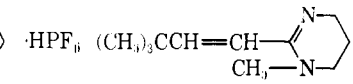
One generality for this series so far has no exceptions: an N-methyl cyclic amidine is always more potent than the corresponding unsubstituted compound (see Tables X–XIII). Substitution of N by groups larger than Me leads to inactive compounds. Substitution on C-4 or C-5 of the ring system also seems to be unfavorable (see Tables XVII and XVIII).

The Aromatic Ring.—An aromatic ring is essential for anthelmintic activity: the simple aliphatic analogs of pyrantel **63**, **64**, and **110** are inactive.

As indicated in Tables II–XIII replacing 2-thienyl by any of its simpler unsubstituted analogs (3-thienyl, phenyl, or 2-furyl) leads to less potent compounds in a wide variety of situations. Also, the 1-pyrrolyl, 1-pyrazolyl, and 2-thiazolyl analogs in Table XX are all inactive. It appears, therefore, that 2-thienyl is the optimum aromatic system for good anthelmintic activity. The decreasing order of potency is 2-thienyl > 3-thienyl > phenyl > 2-furyl.



63, $n = 3$
64, $n = 4$



110

In discussing substituent effects, at least two factors have to be considered: (i) the position substituted, and (ii) the nature of the substituent. To explore these influences, we prepared and tested the series of compounds in Table XIV. With exceptions, substitution at an *ortho* position is compatible with activity, but substitution elsewhere results in a loss of activity or at least a significant reduction in potency. Substitution at both *ortho* positions, however, is unfavorable. As mono-*ortho* substituents both Cl and CH_3 lead to highly potent compounds, but when both *ortho* positions are substituted by these groups activity is lost (see **87** and **96**).

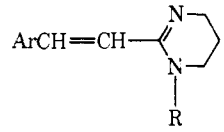
While substitution at one *ortho* position is compatible with activity, a wide range of MED's is nevertheless observed. The nature of the group itself is probably not the sole factor determining potency, *e.g.*, the *o*-tolyl compound **84** is far superior to its parent **82**, but the 3-methyl-2-furyl compound **109** and its parent **108** are essentially equipotent. Therefore, the nature of the aromatic ring must also play a role. It is also not sufficient to explain differences of potency on steric grounds alone: the 2-methoxy analog **101** is inactive, but the 2-ethyl isostere **88** is active. Similarly, if size alone determines whether a group is compatible with activity, then it is surprising that the 2-hydroxy compound **99** is inactive while closely analogous halogen compounds are active. Further, the electronic nature of the group by itself appears to have no relationship to the activity observed, *e.g.*, following the work of Hansch,[24] a plot of the potency index [log (1/MED)] against Hammett's σ substituent constant shows no significant correlation between these two variables.

However, another aspect of Hansch's work offers an

(23) J. W. McFarland and H. L. Howes, Jr., in preparation.

(24) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).

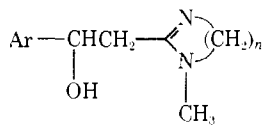
TABLE XXII



No.	Ar	R	Salt	Preparative method[b]	Mp, °C	Recryst solvent	Formula	Analyses	MED, mg/kg	Days given
70	2-C_4H_3S	H	Maleic	F2	153–155	*i*-PrOH–Et$_2$O	$C_{14}H_{16}N_2O_4S$	C, H, N	50	1
71	2-C_4H_3S	CH_3	Tartaric	J2	147–148	EtOH	$C_{15}H_{20}N_2O_6S$	C, H, N	12.5	1
72	2-C_4H_3S (*cis*)	CH_3	Tartaric	J1	160–161	EtOH	$C_{15}H_{20}N_2O_6S$	C, H, N	250	3
73	3-CH_3-2-C_4H_2S	H	HCl	H1	235–237	*i*-PrOH	$C_{10}H_{15}ClN_2S$	C, H, N	>125	1
74	3-CH_3-2-C_4H_2S	CH_3	Tartaric	J1	169–171	MeOH–EtOH	$C_{15}H_{20}N_2O_6S$	C, H, N	3.1	1
75	3-CH_3-2-C_4H_2S (*cis*)	CH_3	Tartaric	J1	141–143[c]	MeCN	$C_{15}H_{20}N_2O_6S$	C, H, N	250	3
76[d]	4-CH_3-2-C_4H_2S	CH_3	HCl	I1	225–226	*i*-PrOH–EtOAc	$C_{12}H_{17}ClN_2S$	C, H, N	125[e]	1
77	5-CH_3-2-C_4H_2S	CH_3	HPF_6	I5	151–152	*i*-PrOH	$C_{12}H_{16}F_6N_2PS$	C, H, N	>250	1
78	3-C_2H_5-2-C_4H_2S	CH_3	Fumaric	J2	161–171 dec	H_2O–*i*-PrOH	$C_{15}H_{22}N_2O_4S$	C, H, N	25	1
79	3-Br-2-C_4H_2S	CH_3	Tartaric	J2	110–113	EtOH	$C_{15}H_{21}BrN_2O_6S \cdot H_2O$	C, H, N	25	1
80	3-C_4H_3S	CH_3	Fumaric	J2	193–194	MeOH	$C_{15}H_{18}N_2O_4S$	C, H, N	25	1
81	C_6H_5	H	Maleic	F2	122–123	*i*-PrOH–Et$_2$O	$C_{16}H_{18}N_2O_4$	C, H, N	>250	1
82	C_6H_5	CH_3	HPF_6	J2	147–148	EtOH	$C_{13}H_{17}F_6N_2P$	C, H, N	85	1
83	2-$CH_3C_6H_4$	H	HCl	H1	210–211	*i*-PrOH	$C_{13}H_{17}ClN_2$	C, H, N	>125	1
84	2-$CH_3C_6H_4$	CH_3	1.5HCl	H1	184–188	*i*-PrOH	$C_{14}H_{19.5}Cl_{1.5}N_2$	C, H, N	8	1
85	3-$CH_3C_6H_4$	CH_3	HCl	H1	189–190	*i*-PrOH	$C_{14}H_{19}ClN_2$	C, H, N	>250	1
86	4-$CH_3C_6H_4$	CH_3	HPF_6	I5	203–202	EtOH	$C_{14}H_{19}F_6N_2P$	C, H, N	>500	1
87	2,6-$(CH_3)_2C_6H_3$	CH_3	Tartaric	J2	203–206	H_2O	$C_{15}H_{24}N_2O_6$	C, H, N	>250	2
88	2-$C_2H_5C_6H_4$	CH_3	HPF_6	I5	159–160	MeOH	$C_{15}H_{21}F_6N_2P$	C, H, N	62.5	1
89	2-FC_6H_4	CH_3	HPF_6	I5	177–178	EtOH	$C_{13}H_{16}F_7N_2P$	C, H, N	62.5	1
90	?-FC_6H_4 (*cis*)	CH_3	HPF_6	e	259–260	EtOH	$C_{13}H_{16}F_7N_2P$	C, H, N	>200	1
91	3-FC_6H_4	CH_3	HPF_6	I5	193–195	EtOH	$C_{13}H_{16}F_7N_2P$	C, H, N	>62.5	1
92	4-FC_6H_4	CH_3	HPF_6	I5	128–131	EtOH	$C_{13}H_{16}F_7N_2P$	C, H, N	>250	1
93	2-ClC_6H_4	CH_3	Tartaric	J2	177–179	EtOH–Et$_2$O	$C_{15}H_{21}ClN_2O_6$	C, H, N	12.5	1
94	3-ClC_6H_4	CH_3	Tartaric	J1	158–160	H_2O	$C_{15}H_{21}ClN_2O_6$	C, H, N	>100	1
95	4-ClC_6H_4	CH_3	HPF_6	I5	184–185	EtOH	$C_{13}H_{16}ClF_6N_2P$	C, H, N	>250	1
96	2,6-$Cl_2C_6H_3$	CH_3	Tartaric	J2	173–185	EtOH	$C_{15}H_{20}Cl_2O_6$	C, H, N	>100	3
97	?-BrC_6H_4	CH_3	HPF_6	I5	151–154	EtOH	$C_{13}H_{16}BrF_6N_2P$	C, H, N	15.1	1
98	?-IC_6H_4	CH_3	Fumaric	J2	208–209	MeOH–EtOH	$C_{17}H_{21}IN_2O_4$	C, H, N	75	1
99	?-HOC_6H_4	CH_3	Fumaric	J5	217–218	H_2O	$C_{17}H_{20}N_2O_5$	C, H, N	>200	1
100	4-HOC_6H_4	CH_3	Tartaric	J2	222–223	MeOH–Et$_2$O	$C_{15}H_{22}N_2O_7$	C, H, N	>250	3
101	2-$CH_3OC_6H_4$	CH_3	HPF_6	I15	119–120	EtOH	$C_{14}H_{19}F_6N_2OP$	C, H, N	>62.5	1
102	3-$CH_3OC_6H_4$	CH_3	H_2CO_4	J2	170–172	EtOH	$C_{15}H_{20}N_2O_6$	C, H, N	>100	1
103	2-$C_2H_5OC_6H_4$	CH_3	Tartaric	J1	126–128	H_2O	$C_{16}H_{22}O_7$	C, H, N	>100	1
104	2-$C_3H_7OC_6H_4$	CH_3	Tartaric	J1	95–97	H_2O–*i*-PrOH	$C_{16}H_{24}N_2O_7$	C, H, N	>200	1
105	2-$C_4H_9OC_6H_4$	CH_3	Fumaric (1.5)	J1	145–147	*i*-PrOH	$C_{18}H_{26}N_2O_5$	C, H, N	>100	1
106	2-$NO_2C_6H_4$	CH_3	Tartaric	J1	186–187	H_2O–*i*-PrOH	$C_{15}H_{19}N_3O_8 \cdot 0.5H_2O$	C, H, N	5.1	1
107	3-$NO_2C_6H_4$	CH_3	HCl	I1	249–250	*i*-PrOH	$C_{13}H_{18}ClN_3O_2$	C, H, N	>250	1
108	2-C_4H_3O	CH_3	Citric	F2	157–158	MeOH–Me$_2$CO	$C_{17}H_{22}N_2O_7$	C, H, N	125	1
109	3-CH_3-2-C_4H_2O	CH_3	HPF_6	I5	193–195	EtOH	$C_{13}H_{17}F_6N_2OP$	C, H, N	125	1
110	$(CH_3)_2C$	CH_3	HPF_6	J5	146–148	EtOH	$C_{13}H_{19}F_6N_2P$	C, H, N	>100	1

[a] Nmr spectrum indicates less than 5% of the 3-methyl isomer to be present (see 4-methyl-2-thiophenecarboxaldehyde in the Experimental Section); the activity of this compound could be entirely accounted for if only 1–3% of **74** were present. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] Isolated in 1% yield during work-up of a reaction mixture leading to **89**. [d] The product was not contaminated by the *trans* isomer of any other material as determined by paper chromatography.

TABLE XXIII



No.	Ar	*n*	Salt	Preparative method[a]	Mp, °C	Recryst solvent	Formula	Analyses	MED, mg/kg	Days given
111	2-C_4H_3S	3	HCl	G2	162–163	*i*-PrOH	$C_{11}H_{17}ClN_2OS$	C, H, N	>250	1
112	4-CH_3-2-C_4H_2S	3	HCl	G2	169–170	*i*-PrOH	$C_{12}H_{19}ClN_2OS$	C, H, N	>250	1
113	C_6H_5	3	HCl	G2	174–176	EtOH	$C_{13}H_{19}ClN_2O$	C, H, N	>250	1
114[a]	2-$CH_3C_6H_4$	2	HCl	G2	161–163	*i*-PrOH–*i*-Pr$_2$O	$C_{13}H_{19}ClN_2O$	H, N; C[b]	250[c]	3
115	2-$CH_3C_6H_4$	3	base	G3	82–83	C_6H_{14}	$C_{14}H_{20}N_2O$	C, H, N	>500	1
116	3-$CH_3C_6H_4$	3	HCl	G2	180–181	*i*-PrOH	$C_{14}H_{21}ClN_2O$	C, H, N	>250	1
117	4-$CH_3C_6H_4$	3	HCl	G2	207–208	*i*-PrOH	$C_{14}H_{21}ClN_2O$	C, H, N	>250	1
118	2-ClC_6H_4	3	HCl	G2	185–187	*i*-PrOH–EtOAc	$C_{13}H_{18}Cl_2N_2O$	C, H, N	>250	1
119	2-$CH_3OC_6H_4$	3	HCl	G2	184–186	*i*-PrOH	$C_{14}H_{21}ClN_2O_2$	C, H, N	*d*	
120	3-$NO_2C_6H_4$	3	HCl	G2	185–187	EtOH	$C_{13}H_{18}ClN_3O_3$	C, H, N	*d*	
121	4-$NO_2C_6H_4$	3	HCl	G2	204–205	EtOH	$C_{13}H_{18}ClN_3O_3$	C, H, N	*d*	

[a] This preparation consisted of approximately 10–15% **68** (as the HCl salt) as determined by nmr and uv spectroscopy. Unlike other members of this group, this compound showed anthelmintic activity. The activity, however, is most probably due to the presence of **68**. [b] The symbols used in this column are explained at the beginning of the Experimental Section. [c] C: calcd, 61.3; found, 62.2. [d] Not tested.

important insight into one effect which we believe plays a dominant role in governing the potency of the *ortho*-substituted phenyl analogs, and, by way of extension, of other analogs in this series. According to Hansch,[24] the potency of a drug in a series of closely related compounds frequently depends upon its lipophilic character. In such cases, there is a regular increase or a regular decrease in potency as the compounds become more lipophilic. Eventually an optimum degree of lipophilicity will be observed, and any further increase or decrease in lipophilic character will result in a less potent compound. To put this effect into quantitative terms, Hansch introduced the π substituent constant which is analogous to the Hammett σ constant, only in this case the related linear free-energy change refers to partition coefficients instead of ionization constants. In his theoretical treatment, Hansch concluded that the relationship of biological response to π will take the form of a parabola, and such a curve should be general for drug series where lipophilicity largely determines potency.

Table XIV lists the π values for the *ortho* substituents in the phenyl series. The more potent compounds in this group are associated with π values of about 0.7 (see **84**, **93**, **97**); compounds associated with larger or smaller π values are less potent almost to the degree that their π values differ from 0.7. Thus, among phenyl analogs of pyrantel, it appears the *o*-methyl derivative is near some optimum degree of lipophilicity for the group, *i.e.*, its associated π value stands near the maximum of some parabolic relationship with potency. However, when these same data are treated in the manner described by Hansch[24] in a multiple linear regression analysis using π^2 and π as the independent variables, no statistically significant correlation is found. This does not mean, of course, that the proposed parabolic relationship is necessarily disproven; among other possibilities, it could also mean that some other complicating factors which have not been taken into account are also influencing potency. Indeed, a very highly significant dependence of the potency upon π^2 and π is found when the effect of a substituent's dipole moment and its bulk are taken into consideration.[25]

In any event, the proposed relationship can be tested further by applying its principle to compounds which lie outside of the *ortho*-substituted phenyl group, *e.g.*, it is quite clear that a nearly parallel relationship exists among the 2-thienyl derivatives **71**, **74**, **78**, and **79** (see Table XIV). Here again the *o*-CH_3 analog **74** is the most potent of the group; however, the bromo compound **79** is less potent than expected. A number of otherwise difficult to explain structure–activity relationships are also accommodated by the hypothesis that lipophilicity plays a dominant role in determining the potency of pyrantel analogs, and that there is an optimum degree of lipophilicity in this series of compounds. One relationship we found initially puzzling is that although substitution of the β position by methyl is compatible with activity (*e.g.*, see compounds **142**, Table I), substitution by hydroxy results in the loss of activity (see compounds in Table XXIII). However, when it is considered that, compared to CH_3, OH is a very hydrophilic group, the mystery disappears, *i.e.*, the compounds in Table XXIII are all much too hydrophilic to be active. The inactivity of the α-CH_3 compound **144** is most probably due to a genuine steric effect. Another relationship we found so far has no exceptions: replacing the N CH_3 group by H always results in lower potency. It is obvious that the hydrogen bonding N–H group should be more hydrophilic than N–CH_3 and this effect should make compounds of the former type less potent than those of the latter.

The lipophilicity argument can also be used to explain, at least in part, why the furan derivative **108** is much less potent than the phenyl analog **82**, and the thienyl compound **71**. Of these three substances **108** is undoubtedly the most hydrophilic because the oxygen atom of the furan is a better hydrogen-bonding base than either the sulfur atom of the thiophene or the π electrons of the benzene system. Therefore, it is really not surprising that the furan compound is not very potent.

The foregoing structure–activity relationships, although complex, successfully guided the investigation of pyrantel analogs to the discovery of a large number of new anthelmintic agents, some of which will be reported in subsequent publications.[26,27]

Experimental Section

Boiling points are uncorrected; melting points were determined on a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.) and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

The meaning of the symbol used under the heading "Preparative Method" in Tables XV–XXV 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 subroutines used to isolate or purify the final product: (1) isolate the salt directly from the reaction mixture and then recrystallize; (2) isolate the product as the crude free base, convert it to a suitable salt, and then recrystallize; (3) isolate the product as the free base, then distil or recrystallize; (4) convert the distilled base to the appropriate salt, then recrystallize; and (5) precipitate the HPF_6 salt from an aqueous solution of the crude HCl or other water-soluble salt by the addition of 65% HPF_6.

Method A. Addition of 2-Chloromethylthiophene to Thioureas. 4,5,6,7-Tetrahydro-2-(2-thenylthio)-1H-1,3-diazepine Hydrochloride (3).—A mixture of 26.0 g (0.2 mole) of 2,3,4,5,6,7-hexahydro-1H-1,3-diazepine-2-thione[28] and 500 ml of MeCN was heated under reflux with stirring, and was subsequently treated with 28.0 g (0.21 mole) of 2-chloromethylthiophene. Stirring was continued for 2 hr. The reaction mixture was concentrated to a small volume, and unreacted thione was filtered from the oily residue which was subsequently triturated under PhH to afford the crude product as a crystalline material; yield 17.0 g (32%), mp 157–159°. This was recrystallized to afford pure **3**, mp 158–159°.

Method B. Cyclic Amidines from Imidate Salts. 1,4,5,6-Tetrahydro-2-[2-(2-thienyl)ethyl]pyrimidine Hydrochloride (10).—The method of Pinner[29] was used to convert 162.4 g (1.18 moles) of 2-thiophenepropionitrile (**124**) to ethyl 2-thiophenepropionimidate hydrochloride, yield 223.5 g (86%), mp 122–124°. This product was used in the next step without further purification.

A solution of 730 g (9.88 moles) of 1,3-propanediamine and 9.9

(25) J. W. McFarland, in preparation. While the complete analysis of these relationships belongs in the paper at hand, it is unfortunately much too lengthy; a considerable amount of theoretical background has to be introduced.

(26) J. W. McFarland, H. L. Howes, Jr., L. H. Conover, J. E. Lynch, W. C. Austin, and D. H. Morgan, in preparation.

(27) J. W. McFarland and H. L. Howes, Jr., *J. Med. Chem.*, **12**, 1079 (1969), paper III.

(28) A. F. McKay and M. L. Kreling, *Can. J. Chem.*, **35**, 1438 (1957).

(29) Review: R. Roger and D. G. Nielson, *Chem. Rev.*, **61**, 179 (1961).

TABLE XXIV
ArC$H_2$$_n$CN

No.	Ar	n	Preparative method[b]	Bp (mm), °C	$n^{25}D$	Literature Bp (mm), °C	Literature $n^{20}D$	Formula	Analyses
122[a]	2-C_4H_3S	0	L	100 (35)		196 (760)			
123[b]	2-C_4H_3S	1	L	96 (6)	1.5388	120 (22)			
124[c]	2-C_4H_3S	2	M	90 (0.5)	1.5418	129 (17)	1.5402 (20)		
125	3-CH_3-2-C_4H_2S	2	M	87 (0.2)	1.5440			C_7H_7NS	C, N; H[d]
126	4-Br-2-C_4H_2S	2	O	106 (0.2)				C_6H_4BrNS	H; C, N[e]
127	2-$CH_3C_6H_4$	2	M	71 (0.01)	1.5265			$C_{10}H_{11}N$	C, H, N
128[d]	2-C_4H_3O	2	N	111 (22)	1.4745	104 (11)			
129[e]	2-Pyridyl	2	L	82 (0.5)	1.5162	99 (12)	1.5175 (20)		
130[f]	1-Pyrrolyl	2	L	94 (0.2)	1.5105	133 (100)	1.5088 (26?)		
131[g]	1-Pyrazolyl	2	L	84 (0.2)	1.4972	129 (11)		$C_6H_7N_3$	N
132	2-Thiazolyl	2	N	[f]					
133	2-C_4H_3S	3	N	145 (25)	[f]				

[a] W. Steinkopf and W. Ohse, *Ann.*, **437**, 14 (1924). [b] F. F. Blicke and F. Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946). [c] See ref 10. [d] F. Sorm and J. Brandejs, *Collect. Czech. Chem. Commun.*, **12**, 444 (1947). [e] V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.*, **75**, 3243 (1953). [f] J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.*, **27**, 1652 (1962). [g] H. Reimlinger, J. F. M. Oth, and F. Billian, *Ber.*, **97**, 331 (1964). [h] The symbols used in this column are explained at the beginning of the Experimental Section. [i] Crude nitrile was used directly in next step without further characterization. [j] H: calcd, 6.0; found, 6.5. [k] C: calcd, 39.4; found, 38.4; N: calcd, 6.5; found, 5.9.

TABLE XXV
Ar-CH=CHCN

No.	Ar	Preparative method[a]	Bp (mm), °C	$n^{25}D$	Ratio[b] trans:cis	Formula	Analyses
134	2-C_4H_3S	K	150 (25)	1.6373	68:32	C_7H_5NS	C, H, N
135	3-CH_3-2-C_4H_2S	K	126 (0.2)		77:23	C_8H_7NS	C, H, N
136	5-CH_3-2-C_4H_2S	K	108 (0.5)		~2:1	C_8H_7NS	C, H, N
137	3-C_4H_3S	K	134 (14)	1.6192	66:34	C_7H_5NS	C, H, N
138	2-$CH_3C_6H_4$	K	71 (0.03)	1.5901		$C_{10}H_9N$	C, H, N

[a] The symbols used in this column are explained at the beginning of the Experimental Section. [b] As determined by vapor phase chromatography and/or nmr spectroscopy.

l. of dry MeOH was treated portionwise with 1975 g (8.95 moles) of ethyl 2-thiophenepropionimidate hydrochloride. The resulting solution was heated under reflux for 2 hr during which time NH_3 evolved from the reaction mixture. After cooling to room temperature, the solution was concentrated under reduced pressure until crystals appeared. The crude product was recrystallized, yield 1820 g (88%), mp 171–172°.

Method C. Reaction of Primary Amines with Isothiuronium Salts. 2-(2-Thenylamino)-2-imidazoline Hydrochloride (6).—A solution of 24.4 g (0.1 mole) of 2-methylthio-2-imidazoline hydroiodide, 11.3 g (0.1 mole) of 2-thenylamine, and 150 ml of H_2O was heated under reflux for 1 hr. After cooling somewhat, the aqueous solution was evaporated under reduced pressure to afford a crystalline residue. The crude product was recrystallized to afford analytically pure **6**, yield 14.1 g (46%), mp 120–122°.

Method D. Condensation of Nitriles with Diamines. 2-(2-Thienyl)-2-imidazoline *p*-Toluenesulfonate (13).—According to the procedure of Oxley and Short,[8] 10.9 g (0.1 mole) of 2-thiophenecarbonitrile[36] was converted to **13**, yield 18.2 g (56%), mp 188–191°.

Method E. Condensation of Nitriles with Diamines Catalyzed by H_2S. 1,4,5,6-Tetrahydro-1-methyl-2-[2-(1-pyrazolyl)ethyl]pyrimidine Dihydrogen Citrate (61).—A solution of 12.1 g (0.1 mole) of 1-pyrazolepropionitrile (**131**) and 8.8 g (0.1 mole) of N-methyl-1,3-propanediamine was treated with 1.1 g of dry H_2S and the resulting mixture was heated to 85°. The temperature was maintained at 85° for 24 hr. Crude 1,4,5,6-tetrahydro-1-methyl-2-[2-(1-pyrazolyl)ethyl]pyrimidine was isolated from the reaction mixture and was converted to the citrate salt, yield 7.0 g, mp 143–148° dec. The product was recrystallized to furnish 5.4 g (14%) of pure **61**, mp 148–150° dec.

Method F. Cyclic Amidines *via* Imidate Salts from Amides and 1,3-Propane Sultone. 2-[2-(2-Furyl)vinyl]-1,4,5,6-tetrahydro-1-methylpyrimidine Dihydrogen Citrate (108).—A mixture of 13.7 g (0.1 mole) of 2-furanacrylamide and 12.2 g (0.1 mole) of 1,3-propane sultone was heated at 120–140° and stirred with a glass rod. After 30 min the solution began to solidify. Heating was continued for an additional 30 min. Upon cooling to room temperature, the reaction mixture was triturated under Me_2CO and was then filtered to furnish 21.6 g (80%) of the crude imidate inner salt, 3-(2-furanacrylimidoyloxy)propanesulfonic acid.

A solution of 8.8 g (0.1 mole) of N-methyl-1,3-propanediamine and 100 ml of MeOH was treated portionwise with 21.6 g (0.08 mole) of the imidate inner salt and heated under reflux for 5 hr. Crude 2-[2-(2-furyl)vinyl]-1,4,5,6-tetrahydro-1-methylpyrimidine was isolated as the free base and converted to the citrate salt **108**, yield 13.6 g (46%), mp 157–158° dec.

The above procedure is based on a method described by Hied and Schmidt.[9]

Method G. Adducts from Arylaldehydes and 1,2-Dimethyl Cyclic Amidines. 1,4,5,6-Tetrahydro-2-(β-hydroxy-2-methylphenethyl)-1-methylpyrimidine (115).—A solution of 69.0 g (0.575 mole) of *o*-tolualdehyde, 66.5 g (0.575 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine, and 75 ml of PhH was allowed to stand at room temperature for 48 hr and then evaporated under reduced pressure to afford a crystalline residue. This material was recrystallized to furnish analytically pure **115**, yield 7.5 g, mp 82–83°. The filtrate was concentrated to afford a second crop of product, yield 33.0 g (25%), mp 81–82°.

1,4,5,6-Tetrahydro-2-[2-hydroxy-2-(2-thienyl)ethyl]-1-methylpyrimidine Hydrochloride (111).—A solution of 11.2 g (0.1 mole) of 2-thiophenecarboxaldehyde, 11.2 g (0.1 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine, and 80 ml of PhH was allowed to stand at room temperature for 48 hr. The more volatile components were then evaporated under reduced pressure, and the residue was taken up in 500 ml of Et_2O. Dry HCl was passed through the Et_2O solution causing a waxy yellow solid to precipitate. The ether was decanted, and the residue was triturated under MeCN. The mixture was filtered, and 7.8 g of crystalline material was collected; another 3.0 g was obtained by concentrating the filtrate. The crystalline fractions were combined and recrystallized to afford colorless crystals of pure **111**: yield 8.0 g (33%), mp 162–163°.

(30) (a) A. Hantzsch, *Ber.*, **24**, 31 (1891); (b) P. Karrer, A. Rebmann, and E. Zeller, *Helv. Chim. Acta*, **3**, 261 (1920).

Methods H and I are elimination reactions of the adducts from method G.

Method H. Catalysis by Ac_2O. 1,4,5,6-Tetrahydro-1-methyl-2-(2-methylstyryl)pyrimidine Sesquihydrochloride (84).—With ice-bath cooling 112.1 g (1.0 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine was treated with 120.1 g (1.0 mole) of *o*-tolualdehyde. After standing overnight in a refrigerator, the mixture was nearly completely crystallized, and consisted almost entirely of the adduct **115**. With ice-bath cooling, the unrefined adduct was treated with 350 ml of Ac_2O. Upon removing the ice bath the temperature rose spontaneously to about 50°. Most of the excess Ac_2O was evaporated under reduced pressure, and the residue was taken up in 150 ml of MeOH. This solution was then treated with a solution of 80 g of dry HCl in 550 ml of MeOH. After 15 min, the alcoholic solution was evaporated, and the thick oily residue was treated with PhH. Evaporation was continued, and a solid residue was obtained. This material was triturated under *i*-PrOH and filtered to afford **84**, yield 62.0 g (23%), mp 184–188°. *Anal.* ($C_{14}H_{19.5}Cl_{1.5}N_2$) C, H, N; Cl: calcd, 19.8; found, 19.2.

Method I. Catalysis by Hydrogen Chloride. 1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine Hydrochloride (147).—A stirred solution of 22.4 g (0.2 mole) of 2-thiophenecarboxaldehyde in 70 ml of EtOAc was treated with a solution of 11.2 g (0.1 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine in 30 ml of EtOAc. The mixture was chilled in an ice bath for several hours. Approximately 0.2 mole of dry HCl was passed through the solution, causing a gum (crude **111**) to precipitate. The gummy material was taken up in 75 ml of 10% dry HCl in *i*-PrOH. The mixture was heated under reflux for 2.5 hr and evaporated under reduced pressure to furnish a viscous oil. This material was triturated with Me_2CO to furnish 13.2 g of crude product, mp 190–194°. The crude material was recrystallized from *i*-PrOH to afford 12.1 g (50%) of pure 1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine hydrochloride (**147**), mp 195–196°. *Anal.* ($C_{11}H_{15}ClN_2S$) C, H, N.

Method J. Direct Condensation of Arylaldehydes with 1,2-Dimethyl Cyclic Amidines. 1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine Dihydrogen Citrate (148).—A solution of 6.16 g (0.06 mole) of 2-thiophenecarboxaldehyde, 5.61 g (0.05 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine, and 25 ml of PhMe was heated under reflux in an apparatus which included a Dean–Stark moisture trap. After 8 hr 0.75 ml (83%) of H_2O had collected in the trap. The more volatile components were evaporated under reduced pressure to afford a dark oily residue which was the crude condensation product. The free base so obtained was converted to the citrate salt: yield 12.0 g (60%), mp 172–176°. One recrystallization from MeOH gave 9.0 g (45%) of analytically pure **148**, mp 177–180°. *Anal.* ($C_{17}H_{22}N_2O_7$) C, H, N.

2,3,4,6,7,8-Hexahydro-8-(2-thenylidene)pyrrolo[1,2-*a*]pyrimidine Hydrochloride (139).—A solution of 14.9 g (0.12 mole) of 1,5-diazabicyclo[4.3.0]-5-nonene, 11.2 g (0.1 mole) of 2-thiophenecarboxaldehyde, and 12 ml of HCO_2CH_3 was heated at 40–45° for 18 hr. The mixture was evaporated under reduced pressure, and the residue was treated with 50 ml of 3 *N* dry HCl in MeOH. The acidified solution was evaporated, and the dark crystalline residue was triturated under *i*-PrOH. The crude product was recrystallized from *i*-PrOH to furnish colorless crystals of **139**, yield 10.5 g (43%), mp 252–255°. *Anal.* ($C_{12}H_{15}ClN_2S$) H, N, S; C: calcd, 56.6; found, 55.4; Cl: calcd, 13.9; found, 13.4.

Method K. 3-Arylacrylonitriles by Condensation of Arylaldehydes with Cyanoacetic Acid.—The procedure of Patterson[31] was adopted to prepare the appropriate compounds in Table XXV.

Method L.—Procedure of the literature reference was followed.

Method M. 3-Arylpropionitriles by Catalytic Reduction of the Corresponding 3-Arylacrylonitriles. 3-Methyl-2-thiophenepropionitrile (125).—A mixture of 101.7 g (0.685 mole) of 3-methyl-2-thiopheneacrylonitrile (**135**), 5.0 g of 10% Pd–C, and 100 ml of dry EtOH was reduced in a Parr hydrogenation apparatus according to the procedure recommended by the manufacturer. After filtering the reaction mixture, the filtrate was concentrated to an oil which was distilled to furnish **125**, yield 68.6 g (67%), bp 87° (0.2 mm), $n^{24}D$ 1.5440, d^{24}_4 1.0908.

Method N. Conversion of an Amide to a Nitrile. 2-Furanpropionitrile (128).—A solution of 41.6 g (0.3 mole) of 2-furanpropionamide,[32] and 120 ml of pyridine was cooled to approximately 5°. With efficient stirring and continued cooling, 53 g (0.3 mole) of $PhSO_2Cl$ was added dropwise. After the addition was complete the mixture was allowed to stand overnight at room temperature. The solution was poured into 1 l. of ice and water. The aqueous solution was adjusted to pH 1–2 by the addition of HCl, and organic matter was then extracted with Et_2O. The extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford an oil which was fractionally distilled to give **128**.

An alternate procedure for converting an amide to a nitrile is that of Mowry and Butler.[33]

Method O. Nitriles by the Action of Sodium Cyanide on Alkyl Halides.—A solution of 4-bromo-2-thienyllithium in Et_2O was prepared according to the procedure of Lawesson.[34] Ethylene oxide (1.5 molar equiv) was then added at −70°. After allowing it to warm to room temperature overnight, the mixture was stirred vigorously with 2 *N* H_2SO_4. The ether phase was separated, and the aqueous phase was extracted with Et_2O. The combined ether phases were dried, filtered, and evaporated under reduced pressure to furnish an oil which was distilled: yield 47%, bp 144–145° (10 mm). This material, 4-bromo-2-thiopheneethanol, was not characterized further and was used directly in the following preparation.

A solution of 10 g (0.0483 mole) of 4-bromo-2-thiopheneethanol and 50 ml of PhH was treated dropwise with 5 g (0.0185 mole) of PBr_3 dissolved in 20 ml of PhH. The mixture was heated under reflux for 2 hr; after cooling, 30 ml of ice water was added, with vigorous stirring. The PhH phase was separated, and distilled to afford 4-bromo-2-(2-bromoethyl)thiophene (**149**), yield 6.7 g (52%), bp 145–147° (11 mm). *Anal.* ($C_6H_6Br_2S$) Br.

A solution of 8.3 g (0.0308 mole) of 4-bromo-2-(2-bromoethyl)-thiophene, 1.85 g (0.0378 mole) of NaCN, 1.8 ml of H_2O, and 40 ml of EtOH was heated under reflux overnight. The EtOH was distilled, the residue was taken up in H_2O, and the aqueous phase was extracted with Et_2O. The ether extract was dried, filtered, and evaporated under reduced pressure. The residue was distilled to furnish 4-bromo-2-thiophenepropionitrile (**126**).

Method P. Photoisomerization. *cis*-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine Tartrate (72).—A solution of 10.0 g of *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine tartrate (**71**) in 1000 ml of MeOH contained in an erlenmeyer flask was exposed for 3 days to direct sunlight. The solvent was evaporated under reduced pressure, and the residue was recrystallized from EtOH to afford colorless crystals of **72**, mp 160–161°.

1,2-Dimethyl-2-imidazoline.—Method B3 was used to obtain 1,3-dimethyl-2-imidazoline as oil (approximately 95% pure as determined by vapor phase chromatography): yield 85%, bp 45–50° (16 mm), $n^{24}D$ 1.4668 [lit.[35] mp 90° (*sic*)]. The dihydrogen citrate salt **150** was prepared and recrystallized from EtOH for analysis: mp 108–109°. *Anal.* ($C_{11}H_{18}N_2O_7$) C, H, N.

1,4,5,6-Tetrahydro-1,2-dimethylpyrimidine.—Method E3 was used to obtain 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine as a blue oil,[36] yield 56%, bp 72–76° (12 mm), $n^{25}D$ 1.4932. The HPF_6 salt **151** was prepared and was recrystallized from *i*-PrOH for analysis, mp 156–157°. *Anal.* ($C_6H_{13}F_6N_2P$) C, H, N.

(31) J. M. Patterson, *Org. Syn.*, **40**, (1960).

(32) 2-Furanpropionic acid was prepared by the procedure of R. J. Rallings and J. C. Smith, *J. Chem. Soc.*, 618 (1953). The acid was converted to its Me ester, and ammonolysis of the ester afforded the amide. The physical properties of and the literature references to the acid, Me ester, and amide are given by A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p 590.

(33) D. T. Mowry and J. M. Butler, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 486.

(34) S.-O. Lawesson, *Arkiv Kemi*, **11**, 317 (1957).

(35) A. Ladenburg [*Ber.*, **27**, 2952 (1894)] reports the preparation of this material by the reaction of 2-methyl-2-imidazoline and methyl iodide, and subsequent isolation of the free base. His product was crystalline, and a good analysis was reported. No other citations for 1,2-dimethyl-2-imidazoline were found in the literature. Ladenburg's method of preparation is somewhat equivocal, because the product of monomethylation is capable of further reaction with methyl iodide. We believe that the liquid state at room temperature is more reasonable for the compound in question.

(36) The same compound prepared in low yield by method B3 was colorless. However, addition of a trace of H_2S caused this material to turn blue also. The nature of this reaction has not been investigated, but the blue oil is essentially greater than 99% pure when fractionally distilled. Initially, the freshly distilled oil is nearly colorless but on standing it again assumes a blue color. It is useable as such in subsequent reactions without detriment to the products thereof.

Ethyl β-Methyl-2-thiopheneacrylate (152).—The procedure for Wadsworth and Emmons[37] was used to convert 126 g (1.0 mole) of 2-acetylthiophene to ethyl β-methyl-2-thiopheneacrylate (**152**), yield 112.6 g (58%), bp 83–85° (0.1 mm) (lit.[38] bp 72–74° at 0.1 mm), n^{25}D 1.5739. *Anal.* ($C_{10}H_{12}O_2S$) C, H.

β-Methyl-2-thiopheneacrylonitrile (140) was prepared in a manner analogous to that described above. Diethyl cyanomethylphosphonate was used in place of triethyl phosphonoacetate. From 12.6 g (0.10 mole) of 2-acetylthiophene there was obtained 11.7 g (79%) of product, bp 68–79° (0.03–0.04 mm), n^{24}D 1.6162. *Anal.* (C_8H_7NS) C, H, N.

β-Methyl-2-thiopheneacrylic Acid (153). Ethyl β-methyl-2-thiopheneacrylate was saponified by NaOH in MeOH to furnish eventually β-methyl-2-thiopheneacrylic acid (**153**), yield 5.6 g, mp 107–108° (from MeOH) (lit.[38] mp 113–115° from hexane). *Anal.* ($C_8H_8O_2S$) C, H.

β-Methyl-2-thiopheneacrylamide (141).—Cramer and Winter's procedure[39] was used to convert 16.8 g (0.1 mole) of β-methyl-2-thiopheneacrylic acid to **141**: yield 11.6 g (70%), mp 122–124°. One recrystallization from PhH afforded an analytical sample: mp 124–125°. *Anal.* (C_8H_9NOS) C, H, N.

Method Q. Cyclic Amidines *via* Imidate Salts Prepared from Amides and $Et_3O^+BF_4^-$. 1,4,5,6-Tetrahydro-1-methyl-2-[2-methyl-2-(2-thienyl)vinyl]pyrimidine Hexafluorophosphate (142).—With magnetic stirring a slurry of 8.36 g (0.05 mole) of β-methyl-2-thiopheneacrylamide in 100 ml of dry Et_2O was cooled in an ice bath and treated with 9.5 g (0.05 mole) of $Et_3O^+BF_4^-$[40] portionwise. The mixture was allowed to warm to room temperature, and stirring was continued overnight. During this time the initially colorless solids turned yellow. Upon filtration 14.0 g (99%) of crude ethyl β-methyl-2-thiopheneacrylimidate fluoroborate (mp 142–146°) was recovered. Without further purification the imidate salt was added portionwise to a stirred, ice-cooled solution of 4.4 g (0.05 mole) of N-methyl-1,3-propanediamine in 100 ml of MeOH. The resulting solution was heated under reflux for 2 days. After the volatile components were evaporated under reduced pressure, the residue was slurried in H_2O and treated with 5 ml of 65% HPF_6. The crystalline solids were filtered and recrystallized from *i*-PrOH–H_2O to yield **142**: yield 7.2 g (39%), mp 136–137°. The product was recrystallized from MeOH–EtOAc to furnish an analytical sample: yield 5.0 g, mp 138–139°. *Anal.* ($C_{12}H_{17}F_6N_2PS$) C, H, N.

α-Methyl-2-thiopheneacrylamide (143).—The procedure of Polya and Spotswood[41] was used to prepare **143** from 2-thiophenecarboxaldehyde and dipropionimide: yield 1.9 g (15%), mp 130–132°. One recrystallization from PhH gave analytically pure material, mp 131–132°. *Anal.* (C_8H_9NOS) C, H, N.

1,4,5,6-Tetrahydro-1-methyl-2-[1-methyl-2-(2-thienyl)vinyl]-pyrimidine hexafluorophosphate (144) was prepared from 8.3 g (0.05 mole) of α-methyl-2-thiopheneacrylamide by method Q. The yield after recrystallization from *i*-PrOH was 3.1 g (17%), mp 123–125°. *Anal.* ($C_{12}H_{17}F_6N_2PS$) C, H, N.

***trans*-2-(2-Thienyl)cyclopropanecarbonitrile (154).**—Procedure N was used to convert 23.3 g (0.139 moles) of *trans*-2-(2-thienyl)cyclopropanecarboxamide[42] to *trans*-2-(2-thienyl)cyclopropanecarbonitrile (**154**): yield 10.0 g (48%), bp 77° (0.2 mm), n^{24}D 1.5622. *Anal.* (C_8H_7NS) C, H, N.

***trans*-1,4,5,6-Tetrahydro-2-[2-(2-thienyl)cyclopropyl]pyrimidine (145).** A solution of 12.1 g (0.081 mole) of *trans*-2-(2-thienyl)cyclopropanecarbonitrile, 3.7 g (4.8 ml, 0.081 mole) of dry EtOH, and 50 ml of dry Et_2O was cooled in an ice bath and saturated with dry HCl. After the reaction mixture stood overnight at 0–5°, the oily imidate salt separated: yield 17.2 g (92%). A solution of the total crude imidate HCl, 5.6 g (0.075 mole) of 1,3-propanediamine, and MeOH was heated under reflux overnight. The reaction mixture was evaporated under reduced pressure to give the crude tetrahydropyrimidine salt which was subsequently converted to the free base. The product was recrystallized from PhH (C_6H_6) to afford 1.07 g (6.4%) of **145**, mp 133–135°. The analytical sample melted at 133–134°. *Anal.* ($C_{11}H_{14}N_2S$) C, H, N.

***trans*-1,4,5,6-Tetrahydro-2-(2-phenylcyclopropyl)pyrimidine (146).**—In a analogous manner, **146** was prepared from 14.3 g (0.1 mole) of *trans*-2-phenylcyclopropanecarbonitrile; yield 4.65 g (23%), mp 161–63° (from PhH–C_6H_{14}). The material was recrystallized once more from PhH to furnish an analytical sample, mp 162–164°. *Anal.* ($C_{13}H_{16}N_2$) C, H, N.

2-(2-Thienylthio)acetonitrile (155).—Under N_2 and with efficient stirring and ice cooling, a solution of 38.0 g (0.328 mole) of 2-thiophenethiol[43] and 80 ml of DMF was treated portionwise with 15.7 g (0.328 mole) of 50% NaH in mineral oil. After the NaH had all reacted and the temperature was again at 0°, 25.7 g (0.34 mole) of chloroacetonitrile was added dropwise over a period of 1 hr with continuous cooling and stirring. The mixture was heated on a steam bath for 30 min, and the more volatile components were then evaporated at approximately 1 mm pressure. The oily residue was taken up in EtOAc and washed with two portions of H_2O. After being dried (Na_2SO_4), the organic layer was filtered and concentrated under reduced pressure. The residue was fractionally distilled to furnish **155**, yield 38.0 g (80%), bp 72–73° (0.1 mm). *Anal.* (C_6H_5NS) N.

α-Methyl-2-thiophenepropionitrile.—α-Methyl-2-thiophenepropionamide[24] was treated with P_2O_5 in the manner described by Mowry and Butler[33] to furnish after distillation a 50% yield of α-methyl-2-thiophenepropionitrile, bp 122–123° (10 mm); vapor phase chromatography indicated 100% purity; ir, 2250 cm^{-1}. The nitrile was not further characterized, and was used to prepare **12**.

2-Methyl-1,3-propanediamine was prepared according to the procedure of Strack and Schwaneberg.[45]

2,2-Dimethyl-1,3-propanediamine.—Under dry N_2 and with efficient stirring, a suspension of 16.0 g (0.42 mole) of LAH in 400 ml of dry Et_2O was treated dropwise with a solution of dimethylmalononitrile (47 g, 0.5 mole) in 100 ml of dry Et_2O at such a rate as to maintain a gentle reflux. After the addition was complete, the mixture was stirred at room temperature for 2 days. It was cooled in an ice bath, and treated dropwise with 80 ml of H_2O. Stirring was continued for 30 min, and a solution of 100 g of NaOH and 250 ml of H_2O was added. The mixture was heated to near boiling, and was filtered hot through a sintered-glass funnel. The aqueous filtrate was extracted continuously with Et_2O for 24 hr. The extract was dried, filtered, and evaporated at a reduced pressure to furnish crude 2,2-dimethyl-1,3-propanediamine, yield 5.5 g; vapor phase chromatography showed this material to be approximately 90% pure. The diamine was not characterized or purified further, and was used directly to prepare **35**.

N-Allyl-1,3-propanediamine was prepared by heating allyl chloride in excess 1,3-propanediamine according to the procedure of Linsker and Evans.[46] The product had bp 174–176° (760 mm). The material was not further characterized and was used to prepare **43**.

2-Thiophenebutyramide (156).—2-Thiophenebutyric acid[47] (25.4 g, 0.149 mole) was converted to the corresponding acid chloride by the action of $(COCl)_2$. The acid chloride was poured into NH_4OH, and the crystalline product was filtered. Recrystallization from *i*-PrOH–*i*-Pr_2O afforded pure **156**, mp 83–84°. *Anal.* ($C_8H_{11}NOS$) C, H, N.

3-Methyl-2-thiophenecarboxaldehyde was prepared from 3-methylthiophene by the method of Gronowitz and coworkers.[48] The product consisted of an 80:20 mixture of the 3- and 4-methyl isomers.[48] Pure 3-methyl-2-thiophenecarboxaldehyde can be obtained by the low-temperature recrystallization process described below.

3-Ethyl-2-thiophenecarboxaldehyde was prepared from 3-ethylthiophene by the method of Gronowitz and coworkers.[48] The product consisted of a 5:2 mixture of the 3- and 4-ethyl-2-thiophenecarboxaldehyde. The mixture was used without further purification or characterization to prepare **78**. Fractional crystallization of **78** removed traces of the 4-Et isomer.

Isolation of Pure 3-Methyl-2-thiophenecarboxaldehyde.—A 22-l. flask equipped with a mechanical stirrer was charged with 6 kg of an 80:20 mixture of 3-methyl- and 4-methyl-2-thiophenecarboxaldehyde and 5 l. of EtOAc. Two gas dispersion tubes were then immersed in the resulting solution, so that the fritted-

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glass ends were close to the bottom of the vessel, but apart from each other. The other ends of the tubes were connected by Tygon tubing to glass tubes which penetrated the rubber stopper of a 12-l. filter flask. A valve to the atmosphere from the filter flask was included as a convenient device for breaking the vacuum.

Stirring was initiated and the solution was cooled in a Dry Ice–Me_2CO bath. Crystalline 3-methyl-2-thiophenecarboxaldehyde formed; stirring was stopped when it was no longer practicable. When precipitation ceased, the remaining liquid phase was drawn off by reducing the pressure in the filter flask. The vacuum was then broken, and the crystalline material in the round-bottom flask was allowed to melt. To the liquid aldehyde was added 1 l. of fresh EtOAc. The new solution was again chilled with stirring, and when no more 3-methyl isomer crystallized, the liquid phase was drawn off. This process was repeated four more times to give finally 1787 g of material from which no trace of the 4-methyl isomer could be detected by gas–liquid partition chromatography. The final melt was fractionally distilled to remove traces of EtOAc and some color, and to give 1670 g of pure 3-methyl-2-thiophenecarboxaldehyde as a clear pale yellow oil: bp 95° (5 mm), $n^{26}D$ 1.5859, mp −9.5° (uncor). The literature[48] values are bp 100–101° (15 mm), $n^{20}D$ 1.5882.

By concentrating the combined filtrates and repeating the process essentially as described above, additional pure 3-methyl isomer was obtained: yield 1498 g.

4-Methyl-2-thiophenecarboxaldehyde was prepared according to the method of Gronowitz and coworkers.[48] The product so obtained consisted of an 85:15 mixture of the 4-methyl and 3-methyl isomers.[48] The mixture of isomers was used to prepare **112** which was subsequently converted to **76**. The nmr spectrum of this latter substance indicated that less than 5% of the 3-methyl isomer could have been present.

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Novel Anthelmintic Agents. III. 1-(2-Arylvinyl)pyridinium Salts

JAMES W. MCFARLAND AND HAROLD L. HOWES, JR.

Pfizer Medical Research Laboratories, Groton, Connecticut 06340

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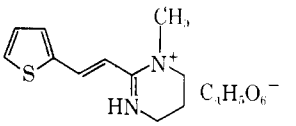
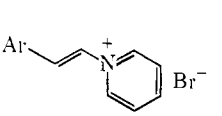
Anthelmintic activity has been discovered among some *trans*-1-(2-arylvinyl)pyridinium salts which are structurally analogous to *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine (pyrantel). The structure–activity relationships in this new series parallel very closely those found in the pyrantel group; *i.e.*, (i) the decreasing order of potency among various aryl systems is 2-thienyl > phenyl > 2-furyl; (ii) *ortho* substituents on the aryl moiety are compatible with activity while substituents elsewhere result in the loss of activity or a reduction in potency; (iii) a 1-(2-arylvinyl) compound is generally more potent than the corresponding 1-(2-arylethyl) analog; (iv) an α-methyl substituent on the vinylene bridge results in the loss of activity; and (v) substitution of the pyridine ring by methyl at the 2 position is compatible with activity; methyl substitution elsewhere on the pyridine ring results in the loss of activity. Among the more potent compounds in this series are 1-[2-(2-thienyl)-vinyl]pyridinium bromide (**62**), 1-[2-(3-methyl-2-thienyl)vinyl]pyridinium bromide (**63**), and 1-(2-methylstyryl)pyridinium bromide (**66**).

Pyrantel[1] is a highly effective broad-spectrum anthelmintic agent and is currently gaining acceptance as a veterinary drug in many areas of the world. We have previously shown[2-4] that pyrantel is one outstanding member of a broad class of amidines which exhibit anthelmintic activity. In another publication[3] we describe the structure–activity relationships in this class of compounds. From these relationships certain structural features appear to be necessary for activity: (i) a positively charged unit, (ii) a simple aromatic system, and (iii) a two carbon atom chain separating the positive charge from the aromatic ring. Other factors limit activity, but consideration of the features postulated above led us to search for other classes of compounds which might also fit this general description and possess useful biological properties.

One class of compounds which meets these structural criteria are the 1-(2-arylvinyl)pyridinium salts[5,6] (see **119**). On the basis of gross similarity to pyrantel, 1-[2-(2-thienyl)vinyl]pyridinium bromide (**62**), which has been previously described,[6] was tested in mice for anthelmintic activity against the roundworm *Nematospiroides dubius* and was found to be equipotent to pyrantel tartrate. This discovery encouraged us to prepare many other 1-(2-arylvinyl)pyridinium salts, and among these several active compounds were detected.[7] The general synthetic sequence outlined in Scheme I was followed throughout the present work. It was also discovered that some of the intermediate 1-phenacylpyridinium salts possess anthelmintic activity. In two cases this activity is against dwarf tapeworm (*Hymenolepis nana*), while in the other cases the activity is against *N. dubius*. It was our purpose to show that structure–activity relationships in the 1-(2 arylvinyl)-pyridinium series parallel those of the pyrantel series, and this consideration guided the selection of compounds for synthesis and evaluation. By showing that such a parallelism exists we would be in a position to



pyrantel tartrate



119, Ar = a simple aromatic system
62, Ar = 2-thienyl

(1) Pyrantel tartrate, Banminth®.

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