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.

Acknowledgments.—The authors wish to thank those workers who made valuable contributions to this investigation: from Sandwich, U. K., Miss A. Berry, A. B. L. Plane, G. S. D. Weir, and P. R. Wood; from Groton, Conn., L. M. Capalbo, F. R. Gerns, P. N. Gordon, R. B. James, G. F. Smith, and R. W. Sumner.

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

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

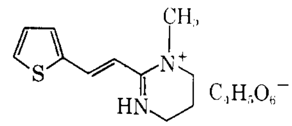
Pfizer Medical Research Laboratories, Groton, Connecticut 06340

Received April 22, 1969

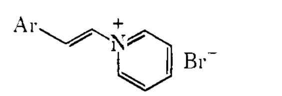
Anthelmintic activity has been discovered among some *trans*-1-(2-arylvinyl)pyridinium salts which are structurally analogous to *trans*-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine (pyrantel). The structure–activity relationships in this new series parallel very closely those found in 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



pyrantel tartrate



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

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

(1) Pyrantel tartrate, Banminth®.

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

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

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

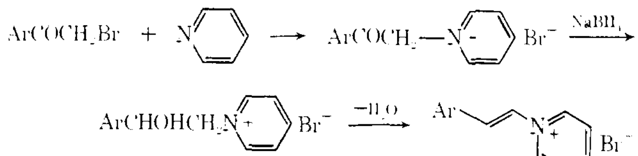
(5) (a) F. Kröhnke, German Patent 682,255 (Oct 11, 1939); (b) F. Kröhnke, J. Wolff, and G. Jentzsch, *Ber.*, **84**, 399 (1951).

(6) L. C. King and W. B. Brownell, *J. Am. Chem. Soc.*, **72**, 2507 (1950).

(7) May and Baker Ltd., Netherlands Application 6,800,807 (Jan 19, 1968); this patent describes the anthelmintic activity of several compounds mentioned in this article. However, the present research was completed before the release of that information [see Chas. Pfizer and Co., Inc., Belgian Patent 700,556 (Dec 27, 1967)].

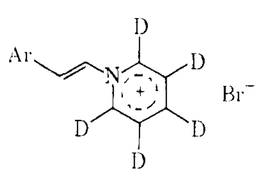
assert more confidently that drugs of both series act by similar mechanisms. It was also of interest to explore the anthelmintic activity of 1-(2-arylethyl)pyridinium salts. Several of these were prepared, and some were shown to be active.

Scheme I



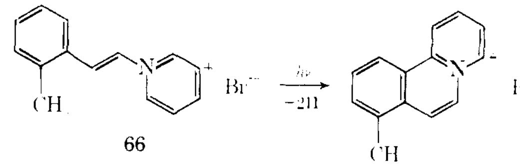
Chemistry.—Excellent synthetic procedures for the compounds presently under discussion have already been described in the literature (see Experimental Section). However, two items of importance should be noted. (1) A superior method for the α bromination of aryl alkyl ketones is that employing $CuBr_2$;[8] this method works particularly well for ketones which might otherwise substitute bromine at aromatic ring positions, *e.g.*, 4′-hydroxyacetophenone. (2) In general, the 1-(2-aryl-2-hydroxyethyl)pyridinium salts are best prepared by $NaBH_4$ reduction of the corresponding ketone;[9] this technique should take precedence over the older method developed by Kröhnke[10] which consists of a base-catalyzed addition elimination reaction between 1-phenacylpyridinium bromide and an arylaldehyde.

The 1-(2-arylvinyl)pyridinium salts are believed to be in the *trans* configuration. This belief rests mainly on the high probability that a *trans* isomer is thermodynamically more stable than its *cis* counterpart, and the nmr spectrum of one compound (**66**-d_5). Some difficulty was met in attempting to establish the geometry of the double bond by nmr spectroscopy. In the simplest system, **62**, there are ten protons, each coupled variously to others to produce a highly complex spectrum in the region of δ 7.0–10.0. To simplify the analysis of this spectrum, the synthesis of **62** was repeated using pyridine-d_5. The product, **62**-d_5, gave an nmr spectrum in D_2O that was easily interpreted. The three thiophene protons have the appropriate chemical shifts and are coupled to each other according to expectation.[11] In addition, at δ 8.06 there is a single peak whose area corresponds to two protons. Thus, the chemicals shifts for the α and β protons on the vinylene bridge are identical, and hence, the coupling constant $J_{\alpha\beta}$ is zero. The same situation prevailed even when the aprotic solvent DMSO-d_6 was employed. Under these circumstances, the geometry of **62** remains equivocal. A similar study was done on **66**-d_5. In this case, a typical AB pattern emerged in the nmr spectrum. With D_2O as the solvent, the chemical shift for the α-proton is δ 7.75 and for the β-proton it is δ 7.99. The coupling constant $J_{\alpha\beta}$ is 14.5 cps which is consistent with a *trans* double bond.[12]



62-d_5, Ar = 2-thienyl
66-d_5, Ar = *o*-tolyl

There was an attempt to make the *cis* isomer of **66**. In a manner analogous to the preparation of *cis*-pyrantel,[3] a 1% MeOH solution of **66** was exposed to direct sunlight. From the solution there was obtained the tricyclic compound **114** in low yield. Doolittle and Bradsher[13] made the perchlorate salt of the same cationic species by essentially the same route. These workers used I_2 as an H acceptor, but also noted that **114** formed in lower yield and was less pure when atmospheric O_2 alone was the oxidant. The same photoreaction was repeated on **66**-d_5. The coupling constant of the protons on the cisoid double bond of the product **114**-d_4 was determined to be 7.5 cps.



66 114

Biological Evaluation.—Compounds were tested for anthelmintic activity in worm-infested mice. Each mouse harbored a natural infection of the pinworm *Syphacia obvelata* and experimentally induced infections of the roundworm *Nematospiroides dubius* and the tapeworm *Hymenolepis nana*. Different substances were dissolved or suspended in a 1% carboxymethylcellulose solution at such a concentration that 0.4 ml delivered an appropriate dose to a 20-g mouse. Treated mice were dosed once each day for 1–3 days. Initially, a high dose (100–1000 mg/kg depending on the compounds's toxicity) was given to a group of four infected male mice. If anthelmintic activity was detected, the compound was tested at successively lower doses until a minimum effective dose (MED) was established. The MED is considered to be the single dose which causes at least a 90% reduction in the *N. dubius* worm burden as compared to untreated infected controls, or the lowest dose which will cause 100% clearance of *H. nana* or *S. obvelata*.

Further details of these testing methods are given by Howes and Lynch.[14] The results of these tests are reported in the last columns of Tables V–XIII.

Structure–Activity Relationships.—Table I summarizes the types of anthelmintic activity exhibited by each major class of compound presently under discussion. The 1-(aroylmethyl)- and 1-(2-arylvinyl)-pyridinium classes show activity against two species. This is not to say each member of a particular class is active against the indicated species, but rather that some are active against both, while others are active against only one or the other species.

In general, the MED of a compound against *S. obvelata* is greater than the MED of the same compound against *N. dubius*. With respect to the dose required

(8) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).
(9) T. Goto, *J. Pharm. Soc. Japan*, **74**, 318 (1954).
(10) F. Kröhnke and A. Schulze, *Ber.*, **72**, 2000 (1939).
(11) C. T. Mathis and J. H. Goldstein, *J. Phys. Chem.*, **63**, 571 (1961).
(12) (a) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 38; (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 85.
(13) R. E. Doolittle and C. K. Bradsher, *J. Org. Chem.*, **31**, 2616 (1966).
(14) H. L. Howes, Jr., and J. E. Lynch, *J. Parasitol.*, **53**, 1085 (1967).

TABLE I

TYPE OF ANTHELMINTIC ACTIVITY BY COMPOUND CLASS

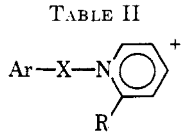
Pyridinium salt	*N. dubius*	*S. obvelata*	*H. nana*
1-(Aroylmethyl)	+	0	+
1-(2-Aryl-2-hydroxyethyl)	0	0	0
1-(2-Arylvinyl)	+	+	0
1-(2-Arylethyl)	+		

and to the number of compounds exhibiting anthelmintic activity, *N. dubius* is the most sensitive of the three species. Therefore, in the following discussion structure–activity relationships will be based on activity against *N. dubius*. This is also consistent with the practice followed in other publications in this series.[3,4,15]

As with other analogs of pyrantel, it is convenient to consider separately the three major structural elements: (i) the aromatic ring, (ii) the system bearing the positive charge (in this case the pyridine ring), and (iii) the link or bridge of carbon atoms between the cyclic systems.

The Link.—One striking similarity between the tetrahydropyrimidine (pyrantel) series and the present group of compounds is the superiority of the *trans*-vinylene link over the ethylene bridge (see Tables II and XIII). Other parallel structure–activity relationships in both series are (i) the lack of activity associated with α-methyl substitution of the vinylene link (see compound **94**), (ii) the inactivity of compounds with a 2-hydroxyethyl bridge (see Tables VI and IX), and (iii) the lack of biological response associated with compounds with only a single carbon atom bridge, *e.g.*, 1-benzylpyridinium hexafluorophosphate (**108**) is inactive at 125 mg/kg; higher doses are toxic.

TABLE II



Ar	R	MED,[a] mg/kg X = CH_2CH_2	X = CH=CH
2-C_4H_3S	H	100	12.5
2-C_4H_3S	CH_3	>200	62.5
3-CH_3-2-C_4H_2S	H	>200[b]	7.8
C_6H_5	H	>250	125

[a] Minimum effective dose *vs. N. dubius*. [b] A 71% reduction of the *N. dubius* burden was observed at 200 mg/kg.

The pyridine system has not been extensively explored; however, the picolinium compounds in Table X have been studied in some detail. Among these compounds one relationship is somewhat analogous to a situation in the pyrantel series. Namely, a methyl substituent at the position adjacent to where the link is attached is compatible with activity (see compound **95**); a methyl substituent at any other pyridine position leads to a loss of activity (see the other compounds in Table X).

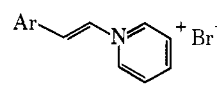
The Aromatic Ring.—At the outset it should be noted that an aromatic ring is essential for an anthelmintic effect to be observed. The salts, 1-methylpyridinium iodide and 1-allylpyridinium hexafluorophosphate (**107**), are both inactive at 500 mg/kg even when that dose is given on 3 consecutive days.

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

It is in the structure–activity relationships of the aromatic ring that the pyridinium salts and tetrahydropyrimidines resemble each other most closely. In both series the decreasing order of potency among the various aryl systems is 2-thienyl > phenyl > furyl (see Table III). The relationship of substituent and position substituted to activity also follows the same pattern found among the amidines: (i) with some explainable exceptions, substitution at an "*ortho*" position is compatible with activity, while substitution elsewhere results in the loss of activity or at least a reduction in potency; and (ii) at the "*ortho*" position, a methyl or chloro group is associated with increased potency, a fluoro substituent reduces potency somewhat, and a methoxy group results in the loss of activity (see Table III). For the tetrahydropyrimidine series, an argument based on Hansch's π substituent constant[16] has been given[3] to account for this behavior. In essence, it was shown that among active phenyl compounds there is an optimum π value of about 0.7 (very nearly the π values for methyl and chloro) and that any increase or decrease in π from this value is associated with the loss of potency. The details of this argument are given elsewhere;[3] therefore, only the parallelism between the pyridinium and tetrahydropyrimidine series needs to be demonstrated, and the present data appear to have accomplished this readily.

TABLE III

EFFECT OF AROMATIC SUBSTITUTION ON POTENCY



Position	Compd	Ar	MED, mg/kg
Unsubstituted	62	2-C_4H_3S	12.5
	65	C_6H_5	125
	83	2-C_4H_3O	250
"*ortho*"	63	3-CH_3-2-C_4H_2S	7.8
	66	2-$CH_3C_6H_4$	15
	70	2-$CH_3OC_6H_4$	>250
	73	2-FC_6H_4	250
	75	2-ClC_6H_4	31
	81	2-$CF_3C_6H_4$	>500
	84	3-CH_3-2-C_4H_2O	>125
"*meta*"	67	3-$CH_3C_6H_4$	>250
	69	3-HOC_6H_4	250
	71	3-$CH_3OC_6H_4$	>250
	76	3-ClC_6H_4	>250
	78	3-BrC_6H_4	>250
	79	3-$NO_2C_6H_4$	>1000
"*para*"	64	5-Cl-2-C_4H_2S	>250
	68	4-$CH_3C_6H_4$	>250
	72	4-$CH_3OC_6H_4$	>250
	74	4-FC_6H_4	>200
	77	4-ClC_6H_4	>250
	80	4-$NO_2C_6H_4$	>250
	85[a]	5-CH_3-2-C_4H_2O[a]	>500

[a] PF_6^- salt.

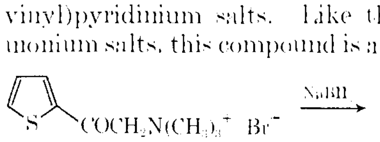
Thus, the reason why the methoxy compound (**70**) is inactive is that it is not lipophilic enough, *i.e.*, the π value, −0.33, is too low. On the other hand, the trifluoromethyl compound **81** is inactive probably because

(16) (a) C. Hansch, P. P. Maloney, T. Fujita, and R. M. Muir, *Nature*, **194**, 178 (1962); (b) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963); (c) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964).

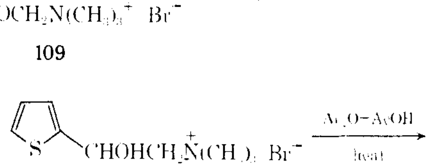
it is too lipophilic (for CF_3 π should be about 1.1). No meaning can be attached to the apparent lack of activity of the 3-methyl-2-furyl compound **84**; because of its toxicity, this compound cannot be tested at 250 mg/kg, the MED of the 2-furyl compound **83**. Nevertheless, at 125 mg/kg a 70% reduction in worm burden was observed for **84**, and past experience with similar compounds indicates that the next higher dose level, 250 mg/kg, would be sufficient to effect at least a 90% reduction. The corresponding furan compounds in the tetrahydropyrimidine series are also equipotent.

Since it is clear that the structure activity relationships among the 1-(2-arylvinyl)pyridinium salts and among the tetrahydropyrimidines are essentially the same, it is reasonable to assume that drugs in both series act at the same receptor, and are influenced by the same steric, electronic, and lipophilic factors.

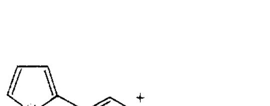
Because the types of drugs presently under discussion might conceivably be acting at a site important to the metabolism or action of acetylcholine or acetylcholine-like transmitter substance, it was of interest to study the activity of some simple compounds combining certain features of acetylcholine and pyrantel. To this end, the amines of Table XI were prepared, and by the action of MeI they were subsequently converted to the corresponding trimethylammonium iodides of Table XII. None of these quaternary ammonium salts is active, but one of the precursor amines (**99**) exhibits activity against *N. dubius*. Significantly, in **99** the basic center is separated from the thiophene ring by a two-carbon chain, in this case ethylene. To go one step further, the *trans*-vinylene compound **111** was prepared in a manner analogous to the preparation of 1-(2-arylvinyl)pyridinium salts. Like the other trimethylammonium salts, this compound is also inactive.



109



110



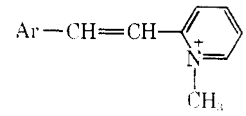
111

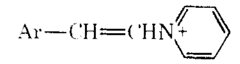
Wood and his coworkers[17] have described the anthelmintic activity of some 1-methyl-2-(2-arylvinyl)pyridinium salts. However, it is doubtful that these compounds are strictly analogous to the ones discussed above. The published work indicates that their best compound is 2-(4-chlorostyryl)-1-methylpyridinium chloride (**120**), yet among the 1-(2-arylvinyl)pyridinium bromides, the corresponding (**77**) is inactive (see Table IV). Further, if these two series of compounds were closely related, one would expect 1-methyl-2-[2-(2-thienyl)vinyl]pyridinium iodide (**106**)[18] to exhibit activity, but it does not.

(17) (a) I. B. Wood, J. A. Pankavich, and E. Waletzky, *J. Parasitol.*, **51** (No. 2, Sec. 2), 34 (1965); (b) I. B. Wood, J. A. Pankavich, and R. E. Bambury, U. S. Patent 3,177,116 (April 6, 1965); (c) I. B. Wood, R. E. Bambury, and H. Berger, U. S. Patent 3,179,559 (April 20, 1965).

(18) This compound was prepared by P. N. Gordon of these laboratories and was kindly donated by him.

TABLE IV





No.	Ar	Active	No.	Ar	Active
106	2-C_4H_3S	No	62	2-C_4H_3S	Yes
120	4-ClC_6H_4	Yes	77	4-ClC_6H_4	No

Thus, arylvinylpyridinium salts appear to constitute a new class of anthelmintic agents. Members of this group of compounds behave biologically more nearly like analogs of pyrantel, a cyclic amidine, than like another type of pyridinium salt which also possesses anthelmintic activity. The differences in activity between these two series may be a question of helminth spectrum as well as site of drug action.

Experimental Section

Boiling points are uncorrected; melting points were determined on a Mel-Temp melting point apparatus (Laboratory Devices, Cambridge, Mass.) and are corrected. The starting ketones were commercially available or have been described previously in the literature. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The physical properties of the compounds are given in Tables V–XIII.

1-(Aroylmethyl)pyridinium salts of Tables V and VIII were prepared from the appropriate aryl alkyl ketones by the method of King and Ostrum.[8]

1-(2-Aryl-2-hydroxyethyl)pyridinium salts of Tables VI and IX were obtained by reducing 1-(aroylmethyl)pyridinium salts with $NaBH_4$;[9] an example follows. A solution of 25.0 g (0.088 mole) of 1-(2-thenoylmethyl)pyridinium bromide (**1**) and 200 ml of H_2O at room temperature was stirred while 0.85 g (0.0225 mole) of $NaBH_4$ was added portionwise. A precipitate formed immediately, and, after a few minutes, the reaction mixture was filtered to furnish the crude product. One recrystallization from H_2O–EtOH afforded pure 1-[2-hydroxy-2-(2-thienyl)ethyl]pyridinium bromide (**35**); yield 13.2 g (52%), mp 239–240°.

1-(2-Arylvinyl)pyridinium salts of Tables VII and X were prepared by methods already described in the literature.[5,6]

Method A.—A solution of the 1-(2-aryl-2-hydroxyethyl)pyridinium salt, Ac_2O, and AcOH was heated in a steel bomb at 220° for 5 hr.

Method B. A solution of the hydroxy compound and C_6H_5-COCl was heated at 190–200° for 1 hr.

Method C. A solution of the hydroxy compound, Ac_2O, and AcOH was heated under reflux for 3 hr.

Method D is the Eschweiler Clark modification of the Leuckart reaction.[19]

Method E. An N,N-dimethylamide was reduced by a THF solution of borane; an example follows. A solution of 18.3 g (0.10 mole) of N,N-dimethyl-2-thiophenepropionamide and 30 ml of dry THF was cooled to −5° and was stirred magnetically while 200 ml (0.20 mole) of a commercial solution[20] of 1.0 *M* borane in THF was added dropwise at such a rate that the reaction temperature did not exceed +5°. Upon completing the addition, the reaction mixture was allowed to warm to room temperature and was then heated under reflux for 1 hr. Work-up of the reaction mixture and fractional distillation of the crude product furnished pure N,N-dimethyl-2-thiophenepropylamine (**100**), yield 9.94 g (59%).

Method L. See literature reference.

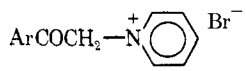
2-Thiopheneethylamine was prepared by the action of 1.0 *M* borane in THF on 2-thiopheneacetonitrile: yield 40%, bp 103–104° (28–30 mm); vapor phase chromatography showed the product to be essentially 100% pure [lit.[21] bp 200–201° (750 mm)].

(19) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 723.

(20) Available from Alfa Inorganics, Inc., Beverly, Mass. 01915.

(21) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938).

TABLE V



No.	Ar	Recrystn solvent[a]	Mp, °C	Lit. mp, °C	Ref	Formula	Analyses	MED,[p] mg/kg	Days given
1	2-C_4H_3S	E	198–200			$C_{11}H_{10}BrNOS$	C, H, N	>250[q]	3
2	3-CH_3-2-C_4H_2S	M	273–274			$C_{12}H_{12}BrNOS$	C, H, N	31	1
3	5-CH_3-2-C_4H_2S	M–A	206–207			$C_{12}H_{12}BrNOS$	C, H, N	>250	3
4	5-Cl-2-C_4H_2S	M–P	204–206			$C_{11}H_9BrClNOS$	C, H, N	>250	3
5	C_6H_5	*b*	199–200	199–200	*c*	$C_{13}H_{12}BrNO$		>1000[q]	3
6	2-$CH_3C_6H_4$	M–P	176–177	182	*d*	$C_{14}H_{14}BrNO$	H, N; C[k]	62	1
7	3-$CH_3C_6H_4$	M–IE	176–178			$C_{14}H_{14}BrNO$	C, H, N	>250	3
8	4-$CH_3C_6H_4$	P	204–206	205	*e*	$C_{14}H_{14}BrNO$	C, H, N	>250	3
9	2-HOC_6H_4	E	195–197	197–200	*f*	$C_{13}H_{12}BrNO_2$	C, H; N[l]	250	1
10	3-HOC_6H_4	M–A	224–226	222–224	*f*	$C_{13}H_{12}BrNO_2$	H, N; C[m]	>250	3
11	4-HOC_6H_4	M	251–253	248–250	*f*	$C_{13}H_{12}BrNO_2$	C, H, N	>250	3
12	2-$CH_3OC_6H_4$	M–P	160–162			$C_{14}H_{14}BrNO_2$	C, H; N[n]	>250	1
13	3-$CH_3OC_6H_4$	M	232–234			$C_{14}H_{14}BrNO_2$	C, H, N	>250	3
14	4-$CH_3OC_6H_4$	E	203–205	203–205	*e*	$C_{14}H_{14}BrNO_2$		*r*	
15	2-FC_6H_4	E	237–238			$C_{13}H_{11}BrFNO$	C, H, N	>250	1
16	3-FC_6H_4	E	224–225			$C_{13}H_{11}BrFNO$	C, H, N	>250	1
17	4-FC_6H_4	P	205–206			$C_{13}H_{11}BrFNO \cdot 0.5H_2O$	C, H, N	>250	1
18	2-ClC_6H_4	*b*	214–215	211	*e*	$C_{13}H_{11}BrClNO$		*r*	
19	3-ClC_6H_4	*b*	249–250	250	*e*	$C_{13}H_{11}BrClNO$		*r*	
20	4-ClC_6H_4	M–A	208–209	206	*g*	$C_{13}H_{11}BrClNO$	C, H, N	>250	3
21	3-BrC_6H_4	M	246–247			$C_{13}H_{11}Br_2NO$	C, H, N	>250	3
22	4-BrC_6H_4	M–E	235–236	230–235	*h*	$C_{13}H_{11}Br_2NO$	C, H, N	>200	1
23	3-IC_6H_4	M–W	254–256			$C_{13}H_{11}BrINO$	C, H, N	>250	3
24	2-$NO_2C_6H_4$	M–W	263 dec	260 dec	*d*	$C_{13}H_{11}BrN_2O_3$	C, H, N	>250	1
25	3-$NO_2C_6H_4$	M	245–246	245–247	*g*	$C_{13}H_{11}BrN_2O_3$	C, H, N	>250	3
26	4-$NO_2C_6H_4$	M	251–253	245–247	*e*	$C_{13}H_{11}BrN_2O_3$	C, H, N	>250	3
27	2-$CF_3C_6H_4$	E	224–225			$C_{14}H_{11}BrF_3NO$	C, H, N	>250	1
28	4-HO-2-$CH_3C_6H_4$	M–W	277 dec			$C_{14}H_{14}BrNO_2 \cdot H_2O$	C, H, N	>250	1
29	2-HO-5-$CH_3C_6H_4$	E	197–198			$C_{14}H_{14}BrNO_2$	C, H, N	>250	1
30	2,4,6-$(CH_3)_3C_6H_2$	E	279 dec	280 dec	*d, e*	$C_{15}H_{18}BrNO$	C, H, N	>250	2
31	2-$C_{10}H_7$	M	213–214	219–220	*i*	$C_{17}H_{14}BrNO \cdot H_2O$	H, N; C[o]	>250	3
32	2-C_4H_3O	M–P	211–213	201–203	*j*	$C_{11}H_{10}BrNO_2$	C, H, N	>250	3
33	3-CH_3-2-C_4H_2O	E	253 dec			$C_{12}H_{12}BrNO_2$	C, H, N	>250	1
34	5-CH_3-2-C_4H_2O	P	203–205			$C_{12}H_{12}BrNO_2$		*r*	

[a] A = Me_2CO, E = dry EtOH, IE = *i*-Pr_2O, M = MeOH, P = *i*-PrOH, W = H_2O. [b] Not recrystallized. [c] J. W. Baker, *J. Chem. Soc.*, 1148 (1932). [d] J. W. Baker, *ibid.*, 445 (1938) [e] F. Kröhnke and W. Heffe, *Ber.*, **70**, 864 (1937). [f] L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964). [g] F. Kröhnke, *Ber.*, **69**, 921 (1936). [h] S. H. Babcock, Jr., F. I. Nakamura, and R. C. Fuson, *J. Am. Chem. Soc.*, **54**, 4407 (1932). [i] J. L. Hartwell and S. R. L. Kornberg, *ibid.*, **68**, 1131 (1946). [j] N. Saldobols and S. Hillers, *Latvijas PSR Zinatnu Akad. Vestis*, 75 (1959); *Chem. Abstr.*, **53**, 17993 (1959). [k] C: calcd, 57.6; found, 57.1. [l] N: calcd, 4.8; found, 5.4. [m] C: calcd, 53.1; found, 52.4. [n] N: calcd, 4.6; found, 4.0. [o] C: calcd, 59.0; found, 59.5. [p] Minimum effective dose against *N. dubius*. [q] Active against *H. nana* at 250 mg/kg (three daily doses). [r] Not tested.

1-Methyl-2-[2-(2-thienyl)vinyl]pyridinium iodide (**106**) was prepared in a manner analogous to that described by Wood, *et al.*[17c] From 0.1 mole of 1,2-dimethylpyridinium iodide and 13.4 g (0.12 mole) of 2-thiophenecarboxaldehyde there was obtained 13.8 g (42%) of **106**, mp 224–226°. One recrystallization from MeOH afforded an analytically pure sample, mp 221–224°. *Anal.* ($C_{12}H_{12}INS$) C, **H**, N.

1-Allylpyridinium Hexafluorophosphate (**107**).—A solution of 72.6 g (0.6 mole) of allyl bromide, 300 ml of $CHCl_3$, and 96 ml (1.2 moles) of pyridine was heated under reflux for 2 hr. After standing at room temperature overnight, the solution was evaporated under reduced pressure, and the residue was dissolved in H_2O. Treatment of the aqueous solution with 100 ml of 65% HPF_6 caused the crude product to precipitate. The crystalline matter was filtered and recrystallized from MeOH–*i*-PrOH to furnish analytically pure **107**, yield 23.6 g (15%), mp 78–79°. *Anal.* ($C_8H_{10}F_6NP$) C, H, N.

1-Benzylpyridinium hexafluorophosphate (**108**) was prepared in a manner analogous to **107**. From 76 g (0.6 mole) of benzyl chloride and 96 ml (1.2 moles) of pyridine there was obtained **108**, recrystallized once from MeOH: yield 49.1 g (26%), mp 147–149°. *Anal.* ($C_{12}H_{12}F_6NP$) C, H, N.

2-Thenoylmethyltrimethylammonium Bromide (**109**).—Crude 2-bromoacetylthiophene was prepared from 12.6 g (0.1 mole) of 2-acetylthiophene by the method of King and Ostrum.[8] The undistilled product was taken up in 100 ml of CH_2Cl_2, and, at −10°, was treated with approximately 10 g of dry Me_3N. A colorless precipitate was collected after the mixture stood in a refrigerator overnight. The crystalline solid was recrystallized from EtOH to furnish an analytical sample of **109**: yield 10.7 g (54%), mp 233–235°. *Anal.* ($C_9H_{14}BrNOS$) C, H, N.

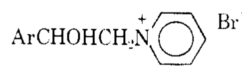
[2-Hydroxy-2-(2-thienyl)ethyl]trimethylammonium Bromide (**110**).—In a manner analogous to the preparation of 1-(2-aryl-2-hydroxyethyl)pyridinium salts, 51.1 g (0.193 mole) of **109** was reduced by 1.82 g (0.048 mole) of $NaBH_4$ to give **110**. After one recrystallization from MeOH the yield was 23.2 g (45%), mp 231–232°. *Anal.* ($C_9H_{16}BrNOS$) C, H, N: calcd, 5.3; found, 4.7.

2-(2-Thienyl)vinyltrimethylammonium Bromide (**111**).—A solution of 1.0 g (0.00376 mole) of **110**, 5.0 ml of Ac_2O, and 5.0 ml of AcOH was heated on a steam bath for 20 hr. After cooling somewhat, the solution was evaporated under reduced pressure, and the residue was recrystallized from MeOH–*i*-PrOH to furnish analytically pure 111, yield 0.21 g (23%), mp 190–192°. *Anal.* ($C_9H_{14}BrNS$) C, H, N.

2-Thiophenepropionyl Chloride.—A solution of 92.7 g (0.594 mole) of 2-thiophenepropionic acid, 250 ml of CH_2Cl_2, and 76.2 g (0.6 mole) of $(COCl)_2$ was allowed to stand at room temperature for 3 days. The volatile components were evaporated under reduced pressure and the residue was distilled to give 2-thiophenepropionyl chloride, yield 66.8 g (63%), bp 130° (33 mm). This product was not characterized further but was used directly in the preparation of N,N-dimethyl-2-thiophenepropionamide (**112**).

2-Thiophenebutyryl chloride was prepared in a like manner

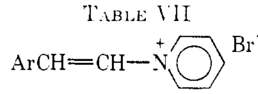
TABLE VI



No.	Ar	Recrystn solvent[a]	Mp, °C	Lit. mp, °C	Ref	Formula	Analyses	MED,[m] mg/kg	Days given
35	2-C_4H_3S	E–W	239–240	232–233	c	$C_{11}H_{12}BrNOS$	C, H, N	>500	3
36	3-CH_3-2-C_4H_2S	W	202–203			$C_{12}H_{14}BrNOS$	C, H, N	>250	3
37	5-CH_3-2-C_4H_2S	M	185–186			$C_{12}H_{14}BrNOS$	C, H, N	>250	3
38	5-Cl-2-C_4H_2S	M	214–215			$C_{11}H_{11}BrClNOS$	C, H, N	>250	3
39	C_6H_5	M	238–239	229–232	d	$C_{13}H_{14}BrNO$	C, H, N	>500	3
40	2-$CH_3C_6H_4$	E	251–253	b	e	$C_{14}H_{16}BrNO$	C, H, N	>250	3
41	3-$CH_3C_6H_4$	M–A	159–160			$C_{14}H_{16}BrNO$	C, H, N	n	
42	4-$CH_3C_6H_4$	M–A	215–216	213	d	$C_{14}H_{16}BrNO$	H, N; C[i]	>250	3
43	3-HOC_6H_4	W	270–272	268	f	$C_{13}H_{14}BrNO_2$	C, H, N	>250	3
44	4-HOC_6H_4	W	263–265			$C_{13}H_{14}BrNO_2$	C, H, N	>250	3
45	2-$CH_3OC_6H_4$	M	207–208	208	g	$C_{14}H_{16}BrNO_2$		n	
46	3-$CH_3OC_6H_4$	E	163–165	165–166	d	$C_{14}H_{16}BrNO_2$	C, H, N	>250	3
47	4-$CH_3OC_6H_4$	E	175–176	180–181	d	$C_{14}H_{16}BrNO_2$		n	
48	2-FC_6H_4	M	256–257			$C_{13}H_{13}BrFNO$	C, H, N	n	
49	4-FC_6H_4	M–P	223–224			$C_{13}H_{13}BrFNO$	C, H, N	n	
50	2-ClC_6H_4	M–W	276–277	275	d	$C_{13}H_{13}BrClNO$		n	
51	3-ClC_6H_4	M	207–209	213–214	d	$C_{13}H_{13}BrClNO$	C, H; N[j]	n	
52	4-ClC_6H_4	E	180–182	182–183	g	$C_{13}H_{13}BrClNO$	C, H, N	>250	3
53	3-BrC_6H_4	M–W	236–237	232–233	f	$C_{13}H_{13}Br_2NO$		n	
54	4-BrC_6H_4	E	206–207			$C_{13}H_{13}Br_2NO$	C, H, N	n	
55	3-$NO_2C_6H_4$	M	214–215	210–212	h	$C_{13}H_{13}BrN_2O$	C, H, N	>250	3
56	4-$NO_2C_6H_4$	M	270–273	270–272	d	$C_{13}H_{13}BrN_2O$	C, H, N	>250	3
57	2-$CF_3C_6H_4$	P	250–251			$C_{14}H_{13}BrF_3NO$	C, H, N	>250	3
58	2-$C_{10}H_7$	E	131–133			$C_{17}H_{16}BrNO$	N; C, H[k]	n	
59	2-C_4H_3O	M	216–217	216	d	$C_{11}H_{12}BrNO_2$	H, N; C[l]	>500	3
60	3-CH_3-2-C_4H_2O	E	169–170			$C_{12}H_{14}BrNO_2$	C, H, N	>500	3
61	5-CH_3-2-C_4H_2O	M–EE	129–130			$C_{12}H_{14}BrNO_2$	C, H, N	n	

[a] A = Me_2CO, E = dry EtOH, EE = Et_2O, M = MeOH, P = *i*-PrOH, W = H_2O. [b] Not characterized. [c] L. C. King and W. B. Brownell, *J. Am. Chem. Soc.*, **72**, 2507 (1950). [d] F. Kröhnke and K. Fasold, *Ber.*, **67**, 656 (1934). [e] R. E. Doolittle and C. K. Bradsher, *J. Org. Chem.*, **31**, 2616 (1966). [f] F. Kröhnke and A. Schulze, *Ber.*, **72**, 2000 (1939). [g] F. Kröhnke, *ibid.*, **68**, 1351 (1935). [h] F. Kröhnke, *ibid.*, **66**, 604 (1933). [i] C: calcd, 57.2; found, 57.8. [j] N: calcd, 4.5; found, 5.0. [k] C: calcd, 61.8; found, 61.3. H: calcd, 4.9; found, 5.4. [l] C: calcd, 48.9; found, 49.4. [m] Minimum effective dose against *N. dubius*. [n] Not tested.

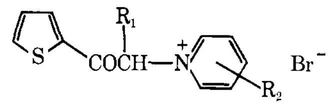
TABLE VII



No.	Ar	Prep method	Recrystn solvent[b]	Mp, °C	Lit. mp, °C	Ref	Formula	Analyses	MED,[l] mg/kg	Days given
	Pyrantel tartrate								12.5	1
62	2-C_4H_3S	B	M–A	180–181	180–181	c	$C_{11}H_{10}BrNS$	C, H, N	12.5	1
63	3-CH_3-2-C_4H_2S	B	M–A	231–232			$C_{12}H_{12}BrNS$	C, H, N	7.8	1
64	5-Cl-2-C_4H_2S	B	M–EA	185–186			$C_{11}H_9BrClNS$	H, N; C[f]	>250	1
65	C_6H_5	B	M–A	158–159	154–156	c	$C_{13}H_{12}BrN$	C, H, N	125	1
66	2-$CH_3C_6H_4$	B	P	197–198	192–193	d	$C_{14}H_{14}BrN$	C, H, N	15	1
67	3-$CH_3C_6H_4$	B	M–A	238–239			$C_{14}H_{14}BrN$	C, H, N	>250	3
68	4-$CH_3C_6H_4$	B	M–A	265–267			$C_{14}H_{14}BrN$	C, H, N	>250	3
69	3-HOC_6H_4	L	W	115–117	117	c	$C_{13}H_{12}BrNO \cdot 2H_2O$	C, H, N	250	1
70	2-$CH_3OC_6H_4$	A	M–A	70–71			$C_{14}H_{14}BrNO$	C, H, N	>250	1
71	3-$CH_3OC_6H_4$	A	M–P	192–193			$C_{14}H_{14}BrNO$	C, H, N	>250	1
72	4-$CH_3OC_6H_4$	A	P	210–211	201	e	$C_{14}H_{14}BrNO$	C, H, N	>250	1
73	2-FC_6H_4	B	P	89–90			$C_{13}H_{11}BrFN$	C, H; N[g]	250	1
74	4-FC_6H_4	B	P	210–212			$C_{13}H_{11}BrFN$	H, N; C[h]	>200	1
75	2-ClC_6H_4	B	M–A	171–172	95	c	$C_{13}H_{11}BrClN \cdot H_2O$	Br[i]	31	1
76	3-ClC_6H_4	B	P	168–170			$C_{13}H_{11}BrClN \cdot 0.5H_2O$	C, H, N	>200	1
77	4-ClC_6H_4	B	M–A	229–231	227	e	$C_{13}H_{11}BrClN$	C, H, N	>250	3
78	3-BrC_6H_4	B	P	198–199			$C_{13}H_{11}Br_2N$	H, N; C[j]	>250	1
79	3-$NO_2C_6H_4$	B	M–A	249–250	243	e	$C_{13}H_{11}BrN_2O_2$	C, H, N	>1000	1
80	4-$NO_2C_6H_4$	B	M–A	273–275	271	e	$C_{13}H_{11}BrN_2O_2$	H, N; C[k]	>250	3
81	2-$CF_3C_6H_4$	B	P–IE	180–181			$C_{14}H_{11}BrF_3N$	C, H, N	>500	1
82	2-$C_{10}H_7$	B	M–A	257–258			$C_{17}H_{14}BrN$	C, H, N	>250	3
83	2-C_4H_3O	L	P–IE	185–186	186–188	e	$C_{11}H_{10}BrNO$	C, H, N	250	1
84	3-CH_3-2-C_4H_2O	C	M–EA	223–224			$C_{12}H_{12}BrNO$	C, H, N	>125	1
85[a]	5-CH_3-2-C_4H_2O	C	E	158–159[a]			$C_{12}H_{12}F_6NOP$	C, H, N	>500	1

[a] PF_6^- salt. [b] A = Me_2CO, E = dry EtOH, EA = EtOAc, IE = *i*-Pr_2O, M = MeOH, P = *i*-PrOH, W = H_2O. [c] L. C. King and W. B. Brownell, *J. Am. Chem. Soc.*, **72**, 2507 (1950). [d] R. E. Doolittle and C. K. Bradsher, *J. Org. Chem.*, **31**, 2616 (1966). [e] F. Kröhnke, J. Wolff, and G. Jentzsch, *Ber.*, **84**, 399 (1951). [f] C: calcd, 43.7; found, 43.2. [g] N: calcd, 5.0; found, 4.3. [h] C: calcd, 55.7; found, 55.1. [i] Br: calcd, 25.4; found, 25.9. [j] C: calcd, 45.8; found, 46.4. [k] C: calcd, 50.8; found, 50.2. [l] Minimum effect dose against *N. dubius*.

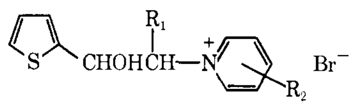
TABLE VIII



No.	R_1	R_2	Recrystn solvent	Mp, °C	Formula	Analyses	MED,[b] mg/kg	Days given
86	CH_3	H	*i*-PrOH	167–168	$C_{12}H_{12}BrNOS$	C, H, N	>250	3
87	H	2-CH_3	EtOH	211–212	$C_{12}H_{12}BrNOS$	C, H, N	>250	3
88	H	3-CH_3	EtOH	219–220	$C_{12}H_{12}BrNOS$	N; C, H[a]	*c*	
89	H	4-CH_3	EtOH	239–240	$C_{12}H_{12}BrNOS$	C, H, N	>500	3

[a] C: calcd, 48.3; found, 43.5. H: calcd, 4.1; found, 3.6. [b] Minimum effective dose against *N. dubius*. [c] Not tested.

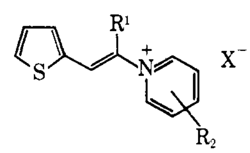
TABLE IX



No.	R_1	R_2	Recrystn solvent	Mp, °C	Formula	Analyses	MED,[c] mg/kg	Days given
90[a]	CH_3	H	*i*-PrOH	186–187	$C_{12}H_{14}BrNOS$	C, H, N	>500	3
91	H	2-CH_3	MeOH–*i*-PrOH	190–191	$C_{12}H_{14}BrNOS$	C, H, N	>250	3
92	H	3-CH_3	MeOH–*i*-PrOH	163–164	$C_{12}H_{14}BrNOS$	C, H, N	>250	3
93	H	4-CH_3	*i*-PrOH	177–179	$C_{12}H_{14}BrNOS$	H, N; C[b]	*d*	

[a] Either the *threo* or *erythro* isomer; a second isomer was not detected. [b] C: calcd, 48.0; found, 48.5. [c] Minimum effective dose against *N. dubius*. [e] Not tested.

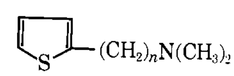
TABLE X



No.	R_1	R_2	Prep method	X	Recrystn solvent	Mp, °C	Formula	Analyses	MED,[a] mg/kg	Days given
94	CH_3	H	B	PF_6	Me_2CO–C_6H_{14}	178–180	$C_{12}H_{12}F_6NPS$	C, H, N	>500	3
95	H	2-CH_3	B	Br	MeOH–*i*-PrOH	188–189	$C_{12}H_{12}BrNS$	C, H, N	62	1
96	H	3-CH_3	B	Br	MeOH–Me_2CO	205–206	$C_{12}H_{12}BrNS$	C, H, N	>100	3
97	H	4-CH_3	B	Br	*i*-PrOH	239–240	$C_{12}H_{12}BrNS$	C, H, N	>250	3

[a] Minimum effective dose against *N. dubius*.

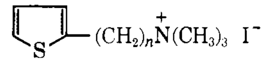
TABLE XI



No.	*n*	Prep method	Bp (mm), °C	$n^{25}D$	Ref	Formula	Analyses	MED,[b] mg/kg	Days given
98	1	L	83 (30)	1.5159	*a*	$C_7H_{11}NS$	C, H, N	>500	1
99	2	D	99 (27)	1.5139		$C_8H_{13}NS$	C, H, N	500	2
100	3	E	86 (15)	1.5078		$C_9H_{15}NS$	C, H, N	>250	3
101	4	E	47 (0.1)	1.5050		$C_{10}H_{17}NS$	C, H, N	>250	3

[a] H. D. Hartough, S. L. Meisel, E. Koft, and J. W. Schich [*J. Am. Chem. Soc.*, **70**, 4013 (1949)] report bp 60–61° (10 mm) and $n^{20}D$ 1.5188. [b] Minimum effective dose against *N. dubius*.

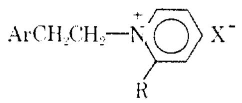
TABLE XII



No.	*n*	Recrystn solvent	Mp, °C	Lit. mp, °C	Ref	Formula	Analyses	MED,[c] mg/kg	Days given
102	1	EtOH	154–156	152–153	*a*	$C_8H_{14}INS$	I	>500	3
103	2	H_2O–EtOH	249–251	236–238	*b*	$C_9H_{16}INS$	C, H, N	>250	3
104	3	EtOH	185–186			$C_{10}H_{18}INS$	C, H, N	>100	3
105	4	EtOH	208–210			$C_{11}H_{20}INS$	C, H, N	>250	3

[a] H. D. Hartough, S. L. Miesel, E. Koft, and J. W. Schich, *J. Am. Chem. Soc.*, **70**, 4013 (1948). [b] G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938). [c] Minimum effect dose against *N. dubius*.

Table XIII



No.	Ar	R	X	Recrystn solvent	Mp, °C	Formula	Analyses	MED,[c] mg/kg	Days given
115	2-C_4H_3S	H	Cl	EtOH–Et_2O	111–112	$C_{11}H_{12}ClNS \cdot 0.5H_2O$	H, N; C[b]	100	3
116	2-C_4H_3S	CH_3	Cl	EtOH–Et_2O	168–169	$C_{12}H_{14}ClNS$	C, H, N	>200	1
117	3-CH_3-2-C_4H_2S	H	Cl	EtOH–Et_2O	183–184	$C_{12}H_{14}ClNS \cdot 0.25H_2O$	C, H, N	>200	3
118	C_6H_5	H	Br	*a*		$C_{13}H_{14}BrN$		>250	3

[a] Commercial material. [b] C: calcd, 56.3; found, 55.8. [c] Minimum effective dose against *N. dubius*.

from 2-thiophenebutyric acid, except the product was not distilled but used directly in the preparation of N,N-dimethyl-2-thiophenebutyramide (113).

N,N-Dimethyl-2-thiophenepropionamide (112).—With ice-bath cooling and efficient stirring, 200 ml of 25% aqueous Me_2NH was treated dropwise with 34.9 g (0.2 mole) of 2-thiophenepropionyl chloride. The resulting mixture was extracted with two 100-ml portions of Et_2O, and the combined extracts were dried (Na_2SO_4). After filtering and evaporating the ether solution, the residue was distilled to furnish pure **112**, yield 26.7 g (73%), bp 106–108° (0.4 mm), $n^{25}D$ 1.5425, d^{25}_{25} 1.1229; vapor phase chromatography showed this material to be essentially 100% pure. *Anal.* ($C_9H_{13}NOS$) C, H, N.

N,N-Dimethyl-2-thiophenebutyramide (113).—In a like manner **113** was prepared from 17.1 g (0.1 mole) of 2-thiophenebutyric acid *via* the acid chloride: yield 11.9 g (60%), bp 112–117° (0.2–0.3 mm), $n^{25}D$ 1.5352; vapor phase chromatography showed the product to be essentially 100% pure. *Anal.* ($C_{10}H_{15}NOS$) C, H, N.

8-Methylbenzo[*a*]quinolizinium Bromide (114).—A solution of 15.0 g (0.055 mole) of **66** in 1500 ml of MeOH was exposed to sunlight for 11 days. The exposed solution was then evaporated to furnish a yellow solid, yield 14.8 g (99.5%), mp 191–197°. After three recrystallizations from *i*-PrOH and one from EtOH, crystals of pure **114** were obtained: yield 0.8 g (5%), mp 264–265°. The uv spectrum of **114** agrees with that reported for the perchlorate salt.[13] *Anal.* ($C_{14}H_{12}BrN$) H, N, C: calcd, 61.3; found, 60.8.

1-(2-Thienylethyl)pyridinium chloride (115) was prepared by the reaction of 2-(2-chloroethyl)thiophene[22] and pyridine. See Table XIII for the physical properties and analytical data.

(22) F. F. Blicke and F. Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

2-Methyl-1-(2-thienylethyl)pyridinium chloride (116) and **1-[2-(3-methyl-2-thienyl)ethyl]pyridinium chloride (117)** were prepared in a similar manner from appropriate starting materials.

2-(2-Chloroethyl)-3-methylthiophene.—A solution of 3-methyl-2-thienylmagnesium bromide was prepared from 56 g (0.32 mole) of 2-bromo-3-methylthiophene and 12.6 g (0.52 g-atom) of Mg in 400 ml of dry Et_2O. This mixture was treated dropwise over a period of 1 hr with a solution of 195 g (0.83 mole) of 2-chloroethyl *p*-toluenesulfonate in 200 ml of Et_2O. After the addition was complete, the mixture was heated under reflux for 2 hr. The crude product was isolated by standard techniques, and was fractionally distilled to furnish an oil: yield 33.5 g (66%), bp 98–102° (16 mm), $n^{25}D$ 1.5620. This material is unstable; without further characterization it was used immediately to prepare **117**.

Acknowledgments.—Thanks are due to Messrs. R. B. James and R. W. Sumner for valuable assistance in preparing the compounds mentioned in this article, to Mr. G. F. Smith for his help in evaluating their anthelmintic activity, and to Drs. L. H. Conover, and J. E. Lynch for their encouragement and advice during the course of this investigation. Also we wish to express our appreciation to Drs. H. C. Richards and R. L. Cornwell of the Pfizer Ltd. Research Laboratories, Sandwich, U. K., for making the chemical and biological data on the 1-(2-arylethyl)pyridinium salts available for this article.