with a slight excess of HNO_3. Filtration of the product (8.0 g) and recrystallization (MeOH–*i*-Pr_2O) gave 5.2 g, mp 169–170°.

1-[β-(*p*-Aminophenoxy)-2,4-dichlorophenethyl]imidazole (58).—A 20-g (0.053 mole) portion of **57** (base) was added to a refluxing mixture of 13.5 g of Fe dust, 10.6 g of NH_4Cl, and 150 ml of H_2O. Refluxing was continued for 6 hr. To the cooled mixture was added 100 ml of CH_2Cl_2, and solids were removed by filtration. Stripping of the dried organic phase left crude product, furnishing 10.0 g of amine after recrystallization from *i*-Pr_2O; mp 95–96°.

2-(Bromomethyl)-2-(*p*-chlorophenyl)dioxolane[6] (10) (Method F).—Br_2 (320 g, 2.0 moles) was introduced dropwise to a solution of 310 g (2.0 moles) of 4′-chloroacetophenone in 600 ml of ethylene glycol at 75°. The colorless mixture was subsequently stirred for 1 hr at 5°. The crude filtered product was taken up in 1 l. of CH_2Cl_2 and washed with dilute NaOH. Drying, removal of solvent, and recrystallization of the residue from MeOH gave 465 g (84%) of the product, mp 61–62°.

2-(Bromomethyl)-2-(*m*-methoxyphenyl)dioxolane (112) (Method E).—3′-Methoxyacetophenone (150 g, 1.0 mole) in Et_2O–dioxane (400:200 ml) was brominated [160 g (1.0 mole) of Br_2] at 5°. To the decolorized mixture was added 250 ml of ethylene glycol, whereupon solvents were removed till the temperature reached 150°. The solution was cooled, 1 l. of C_6H_6 and 5 g TSA were added, and H_2O was removed azeotropically for 18 hr. Washing of the solution with dilute NaOH, drying of the C_6H_6 phase, and removal of the solvent left crude product; this was purified by distillation over 10 g of K_2CO_3, giving 120 g of product, bp 145–155° (1.4 mm). The distillate solidified on standing and was triturated with *i*-PrOH to give 102 g of material, mp 60–61°.

1-[2-(*p*-Chlorophenyl)-1,3-dioxolan-2-ylmethyl]imidazole Nitrate (121).—To a solution of sodium imidazole (1.5 moles) in 500 ml of DMF (see preparation of **19**) was added 277 g (1.0 mole) of **101**, whereupon the solution was kept at 140–145° for 4 hr. Dilution of the mixture with H_2O and subsequent cooling caused deposition of the product base. This was filtered off, dissolved in AcMe–*i*-Pr_2O, and treated with a slight excess of HNO_3, giving 290 g (88%) of product, mp 199–200°.

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Imidoylureas. A New Class of Anthelmintics

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A series of imidoylureas have been synthesized and examined for antihookworm activity in dogs. Among the various types prepared, the alkylimidoyl-substituted phenylureas were found most active, and 1-(*p*-chlorophenyl)-3-pentanimidoylurea was selected as the compound of choice, effective in a single dose of 10 mg/kg.

It has been estimated that more than one-fourth of the world's human population is infected with one or more intestinal nematodes.[1] The consequences of severe and widespread infections with the hookworms *Ancylostoma duodenale* and/or *Necator americanus* are well documented.[2–4] Because remedies currently employed in the treatment of these infections leave much to be desired we have been engaged in the synthesis of compounds with potential antihookworm properties.

In the course of screening compounds in dogs against *Ancylostoma caninum* and/or *Uncinaria stenocephala*, it was discovered that a series of imidoylureas of the general formula, $R_1C(=NR_2)NHCONR_3R_4$, and related structures exhibited interesting activity.

Chemistry.—All of the compounds in Table I with the exception of **24** and **25** were prepared by treatment of equivalent amounts of the appropriate amidine hydrochloride and isocyanate in acetone or chloroform in the presence of a base such as Et_3N or Na in acetone.

$$R_1C(=NR_2)NH_2\cdot HCl \xrightarrow[\text{base}]{R_3N=CO} R_1C(=NR_2)NHCONR_4R_3$$

The synthesis of compounds **33** and **34** was initiated from the thioamide[5] I which was treated with ethyl bromopyruvate to produce the keto ester II (Scheme I). The latter was not isolated but immediately converted to the thiazole III.[6] Compound III was converted to the amide IV[7] by treatment with NH_4OH, and IV was then dehydrated to the nitrile V.[8] In the case of IV (R = CH_3), dehydration was achieved with benzenesulfonyl chloride[9] in 65% yield. However, under these

SCHEME I

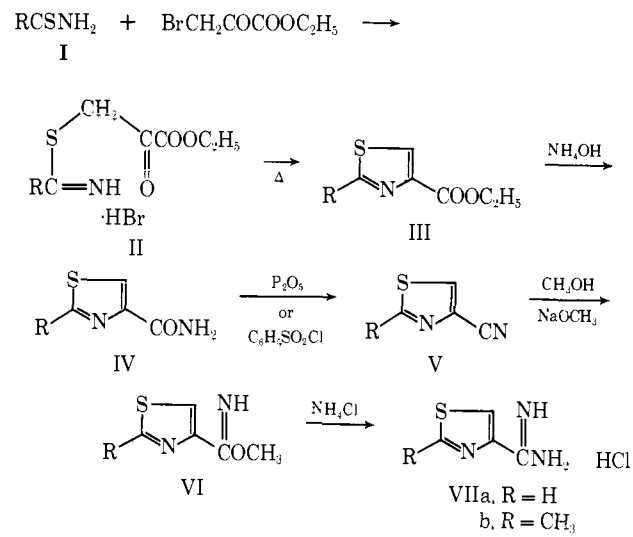

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TABLE I: IMIDOYLUREAS

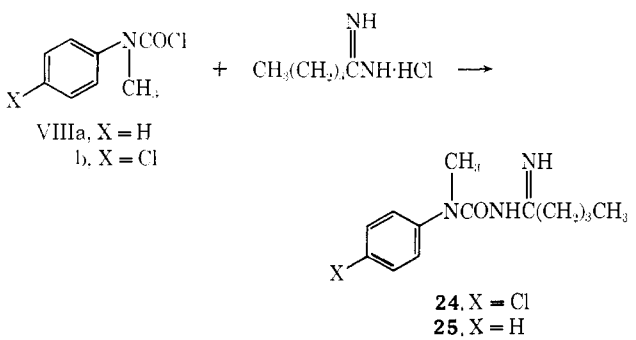
$$R_1C(=NR_2)NR_4CONR_3R_5$$

No.	R_1	R_2	R_3	R_4	Recrystn solvent[a]	% yield	Mp, °C	Formula	Single min effective dose, mg of base/kg
1	Et	H	4-ClC_6H_4	H	A	67	191–196	$C_{10}H_{12}ClN_3O\cdot HCl$	25
2	Pr	H	4-ClC_6H_4	H	A	88	206–208	$C_{11}H_{14}ClN_3O\cdot HCl$	25
3	Bu	H	4-ClC_6H_4	H	A	88	202–204	$C_{12}H_{16}ClN_3O\cdot HCl$	10
4	Pent	H	4-ClC_6H_4	H	A	47	175–179	$C_{13}H_{18}ClN_3O\cdot HCl$	50
5	Hex	H	4-ClC_6H_4	H	A	84	168–169	$C_{14}H_{20}ClN_3O\cdot HCl$	100
6	Hept	H	4-ClC_6H_4	H	B	78	156–165	$C_{15}H_{22}ClN_3O\cdot HCl$	100
7	Oct	H	4-ClC_6H_4	H	B	80	155–157	$C_{16}H_{24}ClN_3O\cdot HCl$	>100
8	But	H	3,4-$Cl_2C_6H_3$	H	C	76	177–179	$C_{12}H_{15}Cl_2N_3O\cdot HCl$	>100
9	But	H	3-$O_2NC_6H_4$	H	D	81	161–163	$C_{12}H_{16}N_4O_3\cdot HCl$	>100
10	But	H	2-$O_2NC_6H_4$	H	A	78	130–132	$C_{12}H_{16}N_4O_3\cdot HCl$	>100
11	But	H	4-$O_2NC_6H_4$	H	A	76	187–191	$C_{12}H_{16}N_4O_3\cdot HCl$	25
12	But	H	3-$F_3CC_6H_4$	H	B	75	167–169	$C_{13}H_{16}F_3N_3O\cdot HCl$	>100
13	But	H	2-Benzyloxyphenyl	H	E	93	145–147	$C_{22}H_{28}N_3O_2\cdot HCl$	>100
14	But	H	2-HOC_6H_4	H	D	56	173–175	$C_{21}H_{27}N_3O_2\cdot HCl$	>100
15	But	H	4-$MeOC_6H_4$	H	A	75	143–145	$C_{13}H_{19}N_3O_2\cdot HCl$	>100
16	But	H	4-BrC_6H_4	H	A	63	212–213	$C_{12}H_{16}BrN_3O\cdot HCl$	100
17	But	H	4-Cl-2-$O_2NC_6H_3$	H	A	85	170–174	$C_{12}H_{15}ClN_4O_3\cdot HCl$	100
18	But	H	3-ClC_6H_4	H	C	77	135–137	$C_{12}H_{16}ClN_3O\cdot HCl$	>100
19	But	H	2-ClC_6H_4	H	D	71	132–134	$C_{12}H_{16}ClN_3O\cdot HCl$	>100
20	But	H	*p*-Tolyl	H	B	63	159–160	$C_{13}H_{19}N_3O\cdot HCl$	100
21	But	H	4-FC_6H_4	H	E	87	167–172	$C_{12}H_{16}FN_3O\cdot HCl$	25
22	But	H	Ph	H	A	82	155–156	$C_{12}H_{17}N_3O\cdot HCl$	>100
23	But	CH_3	4-ClC_6H_4	H	C	81	154–158	$C_{13}H_{18}ClN_3O\cdot HCl$	>100
24[b]	But	H	4-ClC_6H_4	CH_3	E	15	218–220	$C_{36}H_{51}ClN_6O_7$	>100
25[b]	But	H	Ph	CH_3	E	50	201–202	$C_{36}H_{52}N_6O_7$	>100
26	Ph	H	3,4-$Cl_2C_6H_3$	H	A	43	164–166	$C_{15}H_{11}Cl_2N_3O$	>100
27	Ph	H	4-$O_2NC_6H_4$	H	F	98	188–191	$C_{14}H_{12}N_4O_3$	>100
28	Ph	H	2-$O_2NC_6H_4$	H	F	45	144–146	$C_{14}H_{12}N_4O_3$	>100
29	Ph	H	4-ClC_6H_4	H	A	51	213–215	$C_{14}H_{12}ClN_3O\cdot HCl$	>100
30	$PhCH_2$	H	3-ClC_6H_4	H	C	48	170–171	$C_{15}H_{14}ClN_3O$	>100
31	Bu	H	Cyclohexyl	H	E	89	146–148	$C_{12}H_{23}N_3O\cdot HCl$	>100
32	Ph	H	Bu	H	I	81	139–141	$C_{12}H_{17}N_3O\cdot HCl$	>100
33	4-Thiazolyl	H	4-BrC_6H_4	H	G	92	191–197	$C_{11}H_9BrN_4OS$	>100
34	2-Methyl-4-thiazolyl	H	4-BrC_6H_4	H	H	75	185–186	$C_{12}H_{11}BrN_4OS$	>100

[a] A = EtOH, B = MeCN, C = AcMe, D = EtOH–Et_2O, A = *i*-PrOH, F = PhH, G = MeOH, H = ethylene dichloride, I = DMF. [b] Isolated as the pamoate salt.

conditions, the nitrile V (R = H) could not be prepared. Consequently, P_2O_5 was employed and V (R = H) was obtained in 38% yield. The amidines VIIa and b were prepared by treatment of the corresponding nitrile V with NaOMe in MeOH followed by the addition of NH_4Cl to a solution of the resulting imido ester VI.

Compounds **24** and **25** were prepared by treating the carbamoyl chlorides VIIIa[10] and b[11] with valeramidine. In view of the difficulty experienced in crystallizing these compounds, it was found necessary to isolate them as their pamoate salts.



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Testing Procedure.—Mongrel dogs infected in nature or in the laboratory were used in the assay system. Most of the naturally infected dogs harbored *A. caninum* worms; a small number harbored *U. stenocephala*. Dogs were infected in the laboratory by the oral administration of 100–200 filariform larvae of *A. caninum* at least 4 weeks prior to treatment. The presence of sexually mature worms was determined by finding ova in the stools. Prior to drug testing, food (standard laboratory chow) was withheld from the animals for a minimum of 5 hr and for 3 hr after a single oral administration of the test compound. Two or more dogs were tested with each of the compounds. The animals were sacrificed 3–8 days postmedication and the small intestine was examined for worms. The minimal effective dose was taken as the amount of compound that completely eliminated the infection from one or more dogs.

Structure–Activity Relationship.—The initial antihookworm activity was discovered with the 1-(*p*-chlorophenyl)-3-alkanimidoylurea series. The alkyl group was varied from R_1 = Et to Oct (Table I, **1**–**7**). All of the members of this series exhibited some degree of activity, with **3** (R_1 = Bu) demonstrating the highest potency.

In the next stage of this study, the butyl group was maintained and the substituents about the phenyl ring were varied (**8–22**). The activity of the compounds varied in degree with the nature of these substituents. Substitution with Cl in the 4 position of the phenyl ring enhanced activity (**3**) while activity diminished when Cl was moved to the 3 position (**18**) and the 2 position (**19**). A similar effect was produced with nitro substitution (**9–11**). The activity was reduced somewhat when Cl was replaced by F (**21**) and to a larger extent when replaced by Br (**16**). When R_1 was changed to phenyl (**26–29**), the activity decreased.

Finally, several miscellaneous type homologs were prepared (**30–34**), but here again activity against the parasite was substantially diminished.

The most active compound prepared in this series was **3**, 1-(*p*-chlorophenyl)-3-pentanimidoylurea, which was chosen for extensive study. In addition to its activity against hookworm, **3** and several of its homologs when administered at higher doses were active against naturally occurring dog tapeworm infections (*Dipylidium caninum* and *Taenia pisiformis*).

Compound **3** is well tolerated in dogs with some emesis at dose levels exceeding 25 mg/kg. Preliminary studies indicate that this compound is rapidly excreted after oral administration. Comprehensive toxicity and pharmacological studies are underway.

Experimental Section[12]

General Procedure for the Imidoylureas (Table I). 1-(*p*-Chlorophenyl)-3-pentanimidoylurea (3).—To a cooled mixture of 4.6 g (0.2 g-atom) of Na in 300 ml of dry AcMe was added 27.2 g (0.2 mole) of valeramidine hydrochloride[13] suspended in 50 ml of dry AcMe, with vigorous stirring. The mixture was stirred for 20 min and then 30.7 g (0.2 mole) of *p*-chlorophenyl isocyanate dissolved in 100 ml of dry AcMe was added dropwise with cooling to the stirred mixture. The addition took approximately 40 min. After the addition was complete, the mixture was stirred for an additional 2 hr with cooling and finally left at room temperature overnight. The mixture was then concentrated to dryness at 50° *in vacuo* and the syrupy residue was stirred with 400 ml of cold Et_2O. A solid separated. The mixture was shaken with 100 ml of cold H_2O whereupon the solid dissolved. The organic layer was collected and the aqueous layer was extracted twice with 100-ml portions of Et_2O. The Et_2O extracts were combined, dried over Drierite, filtered with charcoal, and cooled. The cooled filtrate was treated with 2 *N* ethereal HCl until the mixture was strongly acidic. The solid was collected, washed with absolute Et_2O, and dried *in vacuo;* yield 50.6 g, mp 196–198°. Recrystallization from 500 ml of EtOH yielded 34.6 g, mp 202–204°. *Anal.* ($C_{12}H_{16}ClN_3O \cdot HCl$) Cl, N.

4-Thiazolecarboxamidine (VIIa) was prepared from 4-thiazolecarbonitrile[8] according to the procedure of Schaefer and Peters.[14] After the solvent was removed, the residue was ground in a mortar and stirred for 15 min in 30 ml of absolute Et_2O. The solid was collected, washed (Et_2O), and dried; 70 g (93%) of the amidine hydrochloride was obtained as the hydrate. The white solid was recrystallized from *i*-PrOH to produce 55 g, mp 120–122°. *Anal.* ($C_4H_5N_3S \cdot HCl \cdot H_2O$) Cl, N, S.

2-Methyl-4-thiazolecarbonitrile (V, R = CH_3).—Compound **IV**[15] (R = CH_3) was dehydrated with benzenesulfonyl chloride according to the procedure of Stephens, *et al.*[9] The material was recrystallized (Et_2O), mp 62–64°. *Anal.* ($C_5H_4N_2S$) C, H, N.

2-Methyl-4-thiazolecarboxamidine (VIIb) was prepared from V in 80% yield in the same manner as described for **VIIa**, mp 149–151°. *Anal.* ($C_5H_7N_3S \cdot HCl$) C, H, N.

Bis[1-methyl-3-(pentanimidoyl)-1-phenylurea] Pamoate (25).—To a solution of 2.3 g (0.1 g-atom) of Na in 400 ml of dry *t*-BuOH was added 13.6 g (0.1 mole) of valeramidine hydrochloride followed by 11 ml of Et_3N. Phenylmethylcarbamoyl chloride[10] (13 g, 0.077 mole) in 300 ml of *t*-BuOH was then added dropwise over a 30-min period and the mixture was stirred at room temperature for 24 hr. The solid (salts) was removed by filtration and the filtrate was concentrated to dryness leaving a viscous oil. The oil was dissolved in MeOH (100 ml) and the solution was acidified with ethereal HCl. It was then concentrated to dryness and the residual oil dissolved in 200 ml of H_2O; 23.0 g (0.051 mole) of disodium pamoate in 200 ml of H_2O was added. The precipitate which formed was collected and dried, 31.1 g (50%) being obtained, mp 188–190°. Recrystallization from *i*-PrOH yielded 17.0 g, mp 201–202°. *Anal.* ($C_{36}H_{35}N_3O_7$) C, H, N.

Bis[1-(*p*-chlorophenyl)-1-methyl-3-pentanimidoylurea] pamoate (26) was prepared in the same manner as **25** from *p*-chlorophenyl-*N*-methylcarbamoyl chloride[11] and valeramidine, mp 180–182°. *Anal.* ($C_{13}H_{18}ClN_3O \cdot C_{23}H_{16}O_6$) C, H, N.

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(12) All melting points were run according to the USP procedure and are uncorrected. Analyses were performed by the staff of M. E. Auerbach and K. D. Fleischer.

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