into a series of 4-ml portions of sterile BBL Trypticase Soy Broth to give concentrations of 200, 48, 24, and 2.4 μg/ml. All of the compounds at concentrations of 200 μg/ml and some at 48 μg/ml precipitated out of the water-based broth solution, and the tests at these concentrations were not performed. The test solutions were inoculated with the microorganisms and incubated, with shaking, for 24 hr. Turbidity readings of the cultures were taken on a Bausch and Lomb Spectronic 20 spectrophotometer at 660 mμ. Per cent inhibition was determined by using a control consisting of broth, solvent, and microorganism, to give a turbidity reading of 100% growth, or 0% inhibition. The percentage inhibition shown is the average from 2 to 4 separate determinations. In view of the limitations of the turbidity method the per cent inhibition shown in Table II has been rounded off to the nearest 10%.

1-Adamantanecarboxylic Acid Amide of 4-Aminoantipyrine

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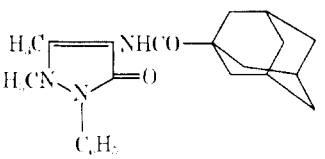
We have prepared 2,3-dimethyl-1-phenyl-4-(1-adamantanecarboxamido)-5-pyrazolone



in order to consider the effect of the highly symmetrical cagelike adamantane molecule and its hydrophobic binding in the form of adamantanecarboxamide of 4-aminoantipyrine, and to test for analgetic and antipyretic activity of this new compound.

Experimental Section

Chemistry.—A mixture of 9.9 g of 1-adamantanecarboxylic acid chloride (0.05 mol) (Aldric Chemical Co., Inc.); 10.5 g of 4-aminoantipyrine (0.05 mol) and 100 ml of dioxane, was kept at room temperature for 3 hr. The reaction mixture was diluted with 200 ml of cold H_2O and the crystalline reaction product was filtered off. It was washed with 5% $NaHCO_3$, and recrystallized from dioxane. The yield was 16.2 g (87%) of white crystals, mp 206–207° (uncorr). *Anal.* ($C_{22}H_{27}N_3O_3$) C, H, N.

Spectroscopic Results.—Ir spectra were recorded on a Perkin-Elmer Model 221 ir spectrophotometer (Nujol) and were as expected: N–H stretching bands near 3320 cm^{-1} and 3420 cm^{-1} (4-aminoantipyrine, starting material) were absent from the spectrum, and a C=O stretching band in the 1650 cm^{-1} region due to the NH–CO group was present. Uv spectrum were characterized by the maximum at 284 mμ (14 mcg/ml) in dioxane using a Beckman spectrophotometer Model D. U. $E_{1cm}^{1\%}$ calculated was 290.

Pharmacology.—The compound was administered in physiological solution containing 6% Tween 80 and its analgetic and antipyretic actions were tested in Swiss mice and rabbits.

Analgetic Activity. Hot Plate Test.[1]—Antipyretic activity was measured by the method of Baker and Coll.[2] Hyperthermia was produced in rabbits by injection of 0.3 ml/kg of TAB-D-ISM vaccine in the marginal vein of the ear.

Mice which received doses of 20 mg/kg i.p. and p.o. of 2,3-dimethyl-1-phenyl-4-(adamantanecarboxamido)-5-pyrazolone showed 30% more heat resistance than mice which received the equivalent dose of 4-aminoantipyrine.

Doses of 19 mg/kg i.p. in rabbits were shown to cause the same antipyretic activity as that produced by an equivalent dose of 4-aminoantipyrine.

In mice the LD_{50} i.p. was 820 mg/kg; *vs.* 280 mg/kg for 4-aminoantipyrine.

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(2) J. A. Baker, J. Hayden, and P. G. Marshall, C. H. R. Palmer, and T. D. Whitted, *ibid.*, **15**, 97 (1963).

2-(Substituted Amino)quinolizinium Bromides. A New Class of Anthelmintic Agents

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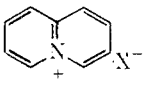
Many different types of compounds have been shown to have varying degrees of anthelmintic activity. Several of these classes, according to Harfenist, have a group bearing a positive charge and a cyclic moiety, which may or may not be separated. Examples of these include naphthamidines, dihydropyridines, pyrrocolines, and stilbazoles.[1] Two additions to veterinary helminthic therapy, tetramisole and pyrantel, contain these two structural features.[2,3]

Emetine dihydrochloride is another example of a compound which possesses these features. This alkaloid, used in the treatment of several helminthic disorders,[4] contains the positively charged quinolizine ring. The investigation reported here was undertaken to determine whether a related but less complicated structure, the completely aromatic quinolizinium ring system (**1**), might retain some of the antiparasitic activity of this alkaloid.



1

In our work a series of 2-(substituted amino)quinolizinium salts was synthesized for screening for prevention of lung invasion by the larvae of *Ascaris suum* in mice.

Chemistry.—The preparation of the 2-(substituted amino)quinolizinium compounds, shown in Table I, proceeded through either of the two intermediates, 2-bromoquinolizinium bromide (**2**) or 2-bromo-6-methylquinolizinium bromide (**3**). These were readily pre-

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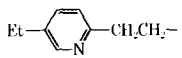
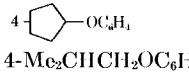
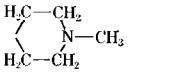
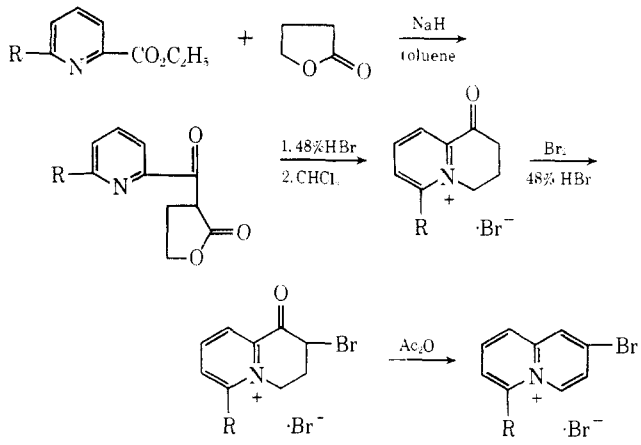
(4) F. L. Bach, Jr. and S. Kushner, in "Medicinal Chemistry," 2nd ed, A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 1075.

TABLE I

No.[h]	R1	R2	Mp, °C	% yield	Recrystallization solvent[a]	Formula	Anal[b]	Dose[c] mg/kg 5 × b.i.d.	A. suum[d] % reduction	A. suum[d] Probability, $P \leq$
4	NH_2		248–252	82	A–B	$C_{18}H_{21}BrN_4 \cdot HBr$	C, H, Br	300	96	0.001
5	$EtOCH_2CH_2$	$EtOCH_2CH_2$	103–104	92	B–A	$C_{17}H_{25}BrN_2O_2$	C, H, Br	300	72	0.001
6	H	4-$Me_2NC_6H_4$	227–228	82	C–D	$C_{17}H_{18}BrN_3 \cdot HBr$	C, H, Br	150	97	0.001
7	H	2-$MeOC_6H_4$	182–183	82	C–B	$C_{16}H_{15}BrN_2O$	C, H, Br	300	98	0.001
8	H	4-$EtOC_6H_4$	172–174	88	C–B	$C_{17}H_{17}BrN_2O$	C, H, Br	300	98	0.001
9	H	4-$CH_2{=}CHCH_2OC_6H_4$	153–154	83	C–B	$C_{18}H_{17}BrN_2O$	C, H, N	300	96.5	0.001
10	H	4-$Et_2NC_6H_4$	220–224	42	A–E	$C_{19}H_{22}BrN_3 \cdot HBr \cdot 0.5H_2O$	C, H, N	150	87	0.01
11	H	4-$HC{\equiv}CCH_2OC_6H_4$	193–194	96	A	$C_{18}H_{15}BrN_2O$	C, H, N	150	72	0.001
12	H	3,4-$Me_2C_6H_3$	236–237	97	C	$C_{17}H_{17}BrN_2$	C, H, N	150	81	0.001
13	H	2,4-$(MeO)_2C_6H_3$	217–219	72	C–B–E	$C_{17}H_{17}BrN_2O_2 \cdot 0.5HBr$	C, H, N	100	62	0.001
14	H	Ph	175–179	77	C	$C_{15}H_{13}BrN_2$	C, H, N, Br[e]	300	71	0.01
15	H	2,4,6-$(MeO)_3C_6H_2$	241–242	62	C–D	$C_{18}H_{19}BrN_2O$	C, H, N, Br	100	15	*f*
16	H	4-$PhOC_6H_4$	205–206	98	C–B–E	$C_{21}H_{17}BrN_2O_3$[i]	C, H, N, Br	300	35	*f*
17	H	4-*n*-$BuOC_6H_4$	221–223	75	C	$C_{19}H_{21}BrN_2O$	C, H, N, Br	300	60	0.02
18	H	2-Me,4-$MeOC_6H_3$	259–263	88	A	$C_{17}H_{17}BrN_2O$	C, H, N, Br	300	72	0.001
19	H	4-*n*-$PrOC_6H_4$	182–184	100	C–B	$C_{18}H_{19}BrN_2O$	C, H, N, Br	300	97	0.01
20	H	5-Cl,2,4-$(MeO)_2C_6H_2$	260–261	88	A	$C_{17}H_{17}BrClN_2O_2$	C, H, N, Br, Cl	300	53	0.01
21	H	3-$CH_3CHOHC_6H_4$	165–167	78	C–B	$C_{17}H_{17}BrN_2O$	C, H, N, Br	300	43	*f*
22	H	4-BrC_6H_4	100–101	98	C	$C_{15}H_{12}Br_2N_2$	C, H, N, Br	300	55	0.01
23	H	2-MeO,5-MeC_6H_3	248–253	83	A–B	$C_{17}H_{17}BrN_2O$	C, H, N, Br	150	50	0.02
24	H	4-$Me_2CHOC_6H_4$	183–186	99	B–C	$C_{18}H_{19}BrN_2O$[i]	C, H, N, Br	300	97	0.001
25	H	3,4-$(MeO)_2C_6H_3$	278–280	92	C–B	$C_{17}H_{17}BrN_2O_2$	C, H, N, Br	300	96	0.01
26	H	2-$EtOC_6H_4$	177–178	100	C–B	$C_{17}H_{17}BrN_2O$	C, H, N, Br	100	88	0.001
27	H	2,5-$(EtO)_2C_6H_3$	246–248	85	C–D	$C_{19}H_{21}BrN_2O_2$	C, H, N, Br	300	82	0.001
28	H		212–213	80	C–B	$C_{20}H_{21}BrN_2O$	C, H, N	300	90	0.001
29	H	4-$Me_2CHCH_2OC_6H_4$	160–162	100	C–B	$C_{19}H_{21}BrN_2O$	C, H, N, Br	250	90	0.001
30	H	4-Cl-2,5$(MeO)_2C_6H_2$	290–292	100	A–D	$C_{17}H_{16}BrClN_2O_2$	C, H, N	300	66	0.001
31	H	4-HOC_6H_4	228–230	92	A–B	$C_{15}H_{13}BrN_2O$	C, H, N	300	73	0.001
32			259–260	89	C–E	$C_{14}H_{18}BrN_3 \cdot HBr$	C, H, Br	300	54	0.001
33	$HOCH_2CH_2$	$HOCH_2CH_2$	152–154	98	A	$C_{13}H_{17}BrN_2O_2$	C, H, Br	300	35	0.05
34	NH_2	$HOCH_2CH_2$	209–210	92	A	$C_{12}H_{16}BrN_3O$	C, H, Br	300	68	0.01
35	H	4-$EtOC_6H_4$	188–189	100	C–B	$C_{18}H_{19}BrN_2O$	C, H, Br	300	99	0.001
36	H	2,4-$(MeO)_2C_6H_3$	248–249	92	C–B	$C_{18}H_{19}BrN_2O_2$	C, H, N	150	89	0.001
37	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	107–109	87	C–B	$C_{16}H_{19}BrN_2$	C, H, Br	50	93	0.01
38	H	4-$MeSC_6H_4$	227–229	76	C	$C_{17}H_{17}BrN_2S$	C, H, Br	300	94	0.01
39	H	3,4-$(MeO)_2C_6H_4$	244–245	100	A	$C_{18}H_{19}BrN_2O_2$	C, H, Br	300	55	0.01
40	H	4-$MeOC_6H_4$	189–191	83	C–B	$C_{17}H_{17}BrN_2O \cdot 0.5HBr$	C, H, Br	300	99	0.001
Dithiazanine iodide								15[g]	76[g]	0.001

[a] A, abs EtOH; B, Et_2O; C, *i*-PrOH; D, H_2O; E, 48% HBr. [b] Analytical results for indicated elements are within ±0.4% of the theoretical values unless otherwise noted. [c] Single dose, in mg/kg (b.i.d. for 5 days). [d] Each group contained initially ten mice. An average control larvae count would be 377 ± 149 (mean ± SD). [e] Calcd: C, 59.81; Found: C, 59.07. [f] Not significant. [g] Toxic at 25 mg/kg. [h] Structure shown elsewhere. [i] 0.25HBr.

SCHEME I



2, R = H
3, R = CH_3

pared by a combination of two published procedures[5,6] as shown in Scheme I.

The reaction of **2** or **3** with an appropriately substituted amine in *i*-PrOH provided the corresponding 2-(substituted amino)quinolizinium bromides (**4**–**40**) shown in Table I.

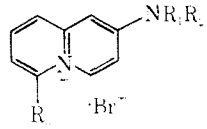
Biological Method. *A. suum*.—Drug administration was peroral to mice twice a day for 5 days. The infection was accomplished with embryonated eggs administered by gavage, halfway between the doses on the second day of medication. The mice were sacrificed and their lungs digested in buffered saline with added trypsin. Larvae were counted with the aid of a microscope. This method is a modification of the procedure outlined by Sprent.[7] Compound effectiveness was calculated as a percentage reduction based on the following formula.

$$\% \text{ reduction} = 100 - \left(\frac{\text{mean of medicated group counts} \times 100}{\text{mean of unmedicated control group counts}}\right)$$

The *A. suum* larvae counts were analyzed statistically by means of the Student "t" test.

Structure–Activity Relationships.—The anthelmintic activity of the compounds prepared in this work and a comparison drug, dithiazanine iodide,[8] are shown in Table I. In general, the compounds most active against *A. suum* contained a substituted anilino group in the 2 position of the quinolizinium ring. The presence of the Me group in the 6 position did not appear to cause a significant change in activity.

The substitution of alkylamino groups (**5**, **32**, and **33**) or hydrazino groups (**4** and **34**) on the quinolizinium ring resulted in somewhat lower activity when compared to compounds with anilino substituents. Substitution on the anilino ring with alkoxy or dialkylamino groups (**6** and **10**) resulted in increased activity over the unsubstituted anilino derivative (**14**). Substitution of halogens (**20**, **22**, and **30**), alkyl groups (**12**, **18**, **21**, and **23**), OH (**31**), or MeS (**38**) on the anilino ring resulted in diminished activity. Alkoxy groups in



5–34, R_1 = H
35–41, R_1 = Me

either the 2 or 4 position of the anilino ring resulted in high activity (**7**, **8**, **9**, **11**, **19**, **24**, **26**, **28**, **29**, **35**, and **40**), but two alkoxy groups in the 2 and 4 positions (**13** and **36**), the 3 and 4 positions (**25** and **39**), or the 2 and 5 positions (**27**) caused a reduction in anthelmintic activity. Three alkoxy groups in the 2, 4, and 6 positions (**15**) on the anilino ring resulted in significantly diminished activity. Extension of the alkoxy chain in the 4 position maintained activity at about the same high degree from Me through Pr and *i*-Pr (**8**, **19**, **24**, **35**, and **40**) but fell off slightly with *i*-Bu (**29**) and cyclopentyl (**28**), and markedly with *n*-Bu (**17**) and Ph (**16**).

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected.

2-(*o*-Anisidino)quinolizinium Bromide (7).—To a solution of 2-bromoquinolizinium bromide[5,6] (30 g, 0.1 mol) in *i*-PrOH (500 ml) was added *o*-anisidine (24 g, 0.2 mol). The stirred mixture was refluxed for 4.5 hr. After chilling the reaction mixture in an ice bath, the product was removed by filtration and washed thoroughly with Et_2O. After drying at 60° for several hours the product weighed 28 g (82%). Recrystallization from *i*-PrOH–Et_2O provided an analytical sample as tan needles.

The remaining compounds in Table I were prepared in a similar manner from **2** or **3** and the appropriately substituted amine or hydrazine.

Acknowledgment.—The authors are grateful to Miss Yvonne Miller, Mr. James Sheffer, and Mr. R. Charles Finch for the preparation of chemical intermediates, and to Mr. Merville Jones and Mr. Stephen Ashton for their assistance in the biological testing. Microanalyses were performed by Mr. Marvin Tefft and Mr. Grant Gustin.

Hypoglycemic Activity of 1-Alkenyl- and 1-Alkenoyl-3-arylsulfonylureas

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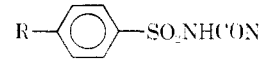
As part of our studies on new arylsulfonylureas,[1,2] we have prepared for hypoglycemic testing a number of compounds having the general formula I, in which R



I

was Cl, Me, or MeO, and R′ was an alkenyl or alkenoyl group. The new substances (Table I) were obtained

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(8) G. Brolly and E. C. Wiest, *Amer. J. Vet. Res.*, **24**, 460 (1963).

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