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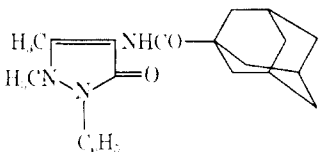
We have prepared 2,3-dimethyl-1-phenyl-4-(1-adamantanecarboxamido)-5-pyrazolone



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.

(1) P. A. J. Janssen and A. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957).

(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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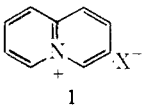
Many different types of compounds have been shown to have varying degrees of anthelmintic activity. Several of these classes, according to Harfenist, have a group bearing a positive charge and a cyclic moiety, which may or may not be separated. Examples of these include naphthamidines, dihydropyridines, 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-

(1) M. Harfenist, *J. Med. Chem.*, **6**, 361 (1963).

(2) A. H. M. Raeymaekers, F. T. N. Allewijh, J. Vandenberk, P. J. A. Demoen, T. T. T. Van Offenwert, and P. A. J. Janssen, *ibid.*, **9**, 545 (1966).

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

(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.